3-16-2021 4:00 PM

PLeurodesis Using hypertonic Glucose administration to treat post-operative air leaks following lung resection surgery (PLUG): Phase I trial

Mehdi Qiabi, *The University of Western Ontario*

Supervisor: Malthaner, Richard A, *The University of Western Ontario*
Co-Supervisor: Dubois, Luc, *The University of Western Ontario*
Co-Supervisor: Fortin, Dalilah, *The University of Western Ontario*
A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Surgery

Abstract

Introduction: Pulmonary air leaks from unhealed lung tissue are one of the most common complications after lung surgery. This adverse event leads to a delay in chest tube removal, prolonged pain, increased infections, prolonged hospital stay, and increased costs to the health care system. **Objective**: To define the most appropriate safe dose of dextrose 50% (D50) to seal air leaks in patients that have undergone lung resection surgery. Primary outcome was the occurrence of any adverse event. **Methods**: Prospective, single-arm, single-center, rule-based escalation traditional 3+3 design phase I trial where patients with an active air leak on postoperative day #2 received intrapleural D50 at various dosage. **Results**: 12 patients were recruited. Increments of 50 mL, 100 mL, 150 mL and 200 mL were tested. There was no severe adverse event. Air leak volume significantly decreased in the 24 hours following D50 administration compared to before (221 vs 31 L, p=0.013). Chest tube output remained similar (282 vs 365 mL, p=0.198). Transient non-significant increase of the glycemia was noted 1 hours after D50 (7.4 vs 10.0 mmol/L, p=0.156). 33% (4/12) were discharged home with a one-way valve. Pain level was not impacted by D50. **Conclusion**: Hypertonic intrapleural glucose to treat air leaks after lung resection appears safe. The optimum dose is 150 mL. Its efficacy is promising and needs to be further studied prospectively.

Keywords

Prolonged air leak; dextrose; glucose; hypertonic; pleurodesis; intrapleural; post-operative; lung resection

Summary for Lay Audience

Lung resection surgery is frequently performed to remove lung cancer. Lung tissue is cut, and a drainage tube is left beside the lung at completion of the surgery to remove fluid that could accumulate around the lung. Air may also be leaking out of the lung, preventing the tube from being removed as the lung would collapse. Air leaks are also associated to infections around the lung, and the longer the leakage persists, the higher the risk of infections. Air leaks prolong length of hospital stay, and therefore once a leak occurs efforts are made to seal it as soon as possible.

Several ways exist to stop those air leaks, including injecting a product in the chest through the existing tube to create inflammation around the lung. This process called pleurodesis has been performed using various agents, including talc. High concentration glucose (sugar) has emerged from reports as being a promising agent to achieve the same purpose, with less toxicity.

Before larger scale studies are performed, we aimed at assessing the safety of various dose of high concentration sugar. We enrolled 12 patients. No major side effects were linked to the injection of sugar in the chest. The air leak rate decreased dramatically. The pain level and fluid drainage did not change. The blood sugar temporarily rose without any meaningful consequence.

Using this data, we can design a larger scale trial where we measure how effective sugar is compared to placebo in sealing those air leaks after lung resection surgery.

Co-Authorship Statement

The systematic review and study protocol in the present document were designed and undertaken by Mehdi Qiabi, whose tasks included but were not limited to study design, participants enrolment, bedside procedures to participants, data collection, data analysis, manuscript production, communications with Health Canada, Lawson Health Research Institute and Western University Health Sciences Research Ethics Board and other entities. This was made possible with constant support from the supervisory committee.

Dr. Richard Malthaner was the primary supervisor and was involved in different aspects of this work.

Acknowledgements

I would first and foremost acknowledge the support and guidance of Dr. Richard Malthaner for his supervision and his indefectible guidance in the conduct of this project. I would like to thank Dr. Dalilah Fortin and Dr. Luc Dubois sitting on the supervisory committee who gave me valuable recommendations throughout. A special thanks to the Division of Thoracic Surgery as a whole with Dr. Richard Inculet always providing thoughtful insights. This project would not have been possible without the help of our fellows, Dr. Alexander Ednie, Dr. Yousef Abu Asbeh and Dr. Jessica Coffey who helped screening patients and delivered excellent clinical care. I would also like to thank all the nurses in our dedicated Thoracic Surgery ward C5-300, and Danielle Lozier, Paul Kaups and Katie Wuite for their collaboration. I would like to recognize the work of Ms. Deb Lewis who is always helping in the background. I express my gratitude to the Data and Safety Monitoring Board composed by Dr. Richard Inculet, Dr. Michael Mitchell, Dr. Nathan Ludwig, and Dr. Amanda Berberich for their participation. I would like to thank Ms. Patricia Dool and Ms. Teresa Longfield from Pharmacy Services for their help with the study drug. A special thanks to Dr. Éric Fréchette who contributed to the initial pilot work while working at LHSC. I am thankful to the Department of Surgery for funding this trial through a grant, to the faculty and colleagues of the MSc in Surgery program, and to Mr. Le Sauvage, librarian who helped with the systematic review. Last and not least, I would like to recognize the love and indefectible support of my family; to my parents Rachida and Abdelmalek who always guided me, to my siblings Sarah, Anas and Hasna, and to my partner Jennifer I say thank you!

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CHAPTER 1

1 INTRODUCTION

1.1 BACKGROUND AND OVERVIEW

Air leaks from unhealed lung tissue are one of the most common complications following lung surgery including wedge resection, segmentectomy and lobectomy. Air leaks can lead to a delay in chest tube removal, prolonged pain, increased infections, prolonged hospital stay, and increased costs to the health care system[1]. Different agents have been used to seal air leaks by creating a pleurodesis (adhesions to obliterate the pleural space between the visceral and parietal pleura). They range from minerals (talc, our current standard) to cytotoxic agents (bleomycin). The success with each of these agents has been variable and come with the cost of complications that have restricted their use during the post-operative period[2]. Cross-contamination of talc with asbestos has been described in the past[3–5], and although medical-grade talc is consider safe, some patients express concerns with its use in clinical practice. There has been recent interest in the use of 50% hypertonic glucose (D50) to create pleurodesis, with encouraging reports coming mostly from Asia[6–8]. We have performed a pilot study using 180 mL of D50 instilled through the chest tube for the management of post lobectomy air leak with encouraging results[9], leading to reduced duration of air leak, chest drainage and hospital stay when compared to an historical cohort. This preliminary study used strict inclusion criteria of only lobectomy patients and excluded many other patients, such as patients with diabetes or any

postoperative hyperglycemia that may benefit from this intervention. Also, the optimal dose of D50 was determined empirically and never clearly defined by previous work. It has been reported that high doses of D50 was associated to acute lung injury in some reports[10]. It is therefore critical that the optimal safe dose is clarified.

The objective of this work was to define the most appropriate safe dose of D50 to heal air leaks in patients that have undergone lung resection surgery (Phase I study).

We hypothesized that in patients with a post-operative air leak following lung resection, the bedside administration of D50 into the pleural space on post-operative day 2 was safe (Phase I trial). This will provide the basis and data to proceed with a formal Phase II study to assess the effectiveness of the chosen dosage in reducing the duration of chest tube drainage, and then a Phase III randomized clinical trial against talc.

We anticipate that D50 will replace talc as our pleurodesis agent of choice and become the new standard not only for sealing air leaks following lung resection surgery, but also to achieve pleurodesis for chronic pleural effusions. Should we be successful in reducing post-operative air leaks in patients undergoing lung resections, we will reduce their hospital length of stay. This intervention should improve patient outcomes by shortening the duration that a chest tube is required

in the pleural space, reducing post chest tube removal pneumothoraces, decrease chest tube related pain, decrease the risk of post-operative infections, hospital length of stay, and health care costs. Should this simple, inexpensive, and novel therapy work to heal pulmonary air leaks, it will be a significant advancement in overcoming this long standing “Achilles heel” in Thoracic Surgery.

In this thesis, dextrose 50%, glucose 50%, hypertonic glucose, hypertonic dextrose, and D50 are used interchangeably.

CHAPTER 2

2 LITERATURE REVIEW

2.1 AIR LEAK AFTER LUNG SURGERY

Leakage of air after lung surgery is frequent. Lung surgery is performed for various indications. Resection of lung parenchyma for benign or malignant disease is routinely performed in tertiary health care institutions. Leakage of air after lung resection is one of the most frequent adverse events and is the most common cause of prolonged length of stay[11]. Data extracted from the European Society of Thoracic Surgeons database reported a rate of prolonged air leak (more than 5 days) of 9.9%[12] after lobectomies or pneumonectomies. The Society of Thoracic Surgeon General Thoracic Surgery database reports a similar rate of prolonged air leak of 10.4%[13] after lung resection. In a series of 319 patients, Okereke and al.[1] quantified that the prevalence of air leak after anatomic lobectomies was 58% immediately at the end of the surgery in the post-anesthesia recovering unit. The median air leak duration was 3 days, but up to 10% of patients were still leaking 7 days later. Our own experience during a randomized controlled trial[14] evaluated the role of autologous platelet rich plasma and concentrated platelet poor plasma on reducing air leak after lobectomies for cancer documented a 43.3% air leak prevalence at 4 days in the control group. A recent analysis of internal data in our group's prospectively maintained institutional database showed that out of 866 patients who underwent a minimally invasive wedge or lobectomy from July 2012 to June 2017, at least 102 patients

(11.8%) suffered from a prolonged air leak (five days or more). Incidence of post-operative air leak has been observed up to 15-26% in other single institution large series[15,16]. As the occurrence of adverse events of any grade leads to prolonged length of stay after lung cancer resection[17], and that prolonged air leaks are directly associated to pulmonary complications (including empyema), readmissions and delayed hospital discharge[18], it is important to find strategies to mitigate the impact of such adverse events.

2.2 PERSISTENT AIR LEAK IN THE SETTING OF SPONTANEOUS PNEUMOTHORAX

Air leaks not only arise post-operatively, but they can also occur spontaneously, giving rise to a pneumothorax. Pleurodesis and resolution of the leak are desired, similar to patients with post-operative air leaks. Treatment usually includes simple drainage of the accumulated air via tube thoracostomy[19] as recommended in the 2010 Guidelines of the British Thoracic Society. The annual incidence rate of primary and secondary spontaneous pneumothoraces is reported to be 22.7 cases/100 000 people[20] in an analysis of the France national database from 2008 to 2011, with a subset that may require additional treatment than just simple drainage. The American College of Chest Physicians guidelines on spontaneous pneumothoraces published in 2001[21] recommended that patients with persistent air leaks (more than 4 days) should be evaluated for surgery to address the leak, followed by pleurodesis to reduce the recurrence rate. This is concordant with the

British Thoracic Society 2010 guidelines[19]. Surgical treatment typically consists on finding the area of lung parenchyma leaking air and surgically remove it by stapling across normal lung tissue, in addition of performing a procedure that will promote pleurodesis post-operatively[19,22]. For non-operative candidates[23], chemical pleurodesis can be attempted. Other methods include keeping the tube with a one-way valve for a prolonged time hoping the leak will eventually stop and the use of endobronchial devices or drugs. Methods applied to promote pleurodesis in the post-operative setting should also be effective in this population.

2.3 MONITORING OF AIR LEAK

Lung resection almost always requires one or more drainage tube(s) left in the pleural cavity to collect the excess of fluid and air that could accumulate around the lung. Such accumulation can lead to catastrophic physiological consequences for the patient, culminating to cardiorespiratory arrest if a tension pneumothorax develops or if bleeding is unrecognized for instance. This tube needs to be connected to a chest drainage system to monitor the amount and quantity of fluid, and also to prevent reflux of air from the outside world back into the chest as the pleural cavity is a negative pressure environment compared to the atmospheric pressure.

Chest drainage systems can be classified as either analog or digital. Analog drainage systems are modifications of the three-bottle chest drainage system[24]. They rely on the visual evaluation of the presence of air bubbles in the water chamber by an observer who then reports it in the patient chart typically using a standardized classification[22,25–27]. These systems are relatively inexpensive but are cumbersome for patients as the device is relatively large, and subjective. In addition, if suction is required, the analog device has to be connected to the suction wall, therefore impairing patient's ambulation. Compared to analog systems, digital pleural drainage systems are a newer technology that have been shown to improve interobserver reliability in the assessment of pulmonary air leak[28], as the objectivity is increased. Additional advantage by design includes recording of the air leak over time and better ambulation for patient as the suction is battery powered. Gilbert performed a randomized controlled trial[29] of digital versus analog pleural drainage systems after lung resection in which the digital system reduced the number of chest tube clamping trials. Using specific air leak flow thresholds for chest tube removal on the digital system, no patients had chest tube reinsertion for worsening pneumothorax or subcutaneous emphysema. These digital devices are being incorporated more and more included in post-operative clinical pathways[30]. A recent meta-analysis including 10 randomized controlled trials enrolling 1268 patients showed that digital systems statistically reduced the duration of chest tube placement, the length of hospital stay, the air leak duration, and postoperative costs[31]. They are now becoming the "standard of care".

2.4 PLEURODESIS

2.4.1 DEFINITIONS AND INDICATIONS

Pleurodesis is defined by Hallifax et al. as the “permanent apposition of the visceral and parietal pleura to seal the pleural space”[32]. Inflammation within the pleural cavity is voluntarily created to generate adhesions and pleural symphysis. It is categorized as chemical when the mechanism involves the administration of an agent within the pleural space, or surgical when the parietal pleura is surgically excised (pleurectomy) or damaged (pleural abrasion). The aim in both cases is to prevent future collapse of the lung caused by either air or fluid.

Several indications exist to perform pleurodesis. Prevention of recurrent spontaneous pneumothoraces and treatment of an active air leak in non-surgical candidates are the main indications[32]. Malignant pleural effusions may also be treated by chemical pleurodesis[33]. Benign effusion such as chylothorax have also been treated by performing chemical pleurodesis[34–36].

2.4.2 AGENTS USED TO ACHIEVE CHEMICAL PLEURODESIS

All the sclerosing agents possess the same attribute: damaging pleural mesothelial cells to trigger an inflammatory cascade where a neutrophilic exudate is formed. Multiple factors come at play including the ability of fibroblasts

and mesothelial cells to produce collagen, and an equilibrium between metalloproteinases and plasminogen activators[37]. Certain anti-inflammatory agents such as steroids and diclofenac reduce the degree of pleurodesis in experimental studies[38,39], while others (cyclooxygenase-2 inhibitors) do not[37].

Several agents exist. In a recent systematic review[32] assessing the effectiveness of chemical pleurodesis in spontaneous pneumothoraces recurrence prevention and in a Cochrane meta-analysis[33] on interventions for the management of malignant pleural effusions, the following agents were listed to induce pleurodesis:

- Talc (mineral, most used agent)
- Tetracycline (antibiotic)
- blood
- minocycline (antibiotic)
- iodopovidone (antiseptic agent)
- silver nitrate (antiseptic agent)
- quinacrine (derivative of anti-malarial drug)
- fibrin glue
- bleomycin (chemotherapy agent)
- Cryptosporidium parvum (bacteria)
- Interferon (immunomodulating agent)
- Mustine (chemotherapy agent)
- mitoxantrone (chemotherapy agent)

- mepacrine (anti-malarial drug)
- doxycycline (antibiotic)
- triethylenethiophosphoramide (chemotherapy agent)
- Adriamycin (chemotherapy agent)
- Viscum (parasitic plant)
- OK-432 (inactivated preparation of Streptococcus pyogenes, very popular in Japan[6])

They all have various risk of toxicity, and a simpler agent such as dextrose could possibly provide similar efficacy with a better safety profile. For example, C. parvum and mepacrine are known to induce fever more frequently than other agents. Blood may be difficult to collect and inject, and may clog the chest tube. Mepacrine, mitoxantrone and C. parvum are associated with pain[33]. Patients may be allergic to some of these agents.

While not listed in the above-mentioned reviews, administration of hypertonic glucose in the pleural cavity has been described to obtain pleurodesis (cf below), and its first documented use to as a chemical pleurodesis agent was in 1906 by Spengler[40], and first success in 1923[41,42].

2.5 HYPERTONIC GLUCOSE TO ACHIEVE PLEURODESIS – SUMMARY OF ALL DATA AND SYSTEMATIC REVIEW

The systematic review was conducted in accordance to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines[43] (Table 1). The search was completed on December 9, 2019 and updated on January 3, 2020. The search strategy is located in Appendix M.

Articles where the intervention was intrapleural administration of any volume of hypertonic glucose (Intervention) on human patients (Population) were included. The objective of the search was to find data on the safety (Outcome) of intrapleural hypertonic glucose to induce pleurodesis. It was mandatory for the article to include the population size, and information on adverse events. Exclusion criteria consisted of non-human or pediatric populations, non-English abstracts and/or articles and review articles.

Two authors (M Qiabi, A Ednie) extracted the data from the eligible studies and cross-checked the results subsequently. There was 100% agreement in the results. Variables that were extracted included: general study characteristics (author, year, study design, location, number of patients), patient population, intervention and occurrence of adverse events.

A total of 98 entries were found after performing the PubMed search. After screening by assessing article's title, abstract, and sometimes the article itself, 13 articles[6–8,10,34,35,44–50] were kept for the review.

Google Scholar search yielded 975 results. After screening by assessing article's title, abstract, and sometimes the article itself, one[9] additional article was added to the review.

SCOPUS search yielded 7 results, none of which were either relevant or new addition compared to the other two databases.

Cochrane search yielded 9 results, none of which were either relevant or new addition compared to the other three databases.

Finally, Web of Science search yielded 88 results, three[36,51,52] of which were new additions compared to the other four databases.

After reading each article and reviewing the references, 6[42,53–57] additional articles have been added to the list. A total of 23 articles were therefore reviewed, covering 447 patients (Table 1). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure 1) and the PRISMA Checklist (Table 2) are attached. The volume of intrapleural dextrose during initial administration ranged from 30 mL to 500 mL. The maximal total volume administered was 1500 mL (3 times 500 mL over 3 days).

2.5.1 INDICATIONS

Administration of hypertonic glucose into the pleural cavity was performed for the following indications:

- spontaneous pneumothorax (17 studies[6–8,10,42,44–50,53,54,56,57], 313 patients)
- prolonged air leak after lung resection (5 studies[6,9,52,54,55], 70 patients)
- chylothorax (3 studies[34–36], 42 patients)
- malignant pleural effusion (2 studies[51,54], 22 patients)

2.5.2 KNOWN POTENTIAL RISKS

In five papers[6,9,52,54,55], the population studied were post-lung resection patients with air leak (70 patients). In these 70 subjects, reported adverse events were as follow:

- mild transient hyperglycemia (n=26/70)
- mild transient chest pain
- mild transient fever
- mild increase in chest tube output

In these 70 patients, reported adverse events were mild. This population is similar to the population we plan to study. The concentration of dextrose was 50%. Except for one study[55] in which the data was not available, they all had administration of 200 mL, repeated up to 2 other times for a total of 600 mL over

3 days. There was no infectious complication in this population with air leak after lung resection.

In the whole population (447 patients) comprising all indications for pleurodesis, infectious complications related to the intervention were rare. One study[7] where 20 patients had spontaneous pneumothoraces and were treated with bullectomy, mechanical abrasion and administration of 500 mL of Dextrose 50% in the operating room had one case of "bacterial pleuritis" as potential complication. The authors mentioned that "the period of thoracic drainage and the volume of air leakage may contribute to the development of a pleural infection". Another study[8] where 13 patients had spontaneous pneumothorax treated with a chest tube and then administration of between 200 to 500 mL of dextrose 50%, repeated up to a total of 3 times (500 mL administered 3 times over 3 days) reported 2 patients with "bacterial pleuritis". Both of them had their chest tubes in place for a prolonged period of time (25 and 35 days), and they both had repeated administration of 500 mL of dextrose 50% (one had a total of 2 doses and the other 3 doses). All these 3 patients were treated conservatively with antibiotics.

Ischemic colitis induced by dehydration was reported after the administration of 400 mL of Dextrose 50% on a 97 years old patient to induce pleurodesis after a spontaneous pneumothorax[53]. This was treated conservatively with rehydration and surgery was not required.

Chee[44] reported a case of dextrose pneumonitis. The 51 years old male with chronic obstructive airways disease complicated by cor pulmonale and hypercapnic respiratory failure had a spontaneous pneumothorax. He had a prolonged air leak for 41 days. Intrapleural instillation of 50 mL of Dextrose 50% was performed and the patient experienced cardiorespiratory collapse requiring cardiopulmonary resuscitation. It was noted that a copious quantity of secretions was coming from the endotracheal tube, positive for glucose by a dipstick. The patient recovered well after that event and the leak stopped. It was postulated that osmotic pulmonary edema may have been caused by the high tonicity of the dextrose 50%.

Of the 447 patients who underwent intrapleural hypertonic dextrose administration for pleurodesis, a total of 3 deaths were reported.

1- In Tsukioka[7] paper, a 79 years old male with severe emphysema, unresectable lung cancer who recently had chemotherapy, underwent a bullectomy, mechanical abrasion of the pleura, and administration of 500 mL of dextrose 50% in the pleural cavity. Twenty-four days after his surgery, he passed away from a pneumonia. It is unclear whether his death is related to the administration of a sclerosing agent.

2- In Hamada[10] paper, a 72 years old male with a stage IV lung cancer and severe emphysema, presented with spontaneous pneumothorax. He was

first treated with 5 rounds of OK-432 (sclerosing agent available in Japan to induce pleurodesis), but it did not work, and the leak was still present. Then, 4 rounds of autologous blood and 200 mg of minocycline were injected into the pleural cavity via the chest tube, again without success. Finally, 200 mL of dextrose 50% was injected into the pleural space. The patient suffered from acute respiratory distress syndrome and had to be intubated. He eventually died from progression of respiratory failure. While there seems to be a temporal association, the causality is uncertain.

3- In Hamada[10] paper, a 84 years old male with idiopathic pulmonary fibrosis, on home oxygen and hypercapnic respiratory failure developed a spontaneous pneumothorax. A chest tube was inserted, and 400 mL of dextrose 50% administered into the pleural space. Immediate pain and respiratory failure occurred. It was recommended for the patient to be intubated, but the family refused. The patient died 1 week later from progression of respiratory failure.

In the case of Patient 1, the death seems to be related to a nosocomial pneumonia and not from the intervention. Patient 2 had multiple attempts at pleurodesis with various agents (OK-432, blood, minocycline) before dextrose was tried. This is not the type of intervention planned in the current proposed study. Patient 3 seemed to have an acute reaction to dextrose 50%. The volume administered is twice the maximum dose we are planning to use.

In summary, after reviewing the current literature, the most common and potential safety concerns our study group is ready to face are:

- acute respiratory distress
- dehydration
- pain
- hyperglycemia
- fever

It is hypothesized that the value of the information gained by performing this study will allow health care providers to have another option when comes the time to offer a patient chemical pleurodesis (instead of offering talc), thoracic surgeons or respirologists will have the option of administering hypertonic glucose. Talc is associated to acute toxicities like the Acute Respiratory Distress Syndrome[58], and healthcare workers with occupational exposure to talc may be at higher risk of developing lung cancer[59]. Of note, the risk of reporting bias exists, as papers with severe adverse events may not have been published. On an individual study level, most of these studies were retrospective, with all the biases associated with this design (selection).

2.5.3 KNOWN POTENTIAL BENEFITS

After pulmonary resection, air leak is one of the most common complications arising from lung parenchyma at sites of division of adhesions, fissure dissection

or lung retraction for exposure. A chest tube inserted at the end of the procedure will drain any ongoing air-leak allowing the underlying lung to re-expand.

Patients who have an air leak on post-operative day 2 typically are offered observation, hoping the air leak will seal by itself. However, previous work showed that a significant number of patients who still leak on POD2 will have a prolonged air leak (more than 5 days), and then will be typically offered one of 3 options:

1- waiting a longer period of time before removing the chest tube, with possibly discharging the patient home with a small one-way valve if the lung stays well inflated, hoping the leak will have stopped at the next outpatient visit
2- injection of a sclerosing agent (such as talc) into the pleural space hoping the leak will stop
3- reoperation, hoping to stop the leak

It is known in the thoracic surgery literature that the longer a leak persists, the more likely the patient may suffer from an infection of the pleural space (empyema)[60,61]. Other complications such as catheter-related discomfort, arrhythmia or deep vein thrombosis could potentially be attributed to prolonged length of stay.

Most reports from Table 1 have shown some efficacy in inducing pleurodesis and achieving the desired outcome. We postulate that participants to the study will therefore potentially be able to be discharged home sooner, have their chest tube

removed sooner (leading to pain relief), and because the leak would stop earlier, there is a hypothetic benefit in reducing the risk of post-operative infectious complications[18].

Author	Year	Study design	Location	n	Population	Intervention	Adverse events
Chen[34]	2010	Retrospective case series	China	5	post-esophagectomy chylothorax	50% glucose + 0.1% lidocaine (volume?) through the tube	self-resolving dyspnea
Chung[49]	2008	Prospective cohort	South Korea	49	primary spontaneous pneumothorax	thoracoscopic procedure (bleb resection/bullectomy/electrocoagulation) + instillation of dextrose 20% 200 cc	rate of fever 22% (dextrose group) vs 10% (no dextrose group)
Tsukioka[7]	2013	Retrospective cohort	Japan	20	secondary spontaneous pneumothorax	VATS bullectomy + mechanical abrasion + dextrose 50% (500 cc)	1 death[a] 24 days after the surgery from a pneumonia,1 prolonged air leak (15 days), 2 prolonged thoracic drainage, 1 "bacterial pleuritis", transient elevation of blood sugar
Hamada[10]	2017	Retrospective case series	Japan	2	spontaneous pneumothorax	1- 200 mL of dextrose 50% 2- 400 mL of dextrose 50%	2 deaths[b]
Peng[50]	2002	cohort	China	45	recurrent pneumothorax	60-80 mL of Dextrose 50% through the tube	7/45 had mild pain
Chee[44]	1992	Retrospective case report	Singapore	1	spontaneous pneumothorax	50 mL dextrose 50%	pulmonary edema[c]
Fujino[6]	2016	Retrospective cohort	Japan	46	35 post-lung resection patients with air leak and 11 patients with pneumothorax and prolonged air leak with a tube in place	200 mL of 50% glucose, between 1 and 3 doses, 7 patients had OK-432 after their 3rd dose for failure of the glucose to work	mild transient hyperglycemia in 20/46 patients
Takanashi[53]	2015	Retrospective case report	Japan	1	spontaneous pneumothorax	50% glucose, 400 mL	ischemic colitis secondary to severe dehydratation (1960 mL/4 hours), prerenal acute renal failure
Togo[54]	2016	Retrospective cohort	Japan	29	14 pneumothorax, 11 post-lung resection air leak, 4 malignant pleural effusion	200 mL of 50% glucose (2 patients had 100 mL for « poor performance status »)	Mild transient hyperglycemia, chest pain and fever
Tsukioka[8]	2013	Retrospective cohort	Japan	13	spontaneous pneumothorax	200 - 500 mL 50% glucose through the tube, they often required more than one treatment	2 "bacterial pleuritis" (both of them required more than 1 treatment, and they had their tube 25 and 35 days, treated with antibiotics only), 1 aspiration pneumonia
Albargawi[9]	2016	Prospective cohort	Canada	10	post-lobectomy air leak	200 mL dextrose 50% with lidocaine, once or twice	mild increase in chest tube output, mild increase in blood sugar
Frick[45]	1990	Cohort	Germany	32	spontaneous pneumothorax	thoracoscopic pleurodesis with electrocoagulation of bullae, visceral/parietal pleurae cauterized, chemical pleurodesis with dextrose 50%	Horner syndrome (secondary to pleural cauterization)
Sumitomo[52]	2017	Cohort	Japan	13	post-lung resection air leak	200 mL glucose 50%, repeated as needed (2 patients had pleurodesis twice)	none
Kitagata[55]	2018	case report	Japan	1	Air leak post right lower lobectomy	glucose 50%	none
Yaginuma[56]	2016	case report	Japan	1	spontaneous pneumothorax on mechanical ventilation	pleurodesis with glucose 50% and minocycline	none
Kajikawa[57]	2017	case series	Japan	5	spontaneous pneumothorax	pleurodesis with 200 mL glucose 50%	transient hyperglycemia
Hennell[42]	1939	case report	US	2	Chronic pneumothorax	glucose 50% 50 mL, then 60% 67 mL	none

Table 1 - List of all studies. VATS: video-assisted thoracic surgery, POD: post-operative day. [a,b,c] cf description of the events in the text

Author	Year	Study design	Location	n	Population	Intervention	Adverse events
Lai[35]	2019	Prospective cohort	China	34	Chylothorax post-esophagectomy (30), lobectomy (2) and mediastinal mass resection (2)	daily 50% dextrose 100 mL (IL-2 if diabetic)	Electrolytes imbalances attributed to chyle leak. No pleural infection
Tsuboshima[47]	2018	Retrospective cohort	Japan	106	Spontaneous pneumothorax	Bullectomy + 50 mL 50% glucose solution for pleural coating on an absorbable sheet	No empyema in the glucose group, mild increase in pain score (3 vs 2), marginal increase in chest tube output. No dehydratation, no long-term restrictive physiology on pulmonary function tests
Yamane[48]	2014	Case report	Japan	1	Spontaneous pneumothorax	50% glucose	None
Van den Brande[46]	1989	RCT	Belgium	10	Spontaneous pneumothorax	30 mL of 30% glucose + 250 mg of oxytetracycline	None (no fever, no pleural effusion)
Li[36]	2011	Case series	China	3	Chylothorax post-pulmonary resection	50% glucose	None reported
Khanna[51]	2010	Retrospective cohort	Great Britain	18	Malignant pleural effusion	Talc slurry in dextrose 50% solution	None reported

Table 1 - List of all studies (continued). VATS: video-assisted thoracic surgery, POD: post-operative day. [a,b,c] cf description of the events in the text

Figure 1 - PRISMA 2009 Flow Diagram

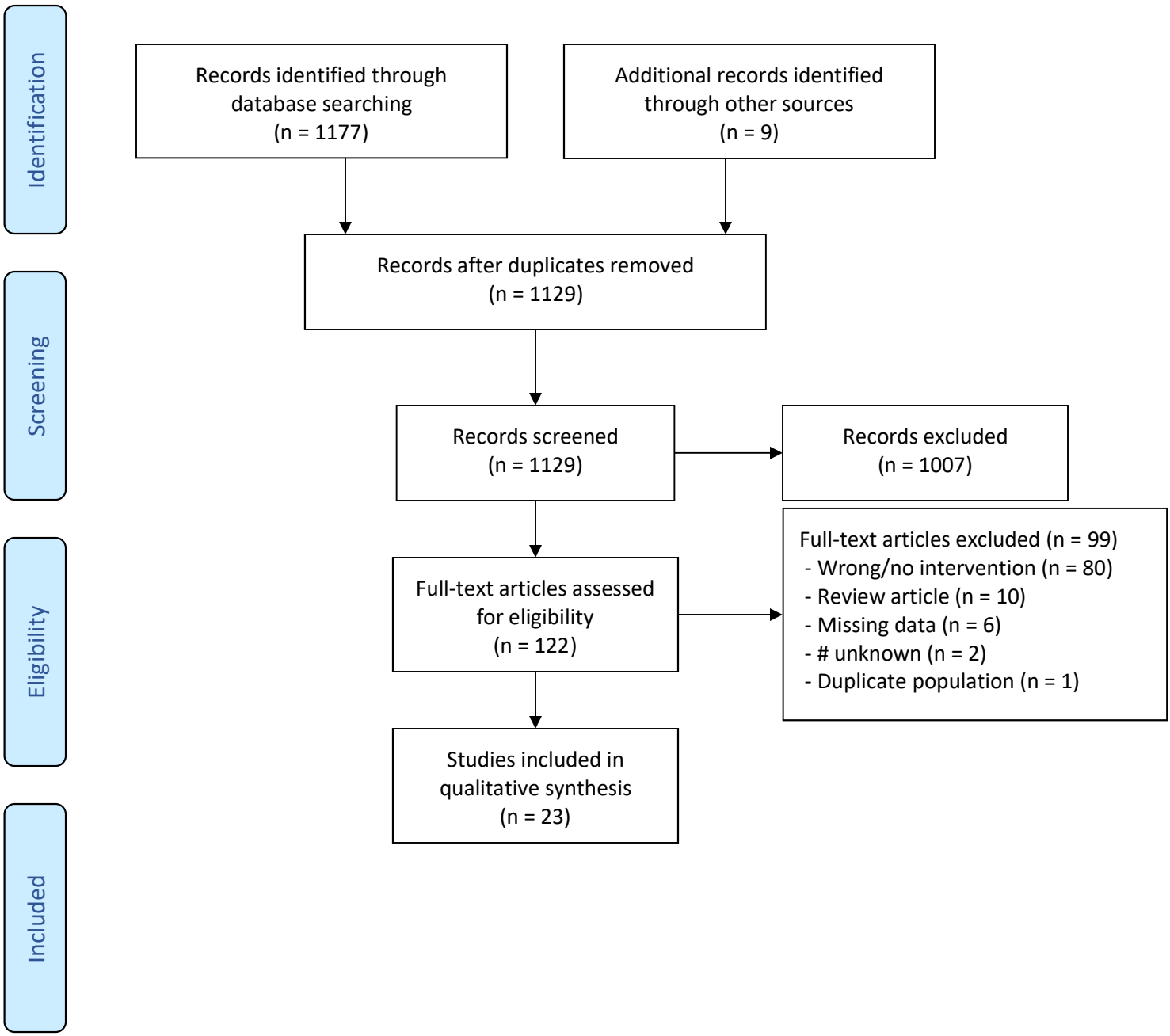

Table 2 - PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	12
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	12-13
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-12
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	13
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	13
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	13-14
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	13 and Appendix M
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	13
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	n/a
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	n/a
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	n/a
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	13

Table 2 - PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a
Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	24
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	22-23
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	22-23
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	n/a
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	n/a

CHAPTER 3

3 RATIONALE, RESEARCH QUESTION, OBJECTIVE AND HYPOTHESIS

Air leaks from unhealed lung tissue are one of the most common complications after lung surgery including wedge resection, segmentectomy and lobectomy. Air leaks can lead to a delay in chest tube removal, prolonged pain, increased infections, prolonged hospital stay, and increased costs to the health care system[1]. Different agents have been used to heal air leaks by creating a pleurodesis (adhesions to obliterate the pleural space between the visceral and parietal pleura). The success with these agents has been variable and come with the cost of complications that have restricted their use the post-operative period[2]. There has been recent interest in the use of D50 to create pleurodesis with encouraging reports coming mostly from Asia[6–8]. We have performed a pilot study using D50 instilled through the chest tube for the management of post lobectomy air leak with encouraging results[9]. This preliminary study used strict inclusion criteria of only lobectomy patients and excluded many other patients such as patients with diabetes or any postoperative hyperglycemia that may benefit from this intervention. Also, the optimal dose of D50 was chosen empirically and never clearly defined by previous work. It has been reported that high doses of D50 was associated to acute lung injury[10]. It is therefore critical that the optimal safe dose is clarified. A phase I study was therefore designed.

Research question: Is intrapleural dextrose 50% administered 2 days after lung resection safe when an air leak is present?

Objective: To confirm safety of various dosage of D50 to heal air leaks in

patients that have undergone lung resection surgery (Phase I study).

Hypothesis: In patients with a postoperative air leak following lung resection, the bedside administration of D50 into the pleural space on postoperative day 2 is safe (absence of severe adverse events related to D50).

We predicted that D50 would be found safe because no severe adverse events occurred with optimum dose (dose providing the best efficacy for the most acceptable toxicity) found in this Phase I study. Results provide the motivation and data to proceed with a formal Phase II study to assess the effectiveness of the chosen dosage in reducing the duration of chest tube drainage, and then a Phase III randomized clinical trial comparing D50 to talc.

CHAPTER 4

4 METHODS

A detailed protocol (Appendix F, protocol MQRM711 v2.05) has been submitted to the Health Canada Therapeutic Products Directorate which issued a No Objection Letter (Appendix E) following evaluation of our Clinical Trial Application (CTA, control number 229051). The protocol was elaborated using the National Institutes of Health (NIH) protocol templates for clinical trials[62]. Training in Part C, Division 5 of the Food and Drug Regulations was completed by the investigating team as part of a Health Canada requirement for the investigation of drugs in regulated clinical trials involving human subjects.

The protocol (Appendix F) outlines the background information and scientific rationale, objectives and purpose, study design and endpoints, study enrollment and withdrawal, study agent, study procedures and schedule, assessment of safety, clinical monitoring, statistical considerations, source documents and access to source data/documents, quality assurance and quality control, ethics/protection of human subjects, data handling and record keeping, study administration, conflict of interest policy, and literature references. This CTA was requested by the Western University Health Sciences Research Ethics Board (HSREB) after Full Board review. The study was subsequently approved by Western University HSREB (#113906) and Lawson Health Research Institute (R-20-071). The trial is registered at ClinicalTrials.gov (NCT03905408).

This trial took place at London Health Sciences Centre (LHSC) – Victoria Hospital, London, Ontario, on the Thoracic Surgery ward (C5-300).

Below is a summary of the protocol.

4.1 DESCRIPTION OF THE STUDY DESIGN

In this prospective single-arm, phase I, single-center trial, patients with air leak on postoperative day 2 following lung surgery were invited to participate in the study. The precise definition of air leak is found in section 4.5. The solution to be used as pleurodesis agent consisted of sterile 50% glucose injected in the chest tube, followed by the administration of 20 mL of 1% lidocaine to flush the tube and ensuring the glucose is in the pleural space, and to provide some local anesthesia to the parietal pleura.

Twenty-four hours after the intervention, if there is air leak cessation (defined below), chest tube removal was considered by the surgical team. If an air leak was still present, no further intervention was planned. The volume of D50 administered was incremental and followed a rule-based escalation, traditional 3+3 design[63] (Figure 2): 3 patients had a set dose, and if there were no dose-limiting toxicities (Appendix H) or less than 2 moderate toxicities, the next group of 3 patients went up one increment following review from the Data and Safety Monitoring Board. In addition, each patient was reviewed on a weekly basis by

the surgical team to ensure concordance in adverse events (if any) noted. The empiric increments were 50 mL, 100 mL, 150 mL, and 200 mL. A maximum of 12 patients were to be enrolled.

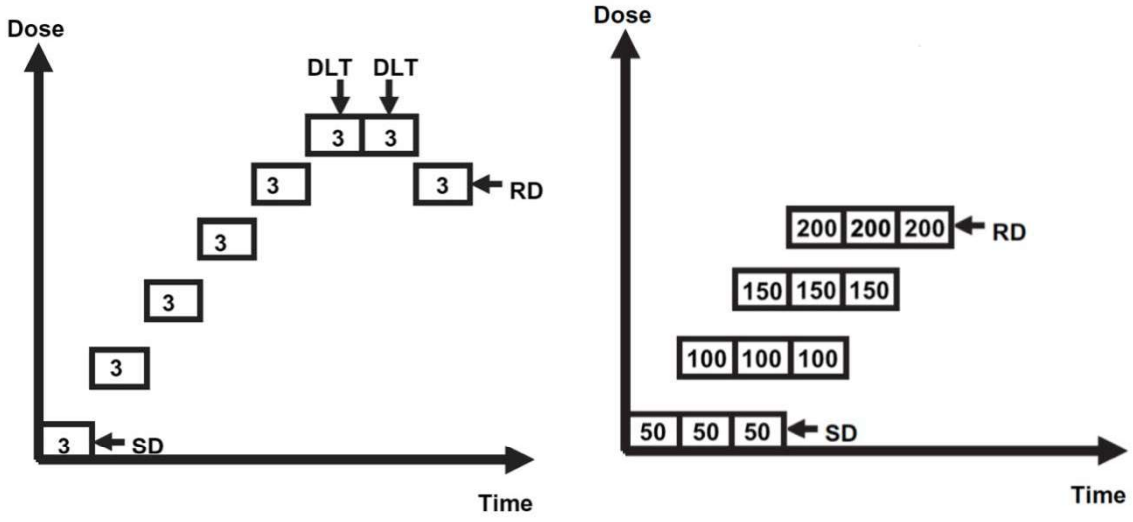

Figure 2 – Traditional 3+3 design (left plot). From Le Tourneau et al.[63] SD = starting dose; DLT = dose-limiting toxicity; RD = recommended dose. This phase I trial use the thresholds displayed in the right plot.

The 3+3 design was selected as it is commonly used in Phase I drug trials (notably in oncology) and uses a progressive approach (rule-based) to find the appropriate dose for further trials or therapeutic uses. The only assumptions are that the drug of interest has both a dose-efficacy and a dose-toxicity curve. Once prespecified dose-limiting toxicities are experienced by at least 2 patients, the escalation stops, and the dose recommended for phase II trials would typically be the increment just below the one that triggered the toxicities. An issue that can arise is that titration can be slow, potentially preventing many patients from

receiving drugs of effective dosage (subtherapeutic) while only very few will actually receive trialled drugs near the recommended dosage used for phase II trials. Most trials using this design will have 6 or more thresholds[63]. In our case, the first increment (50 mL) corresponds to the lower end of the range of volumes administered to patients in the systematic review. Each dextrose 50% syringe comes in 50 mL volumes; therefore, increments were arbitrarily chosen to be 50 mL throughout this study and that is why the suggested modified Fibonacci sequence (smaller dose increments as the dose increases) was not followed. Finally, the highest threshold used was 200 mL as it is one of the commonest volumes administered in the systematic review. At a volume of 200 mL and above, some patients seem to experience adverse events, and therefore we elected not to go higher.

Several variations of the 3+3 design exist, with different rules or accelerated escalation designs (based on plasma drug concentration for example). The main advantage of this traditional design is that it is safe, simple to implement and has a proven track record, being in use for many decades in large studies leading to drug approval by organizations such the U.S. Food and Drug Administration.

Model-based designs use statistical models computing enrolled patients' data in real-time to establish how quickly the dose can be escalated to reach the phase II dose quicker. Biostatistical expertise is mandatory. Several assumptions on the

dose-toxicity curve have to be made beforehand and, if wrong, may fail to reach the recommended dose for the phase II trial.

For all the aforementioned reasons, the traditional 3+3 design was selected in the current study.

4.2 DATA AND SAFETY MONITORING BOARD (DSMB)

As mandated by Health Canada, a DSMB was constituted. Four physicians expert in their field and consultants at LHSC were recruited:

- Dr. Richard Inculet, Thoracic Surgery
- Dr. Nathan Ludwig, Anesthesia & Perioperative Medicine
- Dr. Amanda Berberich, Endocrinology and Metabolism
- Dr. Michael Mitchell, Respirology

These individuals were selected for their knowledge in the pulmonary physiology, the post-operative course after lung resection, the impact of dextrose when administered in high concentration, the treatment of hyperglycemia and the treatment of pain. Members of the DSMB have signed a declaration confirming the absence of any financial or other interest with any of the investigators or other organizations involved in the study that could represent a potential perceived or true conflict of interest.

Communications between the DSMB and the investigators were by secured email. The DSMB reviewed data from REDCap (secure, web-based, institution-approved software), along with a narrative of the 3 patients in each threshold to confirm moving up to the next increment.

The DSMB operated using strict and well-defined halting rules (Appendix H).

4.3 PRIMARY ENDPOINT

The primary outcome of this Phase I study is the safety of intrapleural dextrose 50% as defined by the lack of grade 3, 4 or 5 adverse event at any given D50 volume according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0[64]. Each adverse event has its own criteria to define the grade of the adverse event (AE). Grade 1 is considered a mild AE, while grade 5 is an AE resulting in death.

The AE were collected by the investigators and transmitted to the DSMB with a detailed narrative of the AE. Questions from the DSMB were answered. The DSMB was responsible to approve the final grading of each AE.

4.4 SECONDARY ENDPOINTS

Secondary outcomes include:

- Presence of any adverse event
- Persistence (yes/no) of air leak 24, 48 and 72 hours post dextrose administration, and change in the air leak rate
- Pain score at baseline, 1 hour, 3 hours, 6 hours, and 24 hours after dextrose administration (visual analog scale)
- Point-of-care glucose measurement at baseline, 1 hour, 3 hours, 6 hours, 24 hours after dextrose administration
- Chest tube output during the first 24 hours after dextrose administration
- Length of hospital stay
- Duration of chest tube drainage
- Need to discharge the patient home with a one-way (Heimlich) valve
- Need for an additional chest tube to be inserted after dextrose administration
- Supplemental oxygen requirements
- Patient analgesia consumption
- Need for any intervention to treat hyperglycemia
- Recurrence of air leak

Demographic characteristics (age, gender, smoking status, comorbidities, diagnosis, type of surgery, surgical approach and the air leak rate pre-D50) were also collected. The Charlson Comorbidity Index (CCI)[65] is a prognostic score derived from 19 pre-defined comorbid conditions. Each condition has a different

weight based on the association with 1-year mortality. It is calculated for each patient.

4.5 AIR LEAK DEFINITION

For the purpose of this study, “air leak” and “air leak cessation” are defined as follow using the Medela Thopaz^{TM} digital system (Figure 3 and 4):

- Air leak
    - Air leak equal or more than 40 mL/min for at least 1 hour during the last 12 hours if the tube is on suction, or
    - Air leak equal of more than 20 mL/min for at least 1 hour during the last 12 hours if the tube is on gravity mode
- Cessation of air leak
    - No record of sustained air leak (1 hour or more) of 40 mL/min or more for the last 12 hours if the tube is on suction, or
    - No record of sustained air leak (1 hour or more) of 20 mL/min or more for the last 12 hours if the tube is on gravity mode

This definition is based on Gilbert et al. paper[29] which used those criteria in a randomized controlled trial to decide when to remove chest tubes. Using those criteria, no chest tube reinsertions for worsening pneumothorax or subcutaneous emphysema after chest tube removal occurred.

Figure 3 – Digital drainage system, Medela Thopaz™. There is a sample port where a needle can be inserted, obviating direct trauma to the chest tube. Reproduced after obtaining authorization from Medela Canada, Inc.

Figure 4 – Digital drainage system, Medela Thopaz^{TM}. A graph displays the leak rate over the last 24 hours. Reproduced after obtaining authorization from Medela Canada, Inc.

4.6 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. 18 years old or older
2. Lung resection is a wedge, segmentectomy, lobectomy or bilobectomy

3. Surgery was not performed to induce pleurodesis (no pleural abrasion, no pleurectomy, no talc)
4. Procedure performed by video-assisted thoracic surgery, or by thoracotomy
5. Presence of an air leak on the digital draining system on POD#2

Patients who did receive talc as part of their surgery were not invited in this study, as the effect of concomitant talc plus hypertonic glucose is unknown, and this was not the purpose of the current trial.

4.7 EXCLUSION CRITERIA

An individual who meets any of the following criteria was excluded from participation in this study:

1. Large air leak arbitrarily defined as more than 1,000 mL/min
2. Allergy to local anesthetics
3. Hemodynamic instability
4. Untreated coronary artery disease
5. Need for mechanical respiratory support
6. Any other early post-operative complication
7. Immunity disorder
8. Large fluid output arbitrarily defined as over 500 mL in the last 12 hours

9. Inability to give consent
10. Fasting glucose ≥ 14 mmol/L the morning of the intervention (arbitrarily chosen cut-off in which patients' diabetes is considered very poorly controlled)
11. Endocrinology service not available to co-manage patients with either diabetes, or a fasting blood glucose ≥ 7 mmol/L, or HbA1c > 6.5%
12. Postoperative evidence of an active thoracic (lung or pleura) infection with systemic inflammatory response syndrome (SIRS) (2 or more of temperature > 38, heart rate > 90, respiratory rate > 20, WBC > 12)

Patients had to be competent to participate to this study, proxy consents were not allowed. There is a theoretical risk of increased myocardial demand when pleurodesis is performed due to the inflammatory reaction created, therefore patients with untreated coronary artery disease were excluded. One concern raised by Health Canada was the risk of infectious complications, and it was decided to exclude patients with immunity disorders for this reason.

The last 3 criteria were added after review by Health Canada which was particularly concerned by the risk of severe hyperglycemia and the effect on patients' risk of infectious complications.

4.8 STUDY AGENT AND METHOD OF ADMINISTRATION

The glucose solution is manufactured by Hospira, company owned by Pfizer Inc. Pfizer Canada ULC manufactures and markets this agent under “Dextrose Injection USP 50%”, Drug Identifying Number (DIN) 02468514 (other DIN: 00037974). The agent comes in pre-filled 50 mL syringes (Ansyr™ or LifeShield™). It was not possible to use the Ansyr™ II system due to national shortage in 2019-2020. An equivalent delivery system (LifeShield™, product number 04902L50) was therefore used (Lot 04-431-DK, expiry 20210401). Each syringe was acquired from LHSC pharmacy at a $30.38 CAD unit cost. Thirty-six syringes were acquired from funds granted by Western University Department of Surgery (Appendix A). These syringes were stored on room temperature until their utilization as recommended in the product brochure (Appendix I).

This agent was administered by a single individual (MQ) involved in this study in a standardized approach. The digital draining system was turned off and hanged over an intravenous pole, so it stands over the patient’s body by approximately one meter. The chest tube was not clamped to avoid creation of a tension pneumothorax. The patient is placed on a contralateral lateral decubitus position to facilitate entry of the glucose solution in the pleural space by gravity. The hub of the digital drain was sterilized with alcohol swabs. Administration of the solution was performed on a sterile fashion. Lidocaine 1% 20 mL was then injected to provide topical anesthesia to parietal pleura and to flush the excess of

hypertonic glucose from the chest tube. The patient was then asked to move every 15 minutes from one side to another. After 2 hours, the digital system was placed again on the ground and suction was applied (-20 cm H_2O).

4.9 STATISTICAL ANALYSES

Paired t-test is used to compare paired, continuous variables (volume of air leaked, chest tube output) after ensuring normality of the distribution of the differences using the Shapiro-Wilk test. Repeated-measures ANOVA is used to analyze glycemia data over various time period. Intention to treat analyses are performed. A p-value of 0.05 or less is considered statistically significant.

Post-lung resection air leak tends to naturally decrease over time as the leak seals spontaneously. Comparing the volume of air leaked before and after an intervention without accounting for that previously stated fact could generate misleading results. Interrupted time series analysis/segmented regressions can be used when an outcome variable is measured over time, before and after an intervention. This quasi-experimental design is typically used in population-based studies, notably by governments to determine if a policy is effective[66–71]. A multivariate linear model can be built using a dummy variable with “0” for pre-D50, and “1” for post-D50. Both the immediate impact on the air leak rate right after D50 (seen in a change in the intercept of the regression line in the model post-D50) and the impact on the change of air leak rate over time (slope) can be

assessed. This can statistically confirm the impression of efficacy seen on several patients (Figure 5). A statistical decline in the intercept post-D50 is clinically interesting and a desired effect (immediate air leak decrease after D50 administration). It is more difficult to interpret the slope – it can become less negative (closer to 0) after D50 and this would not necessarily mean D50 is detrimental for the air leak. Therefore, only the immediate impact of D50 (intercept) is analyzed. The R code is found in Appendix L and is adapted from Professors Haider and Law work[72].

SPSS version 26 (IBM Corp. Released 2019. IBM SPSS Statistics for Macintosh, Version 26.0. Armonk, NY: IBM Corp.), R version 4.0.3 (R Core Team (2020))[73] and RStudio version 1.3.1093 (RStudio Team (2020))[74] were used to perform statistical analyses.

CHAPTER 5

5 RESULTS

5.1 DEMOGRAPHICS

From March 12, 2020 to December 24, 2020, 176 consecutive patients were screened for eligibility. The procedures performed were as follow:

- 83 wedge resections
- 78 anatomical lobectomies
- 13 segmentectomies
- 1 bi-lobectomy
- 1 sleeve lobectomy

Of these, 32 fulfilled all inclusion criteria. Of these 32 patients, 17 had at least one exclusion criteria:

- 6 had an air leak over 1000 mL/min
- 2 patients had respiratory failure post-op and were kept intubated
- 2 were on immunosuppressive medication
- 2 had evidence of post-operative bleeding
- 2 had fever and tachycardia of unknown etiology post-operatively
- 1 had delirium and urinary tract infection post-operatively
- 1 was on chronic antibiotics for a mandible infection
- 1 had severe post-operative bronchospasm

As such, 15 patients were invited to be enrolled to this study. Of these 15 patients, 12 consented and received intrapleural dextrose 50%. Three patients were not enrolled for the following reasons:

- 1 refused for personal motives
- 1 could not be enrolled because there were no digital drains available
- 1 could not be enrolled because the researchers were not available to recruit the patient and administer the study agent

The mean (SD) age was 69.2 (5.1) years old. Women constituted 58% (7/12) of the patients. A summary of the demographics of the recruited patients is displayed in Table 3 and 4. Of note, patient #1 and #11 are in fact the same person who underwent 2 distinct surgeries. No patient had preoperative diagnosis of diabetes, however one (patient #4) was diagnosed with type 2 diabetes during her hospital stay. All patients had their surgery for oncological indications.

Variable (n=12)	Mean (SD) Median [Q1 – Q3] N
Age (years)	69.2 (5.1)
Gender M:F	5:7
Smoking status	
Ex-smoker	7/12 (58%)
Non-smoker	2/12 (17%)
Smoker	3/12 (25%)
CCI	3.5 [2 – 4.5]
Diagnosis	
Lung metastases	3/12 (25%)
Lung nodule	3/12 (25%)
Lung cancer	4/12 (33%)
Cancer recurrence	2/12 (17%)
Surgery	
Lobectomy	8/12 (67%)
Wedge	4/12 (33%)
Approach	
Thoracotomy	9/12 (75%)
VATS	3/12 (25%)
Air leak pre-D50 (mL/min)	115 [50 – 332.5]

Table 3 – Patients demographic. CCI = Charlson Comorbidity Index; VATS = video-assisted thoracic surgery; D50 = dextrose 50%; SD = standard deviation.

Patient #	Group (mL)	Volume received (mL)	Age (years)	Sex	CCI	Smoking status	Diagnosis	Surgery	Approach	Air leak pre-D50 (mL/min)
1	50	50	72	F	6	ex-smoker	lung metastases	lobectomy	thoracotomy	50
2	50	50	66	M	6	non-smoker	lung metastases	lobectomy	thoracotomy	30*
3	50	50	66	M	3	smoker	lung nodule	wedge	VATS	400
4	100	100	63	M	4	smoker	lung cancer recurrence	lobectomy	thoracotomy	110
5	100	100	67	F	4	ex-smoker	lung cancer	lobectomy	thoracotomy	120
6	100	100	71	M	2	smoker	lung cancer	lobectomy	VATS	190
7	150	150	81	F	4	ex-smoker	lung cancer	lobectomy	thoracotomy	490
8	150	150	72	M	2	non-smoker	lung nodule	wedge	thoracotomy	310
9	150	150	69	F	3	ex-smoker	lung nodule	wedge	thoracotomy	590
10	200	10†	69	F	2	ex-smoker	lung cancer recurrence	lobectomy	thoracotomy	50
11	200	35†	72	F	6	ex-smoker	lung metastases	wedge	VATS	100
12	200	200	62	F	2	ex-smoker	lung cancer	lobectomy	thoracotomy	40

Table 4 – Individual patient demographics. CCI = Charlson Comorbidity index; D50 = dextrose 50%; VATS = video-assisted thoracic surgery. *This patient fit the definition of air leak, but the last value recorded before administration of dextrose was 30 mL/min. †Those two patients did not receive the full volume as described in manuscript.

5.2 PRIMARY OUTCOME

All adverse events, including grade and relationship with the intervention are displayed in Table 5. Below are the details of each adverse event.

Patient #1 did not experience any adverse event.

Patient #2 was found to have a knee cellulitis on POD#3. On further questionnaire, it was found that the patient already had a cellulitis preoperatively, but it was not disclosed to the investigators nor the medical team. The patient was therefore placed on antibiotics. No other adverse event noted.

Patient #3 had a sputum culture ordered by the nurse on POD#2, without this being disclosed to the investigators nor the medical team. The patient was then enrolled into the study and glucose was administered. On POD#3, it was found that the sputum was positive for 2 bacteria, and intravenous antibiotics were started. It was not clear if the patient was just colonized with those germs, or if he had a true pneumonia. The Infectious Diseases team was consulted. This adverse event was not due to the intervention, as the sputum culture preceded injection of D50. This patient recovered uneventfully from the pneumonia.

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Patient #	Group	Volume received (mL)	Adverse event	Grade	Relationship
1	50	50	None	n/a	n/a
2	50	50	Knee cellulitis	2	not related
3	50	50	Pneumonia	3	not related
			Diarrhea - C. difficile	1	not related
4	100	100	None	n/a	n/a
5	100	100	Atrial fibrillation	2	unlikely to be related
6	100	100	None	n/a	n/a
7	150	150	None	n/a	n/a
8	150	150	None	n/a	n/a
9	150	150	None	n/a	n/a
10	200	10	Chest wall pain	3	definitely related
11	200	35	Cough	1	definitely related
12	200	200	Atrial fibrillation	2	unlikely to be related

Table 5 – Adverse event

On POD#6, the patient was found to have diarrhea and was in fact positive for C. difficile colitis. This was not felt to be related to the intervention, but rather from the use of IV antibiotics.

Finally, an additional chest tube was placed on POD#3, or 22 hours after the dextrose was administered. The original chest tube placed in the operating room was deemed to be position-dependent by the medical team prior administering the dextrose, as reflected by the presence of subcutaneous emphysema a few hours post-operatively and the significant variation in the air leak rate ranging from 0 to 400 mL/min. The insertion of an additional chest tube was not felt to be related to the administration of glucose, i.e. it is not felt that the glucose "plugged" the original chest tube.

Patient #4 did not experience any adverse event.

Patient #5 had a fasting glucose of 7.7 mmol/L, a HbA1c of 6.2%, and a pre-intervention glycemia of 12.6 mmol/L. Given these values, Endocrinology was consulted and concluded that the patient had undiagnosed "pre-existing pre-diabetes/mild type 2 diabetes mellitus". They elected to prescribe an insulin sliding scale. She received 3 units subcutaneously, and then another 2 units. This was not classified as an adverse event. Endocrinology recommended a follow-up with the patient General Practitioner on discharge to manage her type 2 diabetes mellitus.

The patient developed atrial fibrillation on POD#4 (2 days after dextrose administration). She remained asymptomatic and hemodynamically stable and was fully converted back to sinus rhythm after receiving metoprolol 12.5 mg oral. This was classified as a grade 2 adverse event that was “unlikely to be related” to the intervention.

Patient #6 did not experience any adverse event.

Patient #7 did not experience any adverse event. An additional chest tube had to be inserted for a basal space noted on CXR POD#15.

Patient #8 did not experience any adverse event. He tripped on the chest tube 26 hours after dextrose administration, which led to disconnection of the chest tube from the digital drain. When reconnected, there was a new air leak (Figure 5-H, see below).

Patient #9 did not experience any adverse event.

Patient #10 did experience severe pain after administration of only 10 mL of hypertonic glucose. The investigators stopped administration of the intrapleural drug, and placed back the tube on suction, aspirating the glucose. Once the glucose was outside of the pleural space, the pain subsided. This grade 3 adverse event is definitely related to the intervention and resolved quickly after

the glucose was evacuated. This patient did not have another attempt at D50 insertion.

Patient #11 did experience mild to moderate cough after administration of an initial volume of 20 mL of hypertonic glucose. The investigator paused and resumed injection of another 15 mL when the administration was stopped completely for fear that too much of the hypertonic solution may enter the lung parenchyma. The patient was able to taste sugar in her mouth. The chest tube was kept above the patient for the usual 2 hours, and then placed back on the ground and on suction. This grade 1 adverse event is definitely related to the intervention and ceased when we stopped administering the glucose.

Patient #12 did experience asymptomatic atrial fibrillation on postoperative day 3 (24 hours after the intervention). The cardiologist mentioned that this was most likely pre-existing from before the surgery as she had pre-syncopal episodes in the past.

5.3 SECONDARY OUTCOMES

5.3.1 DESCRIPTIVE ANALYSES

Secondary outcomes are displayed in Table 6 and 7. For the whole cohort, the median (IQR) length of stay was 6.9 (5.3 – 8.7) days. Patients were discharged

with a one-way valve in 33% (4/12). The median (IQR) time from D50 administration to last chest tube removal was 6.6 (2.6 – 17.2) days. Mean (SD) chest tube output during the first 24 hours after D50 administration was 365 (246) mL. No patient was discharged on home oxygen, nor readmitted after being discharged, nor experienced recurrent air leak. Two patients (17%) required additional chest tube after the intervention.

The evolution of the air leak rate, the glycemia and the pain level over time is displayed in Figure 5 for each patient. The vertical red line denotes when D50 was administered in the pleural space. Administration of intrapleural glucose did not increase pain as assessed by empirically inspecting the graphs. Most patients (9/12) experienced increase in glycemia (0.1 to 8.2 mmol/L) 1 hour after intrapleural administration but this was not clinically significant. Only one patient (1/12) received additional treatment to control the glycemia (subcutaneous insulin).

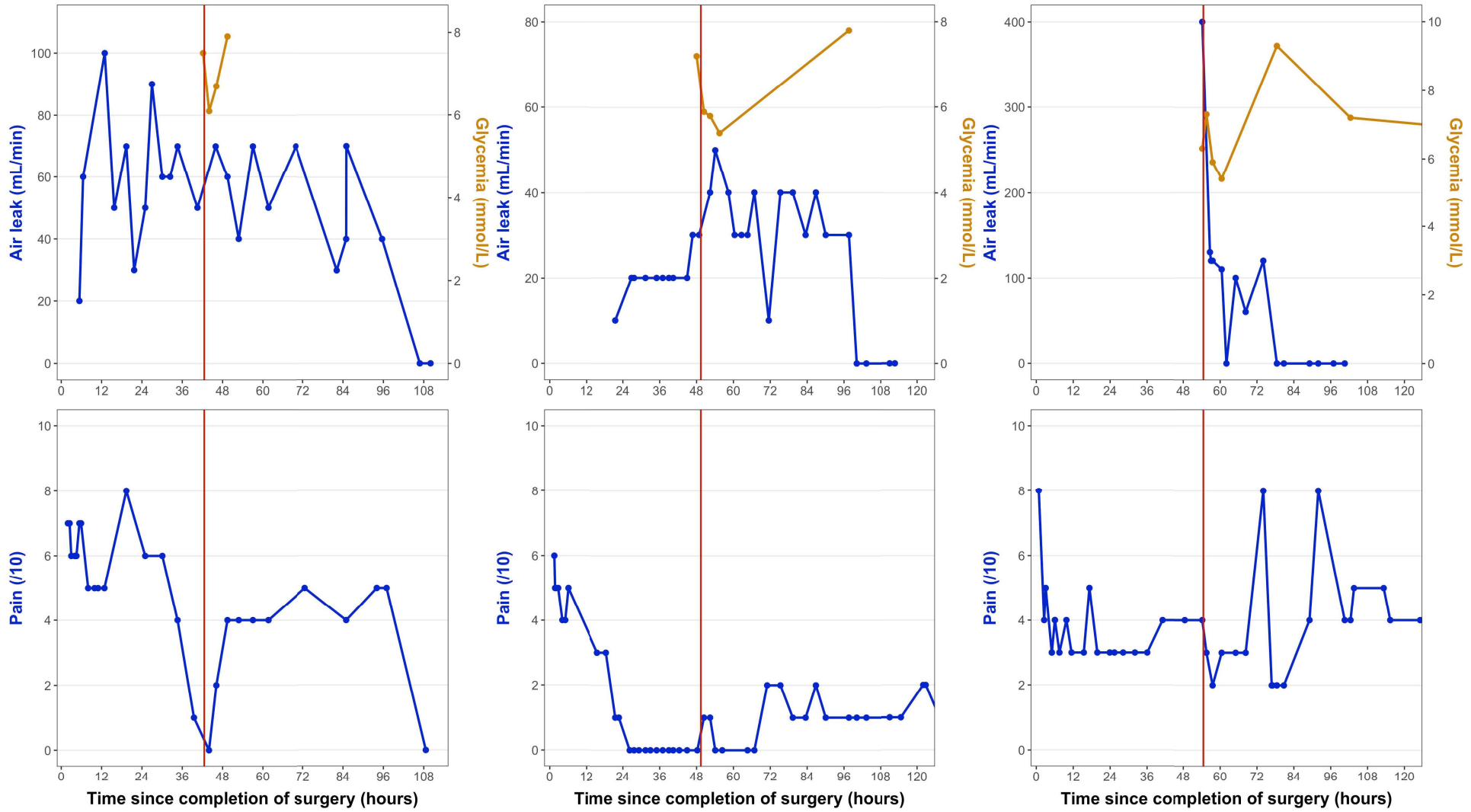
There was no reduction in the amount of air leak with a volume of 50 mL of dextrose 50% as shown in Figure 5 A-C. However, a flattening of the air leak curve was noted at a volume of 100 mL (Figure 5 D-F), and this was even more pronounced at a volume of 150 mL (Figure 5 G-I). Flattening of the air leak curve was also noted in the group 200 mL (Figure 5 J-L).

Variable (n=12)	Mean (SD) Median [Q1 – Q3] N
Length of stay (days)	6.9 [5.3 – 8.7]
Time from D50 to last chest tube removal (days)	6.6 [2.6 – 17.2]
Output 24h post-D50 (mL)	365 (246)
Glycemia pre-D50 (mmol/L)	7.4 (1.9)
Glycemia 1h post-D50 (mmol/L)	10 (3.4)
Heimlich valve	4/12 (33%)
Additional chest tube required	2/12 (17%)
Additional treatment for hyperglycemia	1/12 (8%)
Empyema	0
Discharged on home O_2	0
Readmission	0
Recurrent air leak	0

Table 6 – Secondary outcomes. D50 = dextrose 50%. SD = standard deviation.

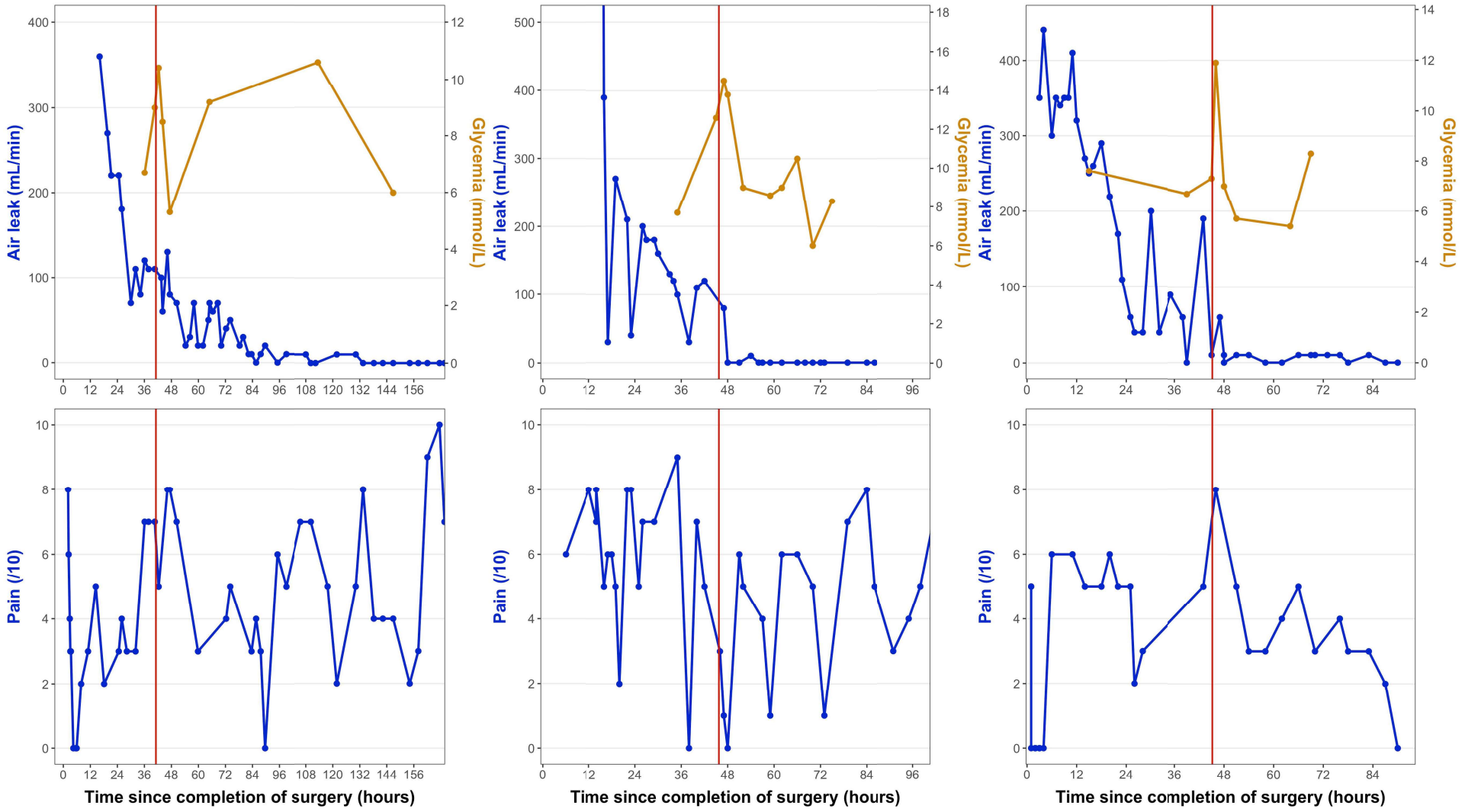
Patient #	LoS (days)	Time from D50 to last chest tube removal (days)	Output 24 h post-D50 (mL)	Glycemia pre-D50 (mmol/L)	Glycemia 1 hr post-D50 (mmol/L)	Δ glycemia (mmol/L)	Heimlich valve	Additional chest tube?	Additional treatment for hyperglycemia	Home O_2?	Readmission?	Recurrent air leak?
1	5.3	9.9	325	7.5	6.1	-1.4	Yes	No	No	No	No	No
2	7.4	4.9	300	7.2	5.9	-1.3	No	No	No	No	No	No
3	9.4	18.8	0	6.3	7.3	1	Yes	Yes	No	No	No	No
4	11	8.1	600	9	10.4	1.4	No	No	No	No	No	No
5	6	1.7	325	12.6	14.5	1.9	No	No	Yes	No	No	No
6	4.3	2.0	500	7.3	11.9	4.6	No	No	No	No	No	No
7	19.4	17.0	775	6.7	14.9	8.2	No	Yes	No	No	No	No
8	6.3	17.8	400	7.8	9.2	1.4	Yes	No	No	No	No	No
9	8.1	24.8	200	6.1	11.4	5.3	Yes	No	No	No	No	No
10	5.3	2.8	100	6.4	*	*	No	No	No	No	No	No
11	3.3	0.7	125	6	6.1	0.1	No	No	No	No	No	No
12	8.5	5.0	385	5.3	12.7	7.4	No	No	No	No	No	No

Table 7 – Individual patient secondary outcomes. LoS = Length of stay; D50 = dextrose 50%. *indicates missing data.



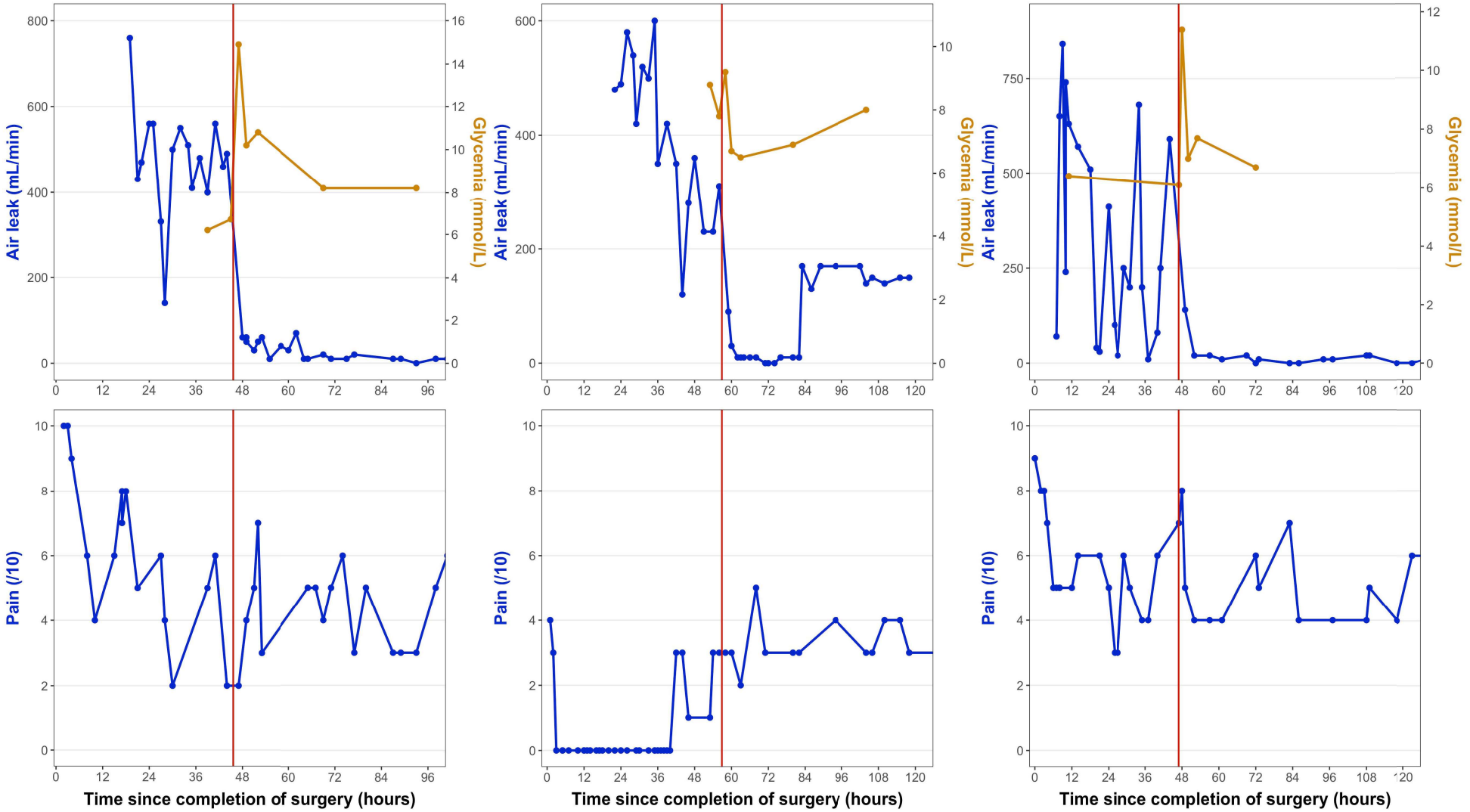
A. Patient #1 B. Patient #2 C. Patient #3

Figure 5 (A-C, 50 mL group) – Top graph shows relationship between air leak rate (blue line) and time, and glycemia (orange line) and time. Bottom graph shows relationship between pain level and time. Vertical red line represents D50 administration in the pleural space.



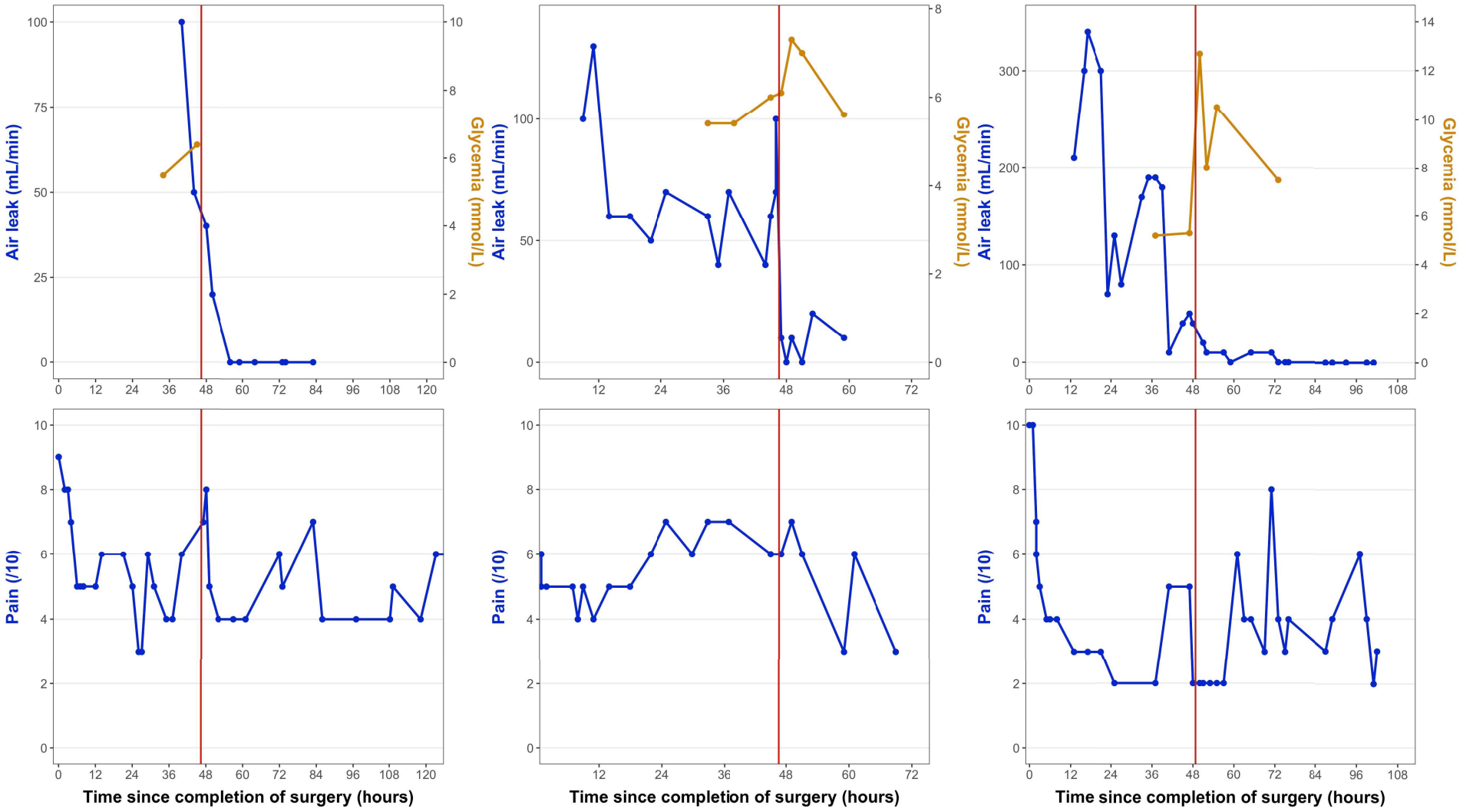
D. Patient #4 E. Patient #5 F. Patient #6

Figure 5, continued (D-F, 100 mL group) – Top graph shows relationship between air leak rate (blue line) and time, and glycemia (orange line) and time. Bottom graph shows relationship between pain level and time. Vertical red line represents D50 administration in the pleural space.



G. Patient #7 H. Patient #8 I. Patient #9

Figure 5, continued (G-I, 150 mL group) – Top graph shows relationship between air leak rate (blue line) and time, and glycemia (orange line) and time. Bottom graph shows relationship between pain level and time. Vertical red line represents D50 administration in the pleural space.



J. Patient #10 K. Patient #11 L. Patient #12

Figure 5, continued (J-L, 200 mL group) – Top graph shows relationship between air leak rate (blue line) and time, and glycemia (orange line) and time. Bottom graph shows relationship between pain level and time. Vertical red line represents D50 administration in the pleural space. Patients #10 and #11 each received less than 200 mL of D50 (see text).

5.3.2 EFFECT OF INTRAPLEURAL DEXTROSE ON THE AMOUNT OF AIR LEAKING FROM THE LUNG

The volume of air leaking out of the lung can be approximated using the trapezoidal rule[75] (Appendix J). For each patient, the last 24 hours preceding administration of dextrose was calculated, along with the following 24 hours. Patients #1-2, #4-7 and #9 had enough data to calculate the amount of air leaking for 24 hours prior and after dextrose administration. Patient #3 did not have meaningful data before dextrose administration and was therefore excluded for the purpose of this analysis. Patient #8 disconnected the chest tube 22.9 hours after dextrose was administered (Figure 5-H), and therefore only this time window was used prior and after dextrose insertion to calculate the amount of air leaking. Patient #10 only had 4.1 hours' worth of data prior to dextrose administration (Figure 5-J), and patient #11 only 11.6 hours' worth of data after dextrose administration (Figure 5-K). The volume of air leaking that was calculated for each of these 2 patients was adjusted accordingly to use the same time period before and after dextrose (4.1 hours for patient #10, 11.6 hours for patient #11). These patients are analyzed as per the intention to treat design.

Individual patient data is presented in Figure 6 (organized according to D50 volume).

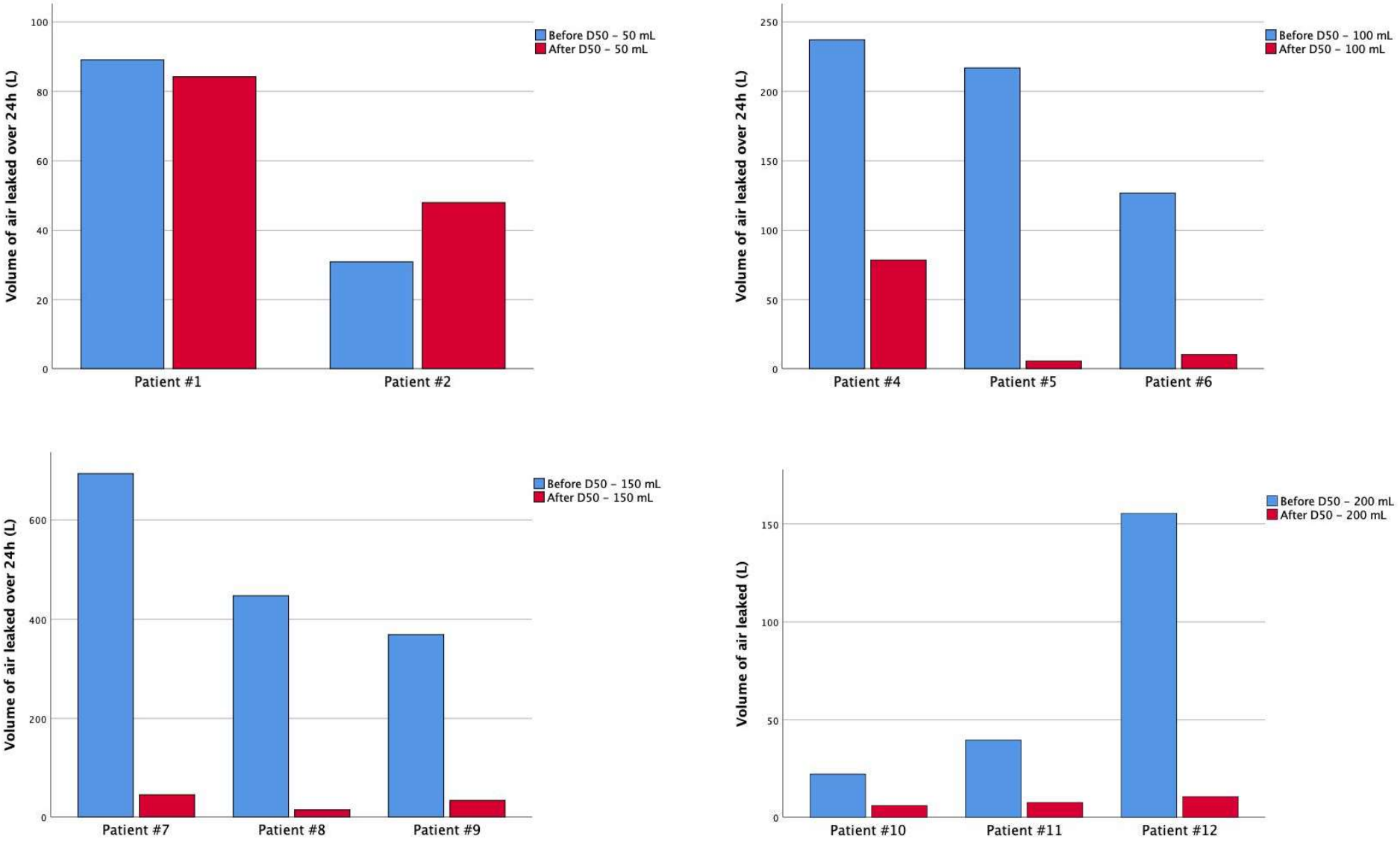


Figure 6 – Volume of air leaking out of the chest in the 24 hours preceding (blue) or following (red) dextrose administration.

For patients #8, #10 and #11, a 22.9 hours, 4.1 hours and 11.6 hours window was used (see text for details).

Figure 7 shows the effect of intrapleural dextrose on the volume of air escaping the lung in the 24 hours (22.9 hours for patient #8, 4.1 hours for patient #10, and 11.6 hours for patient #11) before/after dextrose administration. There was a statistical difference in the mean volume leaked before compared with after dextrose administration (221 vs 31 L, p=0.013). Subgroup analysis is shown in Figure 8. Using again paired t-test, statistical differences were found in the groups D50 100 mL and D50 150 mL (194 vs 31 L, p=0.028 and 503 vs 31 L, p=0.036 respectively).

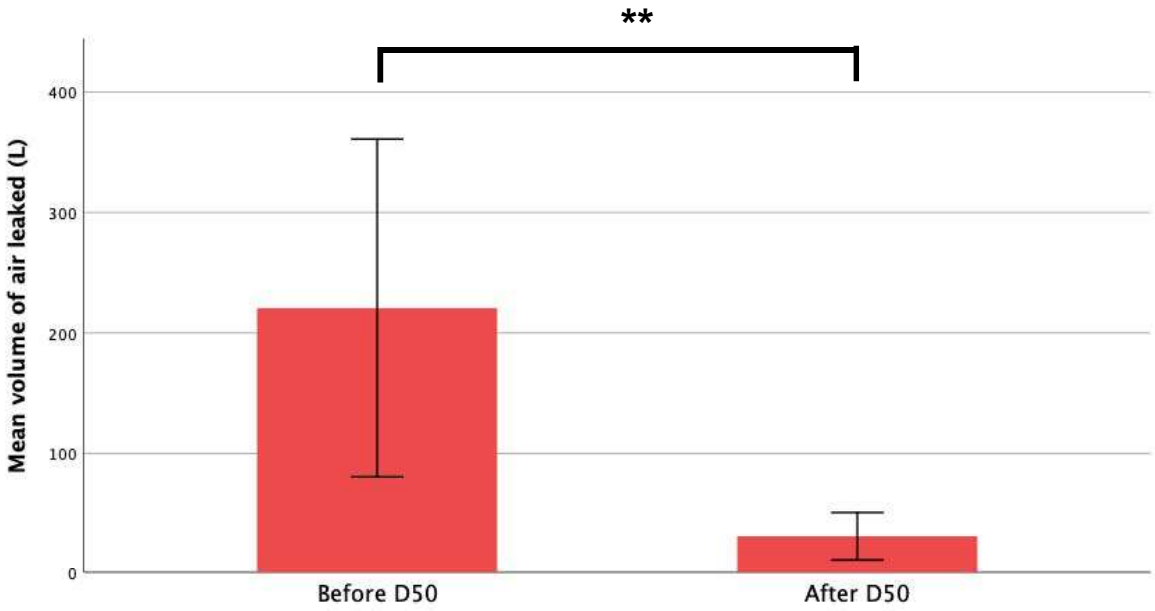


Figure 7 – Mean volume of air leaked (L) in the cohort before or after administration of D50. ** denotes statistical significance. All patients except patient #3.

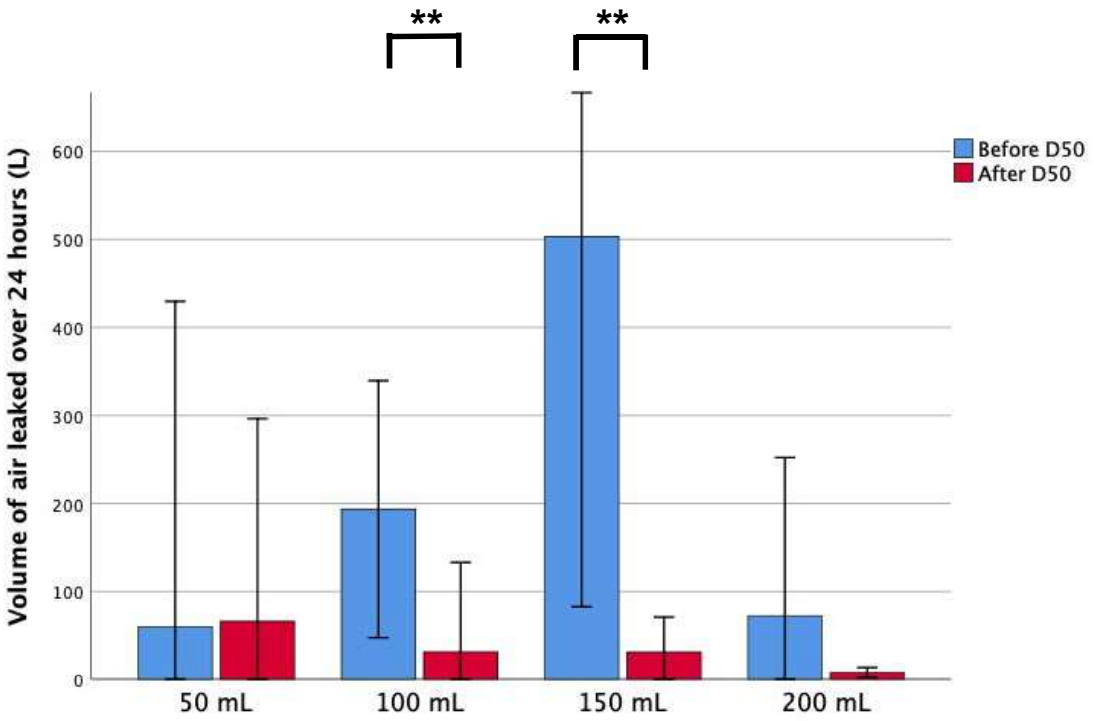


Figure 8 – Mean volume of air leaked (L) in the cohort before or after administration of D50 in each subgroup. ** denotes statistical significance.

Figure 5 showed the relationship between the time after the surgery and the air leak rate for each patient, with a vertical bar denoting when D50 was administered. There seems to be an immediate decrease in the air leak rate following D50 in patients #5 to #12. This decrease was statistically significant only for patients #7, #8 and #11 as shown in Figure 9.

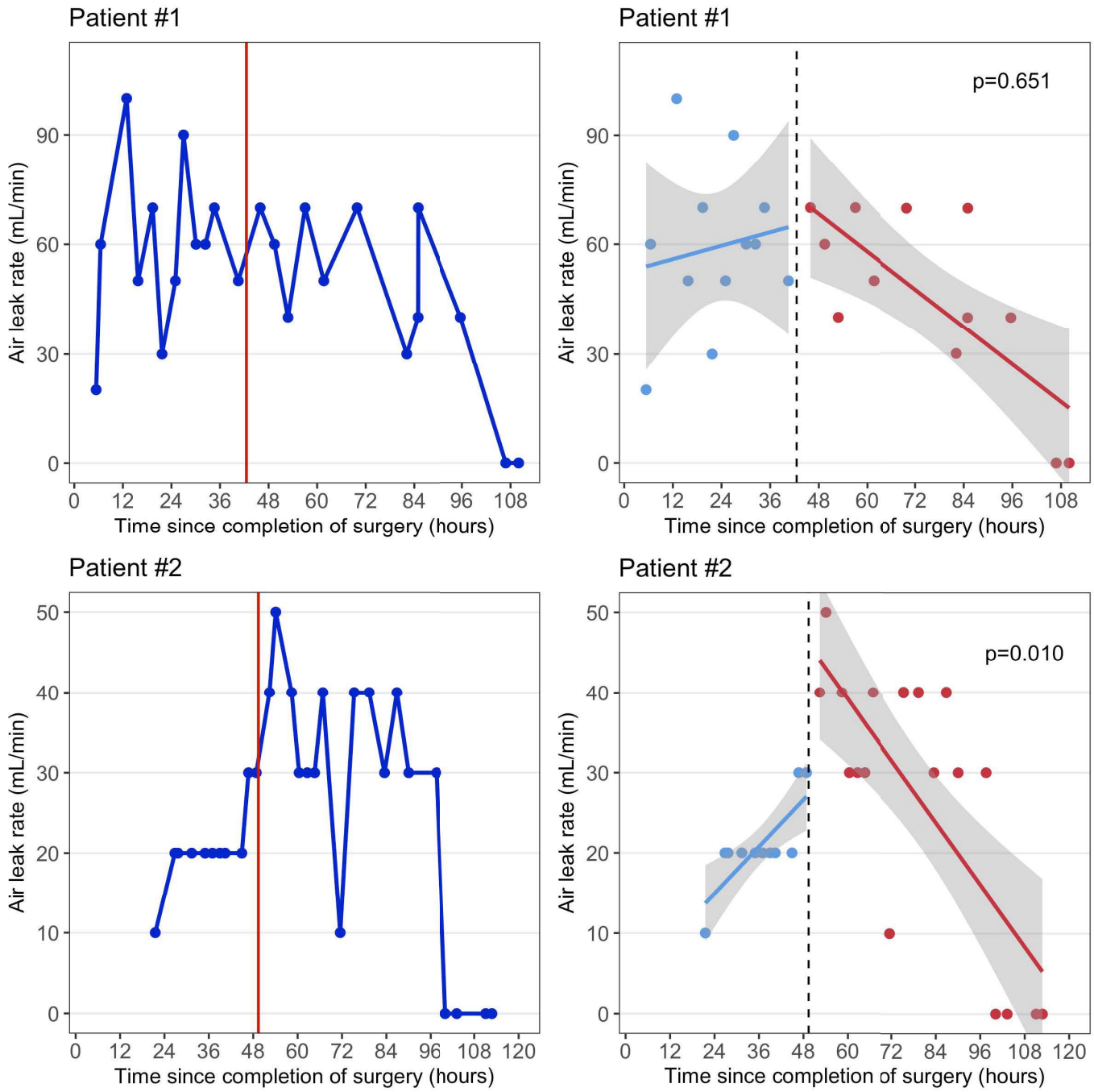


Figure 9, 50 mL group (patients #1-2) – Relationship between air leak rate and time after surgery, before and after D50. Raw data from the digital drain is displayed on the left, and data analyzed using interrupted time series method is displayed on the right. Shaded area represents 95% confidence interval. The impact of D50 is not statistically significant for patient #1 (p=0.651), and is statistically significant for patient #2 (p=0.010).

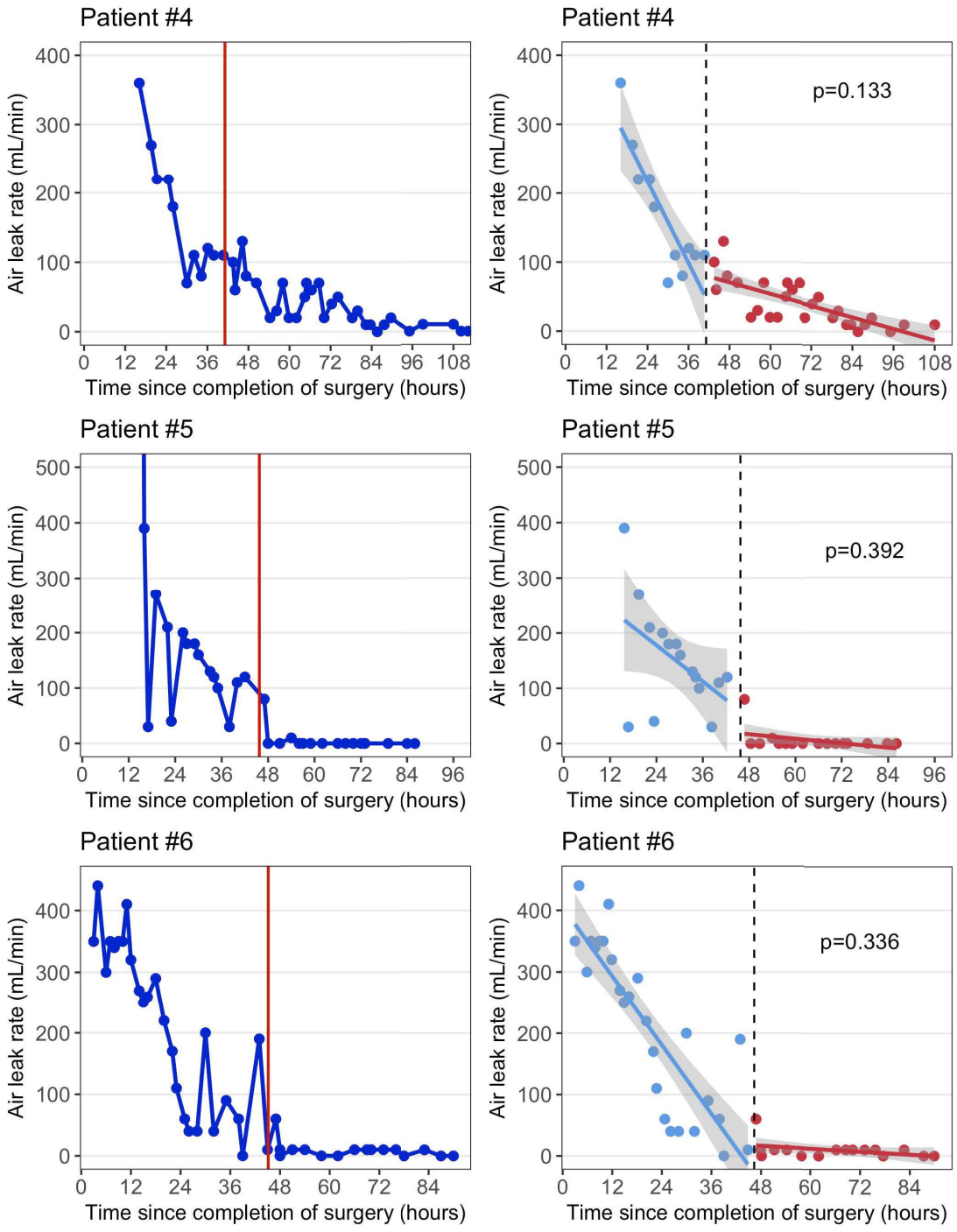


Figure 9, continued (100 mL group, patients #4-6) – Relationship between air leak rate and time after surgery, before and after D50. Raw data from the digital drain is displayed on the left, and data analyzed using interrupted time series method is displayed on the right. Shaded area represents 95% confidence interval. The impact of D50 is not statistically significant for patient #4 (p=0.133), patient #5 (p=0.392) and patient #6 (p=0.336).

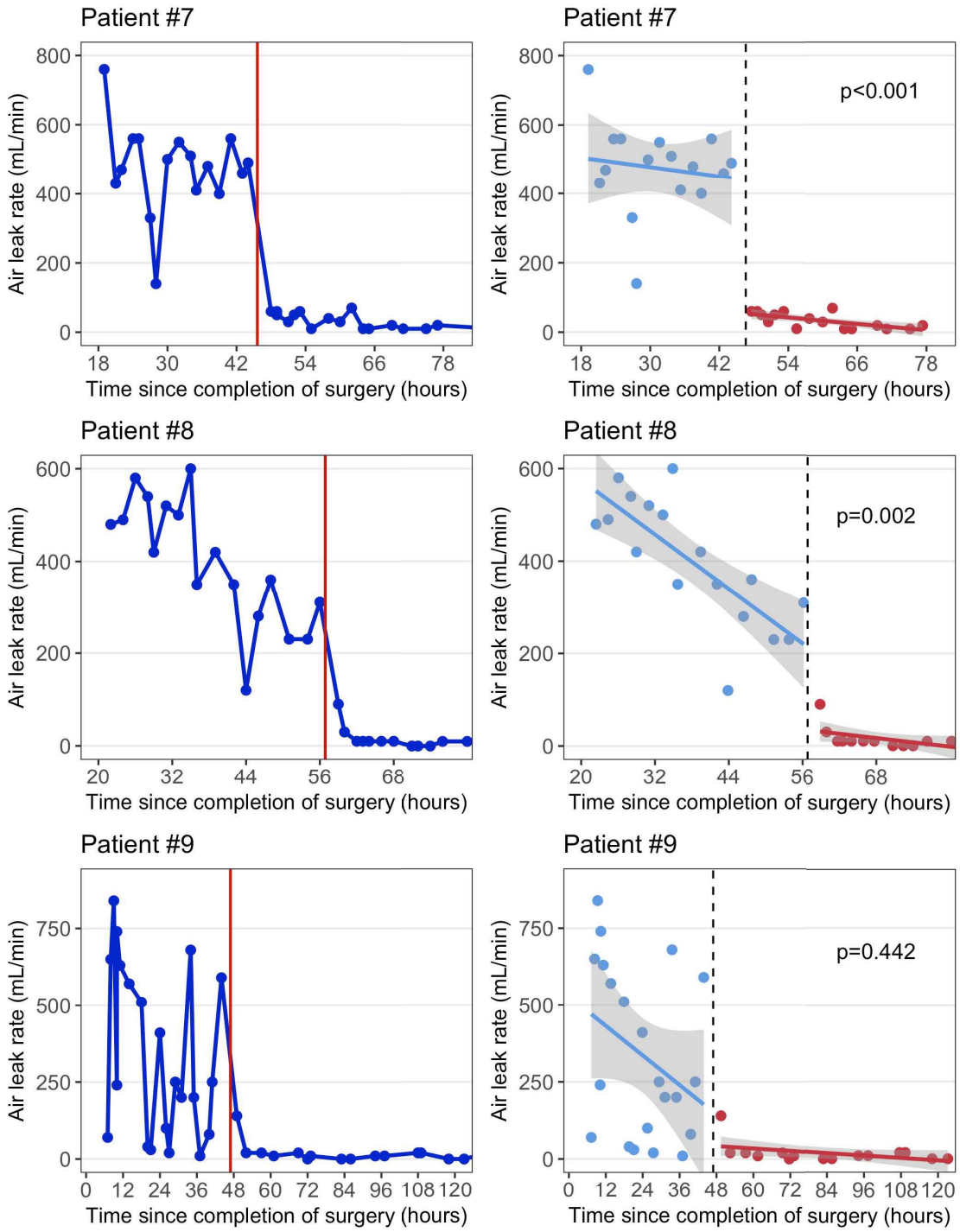


Figure 9, continued (150 mL group, patients #7-9) – Relationship between air leak rate and time after surgery, before and after D50. Raw data from the digital drain is displayed on the left, and data analyzed using interrupted time series method is displayed on the right. Shaded area represents 95% confidence interval. The impact of D50 is statistically significant for patient #7 ($p<0.001$), patient #8 ($p=0.002$) but not for patient #9 ($p=0.442$).

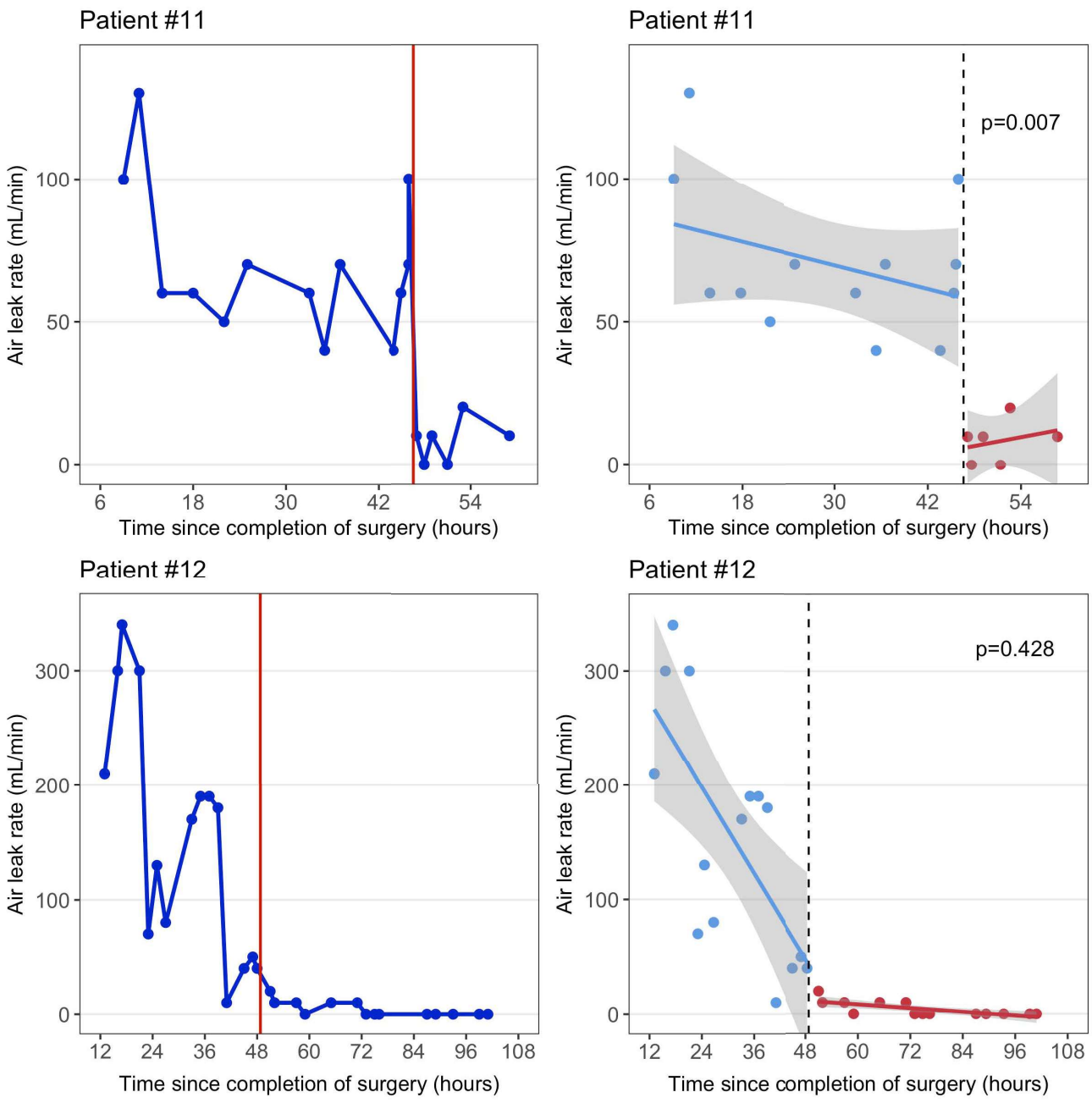


Figure 9, continued (200 mL group, patients #11-12) – Relationship between air leak rate and time after surgery, before and after D50. Raw data from the digital drain is displayed on the left, and data analyzed using interrupted time series method is displayed on the right. Shaded area represents 95% confidence interval. The impact of D50 is statistically significant for patient #11 (p=0.007) but not for patient #12 (p=0.428). Patient #10 was excluded as only 2 time points were available pre-D50.

5.3.3 EFFECT OF THE INTRAPLEURAL DEXTROSE ON THE CHEST TUBE FLUID OUTPUT FROM THE PLEURAL SPACE

For each patient, the 24 hours chest tube fluid drainage was compared before and after administration of D50. Patient #11 had her chest tube removed 18 hours after D50, and therefore only the output of the preceding 18 hours was taken into consideration. Figure 10 shows the impact of D50 on the chest tube fluid output. There were no statistical differences (282 vs 365 mL, p=0.198). Subgroup analyses also did not show any differences (Figure 11). Patient-specific changes in the chest tube output are displayed in Figure 12.

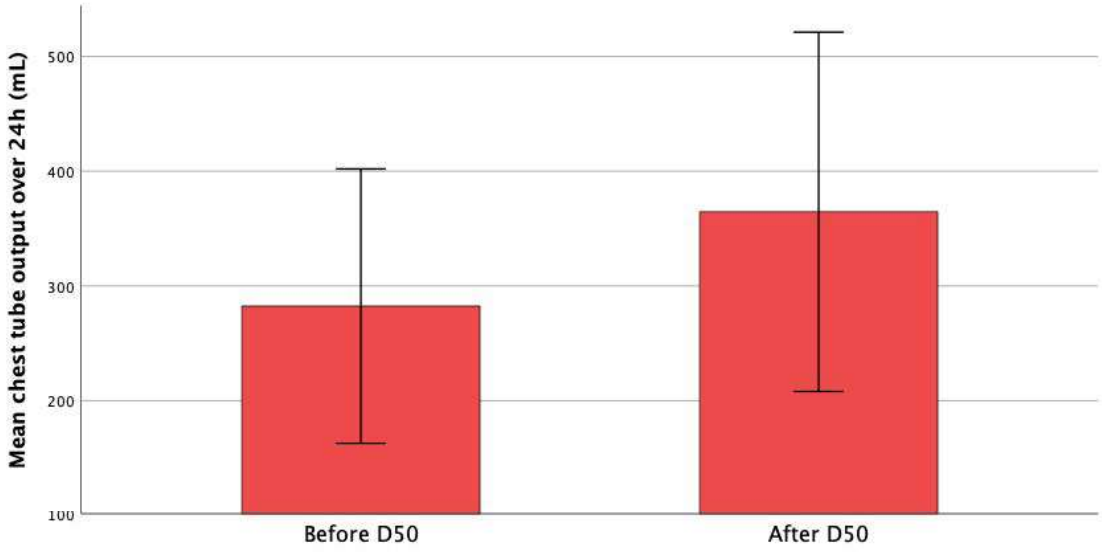


Figure 10 – Chest tube output in the 24 hours before and after D50 administration

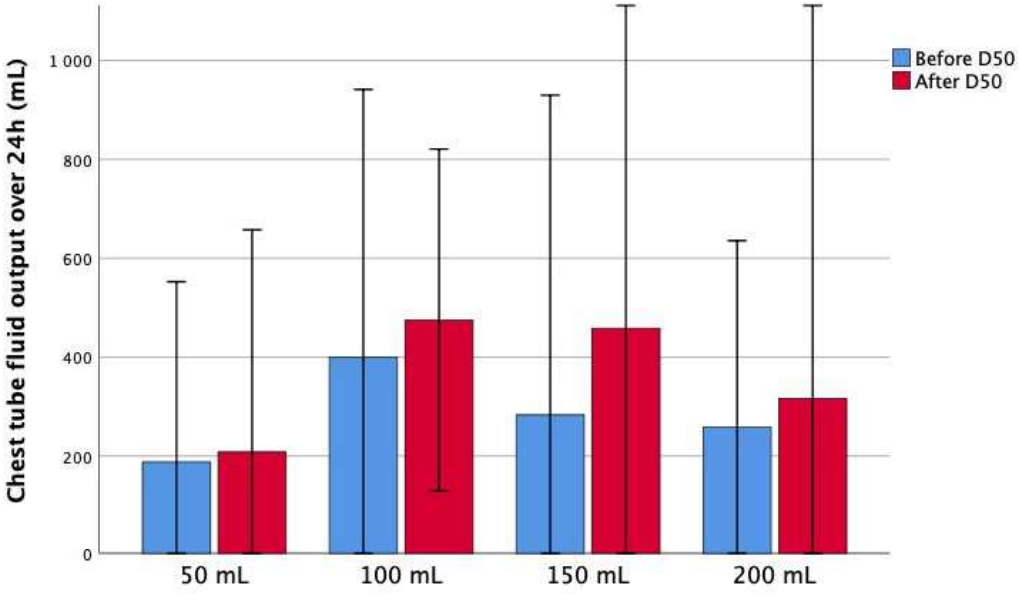


Figure 11 – Chest tube output in the 24 hours before and after D50 administration, per subgroup

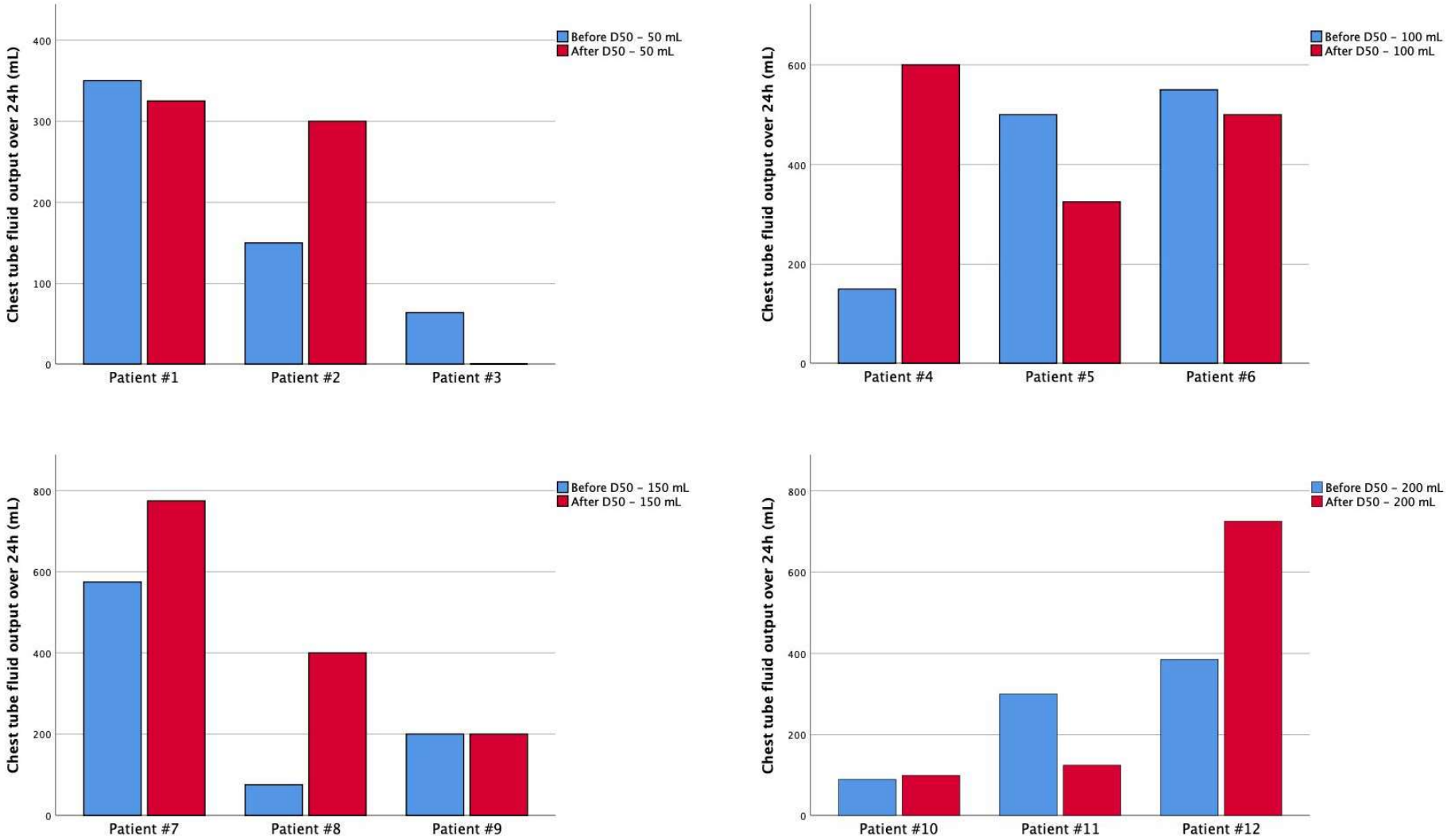


Figure 12 – Chest tube output in the 24 hours before and after D50 administration, per patient

5.3.4 EFFECT OF THE INTRAPLEURAL DEXTROSE ON THE GLYCEMIA

For each patient, glycemia was measured minutes before dextrose administration (baseline), at 1 hour, 3 hours and 6 hours. Findings are displayed in Figure 5 (patient-specific), and in Figure 13 as a mean for the 11 patients for which data was available (Patient #10 did not have glycemia recorded after D50 administration). A repeated-measures ANOVA determined that mean glycemia differed significantly across the four time points ($F(3, 30) = 5.498$, $p=0.004$). A post hoc pairwise comparison using the Bonferroni correction showed an increased glycemia between baseline and 1 hour after D50 administration (7.4 vs 10.0 mmol/L), but this was not statistically significant ($p=0.156$). Therefore, we can conclude that the apparent transient increase in blood sugar following intrapleural D50 is not statistically significant in our cohort. This could be due to the small size of our cohort resulting in a lack of statistical power.

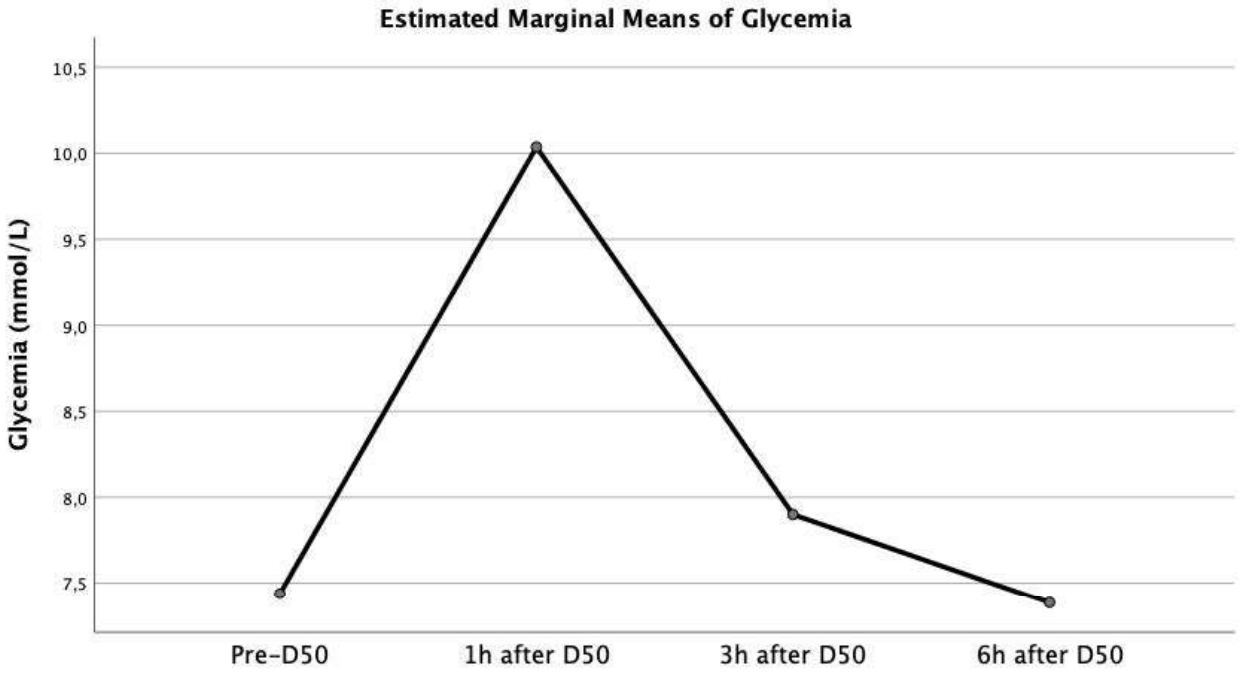


Figure 13 – Glycemia at various points before and after administration of D50

CHAPTER 6

6 DISCUSSION AND CONCLUSION

6.1 DISCUSSION

Air leaks following lung resection are a cause of prolonged hospital length of stay, morbidity and increased costs. Preoperative interventions to prevent them are scarce. Some may benefit from being weaned off steroids, or their nutritional status optimized[76], but patients who would actually benefit from these actions are in the minority. Patients with severe bullous emphysema are sometimes offered alternative treatment such as stereotactic beam radiation therapy as a way to avoid the morbidity associated with surgical resection with mixed results[77].

Intraoperative prevention of air leaks involves meticulous fissure-less dissection, minimizing residual space, and sometimes the judicious use of sealants[78,79]. Benefit in the reduction of postoperative air leaks have been shown on severe emphysematous patients with bovine pericardium reinforced staple lines[80].

Optimal chest tube management (suction or not) after lung resection is still matter of debate[81]. The European Society of Thoracic Surgeons Early Recovery After Surgery (ERAS) consensus recommends against the routine use of suction[82], but comments that the available evidence is conflicting.

When there is persistent air leak postoperatively, several strategies including observation-only, placement of a one-way valve, bedside chemical pleurodesis, blood patch, reoperation with possible muscle flap or pneumoperitoneum are options available to the clinician[83]. All these approaches have their pros and cons. As mentioned in the Literature Review, there are several agents used for chemical pleurodesis. Hypertonic glucose has emerged as an agent which may have its place in the thoracic surgeon's armamentarium. It certainly does not have the bad publicity talc had in recent years[59,84]. Patients undergoing lung cancer resection often have surgery as part of a multimodality plan of care and it is critical that they avoid post-operative infectious complications occasionally associated with prolonged air leaks.

The mechanism in which hypertonic glucose may induce pleurodesis is unknown. Pleurodesis often involves a systemic reaction leading to increased erythrocyte sedimentation rate, C-reactive protein, leukocyte count, and a febrile state. Ukale et al. showed that the degree of patient systemic response to either talc or quinacrine correlated with pleurodesis success[85]. Teixera[37–39,86,87] et al. worked extensively on the physiology of pleurodesis in their experiments with New Zealand rabbits using talc or silver nitrate. Following introduction of a sclerosing agent in the pleural space, damage to mesothelial cells occur. This leads to neutrophilic exudate and secretion of several cytokines (IL-8, VEGF and TGF-β_1). This in turns alters the balance between metalloproteinases and plasminogen activators and affects mesothelial cells and fibroblasts' ability to secrete collagen.

Pleural fibrosis becomes evident one week after the insult. Pleural adhesions are still maturing at 4 weeks while the active microscopic pleural inflammation is already declining. It is unclear how hypertonic glucose may induce pleurodesis. The osmolarity of the 50% glucose solution used in this trial is 2526 mOsm/L, and a pH of 4.2. This is in contrast to plasma osmolarity in the range of 275 – 299 mOsm/L. Direct mesothelial cell damage may occur, as mentioned above. This 50% glucose solution, while liquid, also has the property to be “sticky”, like syrup. Another mechanism of how this hypertonic solution seals air leaks could be by mechanical “plug” and occlusion of the tears in the lung parenchyma.

While the first documented use was reported in 1906, hypertonic dextrose is still not very commonly used compared to other chemical pleurodesis agents – it is unclear why. We postulate practitioners view other agents as more aggressive and irritant for the pleura and thus leading to better pleurodesis. Our systematic review showed that the dextrose concentration, volume, duration, frequency, timing, and use with additional adjuncts varied greatly. In this era where ERAS is promoted, treatment of air leaks by an agent widely available, easy to store, safe, and effective is encouraged.

6.1.1 ABOUT THE OUTCOMES

This study’s primary outcome was the assessment of adverse events. The Data and Safety Monitoring Board rigorously assessed all reported event, evaluated

the relationship with the intervention (administration of glucose) and then issued recommendation as to whether continuation of the study was possible. A member of the DSMB is also a thoracic surgeon who attended the weekly Thoracic Surgery review of adverse events, further consolidating the oversight of this Board on this trial. A DSMB halting rule chart was available to guide them in their recommendation.

In our cohort, no major or severe adverse event was noted. Two patients had an episode of atrial fibrillation on POD#3-4, or 1-2 days after receiving the glucose. Supraventricular arrhythmias are common after lung resection. In these particular instances, the Board recommended that this event be classified as “Unlikely to be related”, and a cardiologist stated that this tachyarrhythmia was probably preexisting the surgery. Two non-dose related adverse events happened in the 200 mL group. Patient #10 had immediate, severe chest wall pain after injecting only 10 mL of the solution. The pain was severe enough that the patient wished to stop the procedure. The solution was aspirated from the chest and the pain subsided immediately. It is not clear why this patient experienced this degree of discomfort. One hypothesis is that she must have had some pleuritis where the tube abutted. Patient #11 developed clinically significant cough during administration of the hypertonic solution and could taste it in her mouth. This was the case despite the air leak rate being only 100 mL/min which was in the acceptable range. Leaks over 1,000 mL/min were deemed too large, and thus a surrogate of a large defect in the lung parenchyma with higher potential for

aspiration of the pleural fluid into the lung and the airway, increasing the risk of pneumonitis and/or respiratory distress. It is worth mentioning that those 2 adverse events were triggered at a volume inferior to the minimal increment tested (50 mL). Both patients did well, and it highlights the clinical judgement required when administering intrapleural solutions. One strategy that could have possibly helped mitigating both situations would have been to administer local anesthesia (lidocaine) prior to D50 insertion in the chest. Lidocaine was selected to be administered following the D50 in order to flush the tube of any residual dextrose solution, out of the theoretical apprehension that the chest tube could possibly clog if this hypertonic solution sits for 2 hours before the tube placed back on suction. Administering the lidocaine first could block the nociceptive stimulus triggered by dextrose on the parietal pleura. However, if a sizable pleuroalveolar communication exists, lidocaine could also blunt the coughing reflex leading to more dextrose ultimately going into the lung and airway. We propose an approach that would administer 10 mL of lidocaine first, and then flush the tube with another 10 mL after introducing the dextrose.

Intrapleural glucose led to a significant reduction in the volume of air leaked. Post hoc exploratory analyses were performed. For the entire cohort, the reduction in the mean volume leaked was 86% (from 221 L to 31 L). There appeared to be a dose-response effect (Figure 6). The effect of the glucose on air leak reduction was assessed both empirically inspecting the air leak rate over time graphs (Figure 5) and statistically (Figure 9). The decision to remove a chest tube after

lung surgery depends mostly on a reduction of the air leak, but it is unclear how much air can still be leaking before the chest tube can be removed without needing to reinsert one. Gilbert et al.[29] have suggested that a chest tube can be removed safely with an active air leak of up to 30 mL/min (or 43.2 L / 24 hours). Our trial suggests that D50 does reduce the volume of air leaks after lung surgery and may have a role in expediating the removal of chest tubes. A volume of 150 mL appeared to be optimal.

Our trial did not address the effect of repeated intrapleural dextrose administration, but it is theorized that it could lead to further reduction in the volume of air leaking from the lung parenchyma. In the systematic review, 2 papers[6,52] described repeated administration after a first fail attempt in retrospective cohorts. Sumitomo described that the 2 patients who had repeated D50 sealed their leak. Additionally, Fujino described reported that out of 18 patients who did not seal their leak immediately after a first attempt, 8 had a successful second injection.

The outcome used was the volume of air leaked and not the air leak rate as while excellent interobserver reliability using the Medela Thopaz™ was reported[28], our data shows that there can be significant variation of the air leak rate over time, both before and after the pleurodesis. A patient with several spikes of air leak overnight who would then have a much smaller leak when assessed by the medical team a few hours later may not have his tube removed by fear of the

leak reactivating. This scenario is not that uncommon, and perhaps using the total volume of air leaked in a certain time frame may be a better metric in certain circumstances than looking only at the flow. The question then would be when, after dextrose injection, would the air leak rate be documented and compared to the pre-pleurodesis value to ensure success of the air leak resolution. Chest tube are typically removed when the fluid output falls under a certain threshold. Since the chest tube purpose is to evacuate both fluids in the pleural space and the air potentially leaking from the lung, it made sense to treat both states as volumes for statistical considerations.

Contrary to some reports[6,53], there were no dramatic increase in the chest tube fluid output following dextrose administration. Fujino reported on a patient who drained 780 mL of fluid in the 2 hours following D50 after the tube was placed back on suction. The mean volume drained after successful pleurodesis was 605 mL, and this was significantly higher than in patients who did not have successful pleurodesis (297 mL). Takanashi reported on a 97-year-old man with spontaneous pneumothorax who received 400 mL of D50, and subsequently drained 1,960 mL of fluid over 4 hours. This led to severe dehydration, acute kidney injury and resultant ischemic colitis from hypoperfusion. The patient was treated conservatively and recovered. We did not see such increase in the chest tube output following D50 administration in the present study, but this may be due to the relative lower volume used in this trial compared to others.

Most patients had a slight increase in their glycemia, although it was not statistically significant, and it reverted back closer to baseline within 3 hours. This is similar to Tsukioka et al. findings[8]. In our trial, nobody had preexisting diabetes. One patient was diagnosed as having diabetes by Endocrinology the day she was enrolled in the study. She required a minor amount of supplemental subcutaneous insulin (total of 5 units in 2 divided doses) and there were no clinically significant adverse events.

6.1.2 LIMITATIONS

Our study has some limitations. This is a small cohort of patient and hence, any statistical analyses are subject to a lack of power. The COVID-19 global pandemic was declared just one day prior to this study started to screen patients. Operating room shutdown led to decrease surgical volumes. To compensate the lack of OR time, we had started doing cases by thoracotomy instead of video-assisted as these surgeries are typically performed faster open. We anecdotally noticed that this led to a decline in the incidence of air leaks, presumably due to gentle retraction of the lung parenchyma during thoracotomy compared to tight grasp of a thoracoscopic grasper. The lack of postoperative air leaks hindered patient accrual.

There are some missing data that limit our ability to perform some analyses. However, we believe our results are robust because the safety profile of D50 at

the volume used in the current prospective trial corresponds to findings from retrospective studies. In addition, some missing data are in fact on air leak flow due to early chest tube removal secondary to rapid pleurodesis.

This study is performed in one center only, and better external validity could be achieved if a multicenter trial is performed. We are hoping to invite other centres in the next phase of this research.

6.1.3 STRENGTHS

This study is one of only two to prospectively evaluate the safety of the bedside administration of hypertonic glucose to treat post-operative air leak. The other prospective study on the topic was performed by Albargawi et al. also from our institution and has only presented in abstract[9]. The current study has several differences. First, this is a Phase I trial assessing safety and collecting data to assist in designing a phase II trial down the road. Information on air leak resolution, chest tube removal or length of stay are all data that will be useful for sample size calculation and research planning. Rigorous oversight by regulatory agencies (Health Canada) and a DSMB was required. Secondly, we used a rule-based escalation, traditional 3+3 design to move to the next dose threshold. This approach is considered the standard and is commonly used when new drugs need to be approved, notably in oncology. This makes the methodology very robust.

Our study prospectively collected data. To minimize selection bias, all consecutive patients were screened and considered for the trial. There were no patients lost to follow-up. There was consistent and thorough reporting and oversight by a diverse group of experts on the DSMB throughout the study.

We used a commercially available product from Hospira/Pfizer as our study agent rather than requiring our hospital pharmacy to prepare the D50. This was considered superior because: it was more convenient in terms of storage, more convenient for the researchers to have immediate access to the drug including during weekends, it was more cost effective by not requiring a pharmacy technician to prepare an immediate-use injectable for research purposes while clinical work may have been requested at the same and we secured doses for the whole Phase I trial.

The process in which the drug was administered was very standardized, starting by confirming the presence of a leak using a digital drain system, administering the drug to all patients on POD#2, having only one researcher who obtained consent and administered the study agent to be the most consistent possible. This leads to reliable data, with good internal validity.

6.2 FUTURE DIRECTIONS

Exploratory analyses in this cohort have shown that there is some efficacy in the use of intrapleural administration of dextrose 50% to treat air leaks. We arbitrarily elected to dispense this drug once, but perhaps there could be a role for repetitive administration of intrapleural glucose. Additionally, intrapleural glucose was administered intraoperatively in a few papers, including in Tsuboshima[47] et al. trial where 50 mL of D50 was sprayed over the staple line and an absorbable mesh to prevent recurrent spontaneous pneumothoraces. This may have the drawback to expose some patients to D50 while they may not have needed.

Performance of bedside pleurodesis as early as POD#1 instead of POD#2 could be done. This would potentially lead to further reduction of the hospital length of stay. Administration of D50 on POD#2 was chosen for practical reasons: due to the scarcity of Medela Thopaz™ at our institution when the trial was designed, we were apprehending that too many of these digital drains may be used, preventing patients with other clinical indications (large leak and need to ambulate, prolonged air leak with lung collapse when off suction) from being able to utilize them. We now have access to more of these drains. In addition, this trial primarily assessing safety – performing the intervention later in the postoperative course prevented recruiting patients who may have had unrelated adverse events that would have happened between POD#1 and POD#2. Out of the 32 patients who met inclusion criteria, 4 were excluded for adverse event that could

have been attributed to D50 but would in fact not be linked to the intervention (2 had fever/tachycardia of unknown etiology on POD#1 or early POD#2, 1 had severe post-operative bronchospasm late POD#1 – early POD#2, and 1 had delirium and urinary tract infection on POD#1). Due to the design of our Phase I, those events may have jeopardized the ability to pursue to study further, even if the plausibility of a relationship between D50 and those events is small. Adverse events would be recorded during a Phase II trial, but this would not be the primary outcome. In addition, initial concerns were raised on whether post-operative bleeding would clog tubing of the Medela Thopaz easily (the diameter is smaller than the standard analog drainage system). This worry did not materialize. Lastly, performing the intervention on POD#2 meant being able to introduce the study to patients on POD#1, and have time to obtain consent by POD#2. Since we now have a track record using D50, patients may be able to give consent sooner.

6.3 CONCLUSION

In conclusion, intrapleural administration of glucose 50% at a volume ranging from 50 mL to 200 mL on post-operative day 2 after lung resection surgery to treat air leaks appear safe and well tolerated. Optimal dose is 150 mL. Precautions during the intrapleural administration have to be taken to detect and prevent increased chest discomfort or severe cough. Further work is needed to confirm safety and establish efficacy of hypertonic glucose to seal air leaks.

CHAPTER 7

7 PROPOSAL FOR A PHASE II TRIAL

The next phase is to evaluate the efficacy of intrapleural glucose in treating post-lung resection air leaks in a randomized pilot Phase II trial. To our knowledge, this would be the first prospective randomized trial assessing efficacy and effectiveness of D50 in reducing prolonged air leaks in patients undergoing lung resection.

7.1 HYPOTHESIS AND OBJECTIVES

Question: Does the intrapleural administration of 150 mL of D50 in patients undergoing lung resection decrease air leak duration compared to intrapleural normal saline placebo?

Hypothesis: Intrapleural D50 at a volume of 150 mL repeatable once (2 injections maximum) is effective at treating post-lung resection air leaks.

Objective: To evaluate if the postoperative intrapleural instillation of D50 in patients undergoing surgical lung resection will decrease the duration of chest tube drainage (air leak resolution) compared to placebo.

7.2 PROJECT PLAN

To further define efficacy of intrapleural dextrose in sealing post-operative air leaks, we would like to perform a multicentre, double-blind, randomized controlled trial between administration of intrapleural dextrose vs. placebo. Trial

flowchart is detailed in Figure 14. Twenty patients per group are required. This phase II trial would have the following PICO:

Population:

- Adult patients undergoing lung resection surgery for cancer
- The air leak would need to be present and confirmed on POD#1 (at least 100 mL/min documented)

Intervention:

- Intrapleural administration of 150 mL of D50 on POD#1
- D50 can be repeated on POD#2 if there is still evidence of air leak

Comparison:

- Intrapleural administration of 150 mL of placebo (normal saline) on POD#1, to be repeated on POD#2 if there is still evidence of air leak

Outcome:

- The primary outcome will be the duration of chest tube drainage (DCTD), defined as the time between completion of surgery and last chest tube removal
- Two secondary outcomes of importance are the time to last chest tube removal (TCTR), defined as the time between intrapleural injection and last chest tube removal, and the time to air leak resolution (TALR), defined as the

time between intrapleural injection and the air leak volume in 12 hours falling under a predefined threshold depending on if intrapleural suction is applied or not

- Additional secondary outcomes would include quality of life using the Functional Assessment of Cancer Therapy-Lung (FACT-L)[88], the EQ-5D[89] and the SF-36[90] instruments, pain levels, narcotics consumption, adverse events (Ottawa Thoracic Morbidity & Mortality System)[91] and their relationship with the study agent, and all the other endpoints collected during our Phase I trial

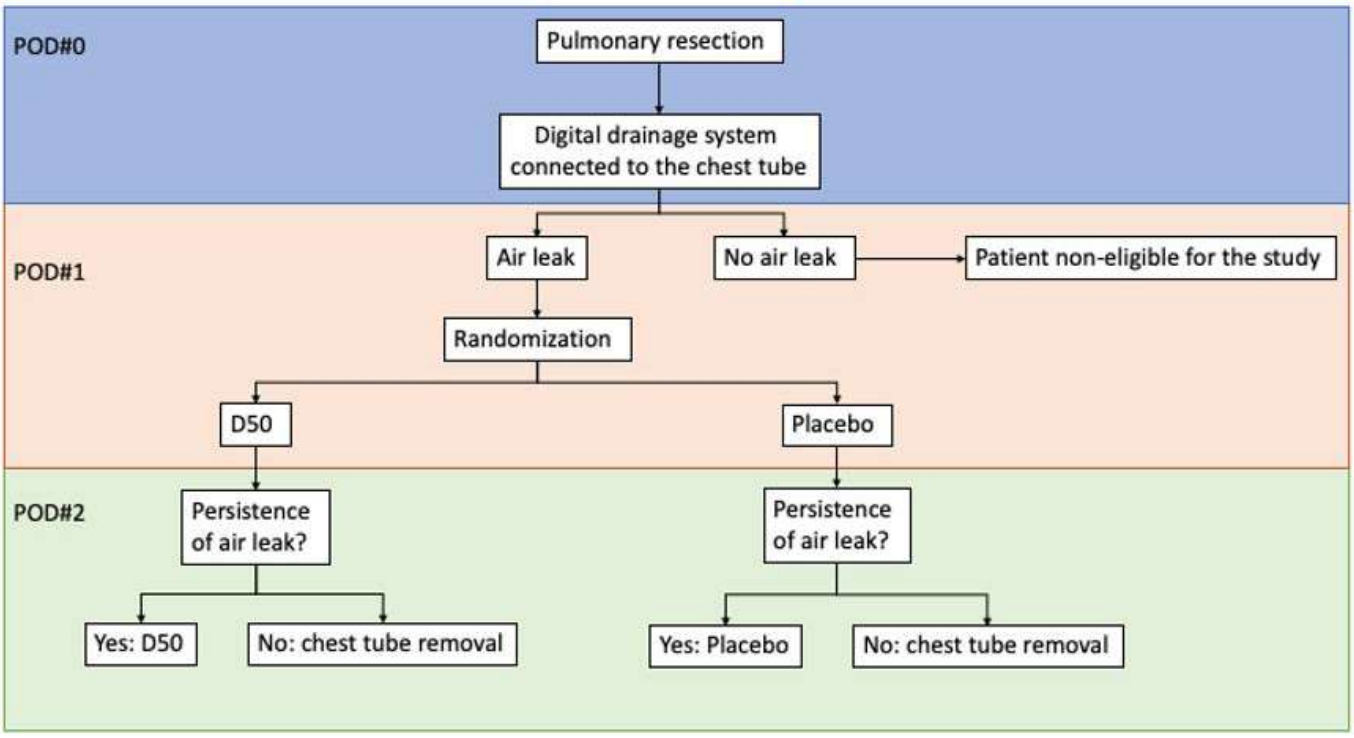


Figure 14 – PLUG-2 trial flowchart

7.3 SAMPLE SIZE CALCULATION AND DATA ANALYSIS

A peak air leak over 100 mL/min has been shown to be a predictor of prolonged air leaks (OR 4.97) by Takamochi et al.[92], and thus increased morbidity. This population is the one we are planning to target in our Phase II study using 150 mL of intrapleural dextrose 50%, volume that should be effective at stopping the air leak and reducing the duration of chest tube drainage (DCTD).

Chest tubes can be safely removed on patients if, over the last 12 hours, air leak rate has dropped to $\leq$ 40 mL/min if the drain is on suction, or $\leq$ 20 mL/min if the drain is not on suction as per Gilbert et al.[29] work.

Four individuals in our Phase I study received a volume of D50 $\geq$ 150 mL. All those patients had a peak air leak > 100 mL/min before D50. Effect on the air leak was remarkable. They would have been included in the Phase II study. Their air leak rates have decreased dramatically after injection of D50. Using Gilbert criteria for safe chest tube removal and accounting for chest tube removal in the morning as standard safe practice, those 4 patients would have kept their chest tubes a mean duration of 3.04 days (SD 0.48) since completion of surgery. This is deemed the expected mean DCTD in the experimental arm (D50).

In Takamochi et al., 27 patients had a peak air leak $\geq$ 100 mL/min. Mean $\pm$ SD duration of chest tube placement in this group was 5.9 $\pm$ 2.9 days. Of note, 48%

of these patients did have prolonged air leak. This group is considered the control arm for sample size calculation purposes. The aforementioned mean (5.9 days) is likely conservative as some patients may have received sclerosing agents if they were leaking for more than 5 days. The mean DCTD of a true control group (placebo only) is probably higher (resulting to an even larger difference between Takamochi paper and our D50 Phase I trial).

We use the following formulas to calculate the sample size for two independent samples, continuous outcomes (*Clinical Research for Surgeons*[93] and Pr Lisa Sullivan course[94]):

$$n_i = 2\left(\frac{Z_{1-\alpha/2}+Z_{1-\beta}}{ES}\right)^2 \qquad ES = \frac{|\mu_1-\mu_2|}{\sigma} \qquad S_p = \sqrt{\frac{(n_1-1)s_1^2+(n_2-1)s_2^2}{(n_1+n_2-2)}}$$

ES is the Cohen's *d* effect size. An α of 0.05 and a β of 0.2 for a power of 80% are desired. σ reflects the standard deviation of the outcome variable. This is not known, but can be estimated by generating S_p, the pooled estimate of the common standard deviation derived from the 2 aforementioned studies (D50 Phase I trial and Takamochi paper). There, n_1 is the sample size of the D50 study (4), s_1 is the SD of the D50 study (0.48), n_2 is the sample size of Takamochi group (27), s_2 is the SD of Takamochi group (2.9). The S_p generated is 2.75. Using this S_p in lieu of σ and with $\Delta = \mu_1 - \mu_2$ where μ_1 is 3.04 and μ_2 is 5.90, we obtain a sample size per group of 14.5 (rounded up to 15).

Alternative calculation is performed to evaluate the sample size needed to reach a power of 80% to detect a difference of 2.86 days (5.90 – 3.04) in the duration of chest tube placement with an α of 0.05. The Cohen *d*'s effect size calculated (μ_1 = 3.04, μ_2 = 5.90, $\sigma = S_p$ = 2.75). ES is therefore 1.04. This effect size is considered large[95], which corresponds to our expectation of the impact of D50 on air leak rate. Using this parameter, we can plot the power of an eventual Phase II trial with different sample sizes using the "pwr" package[96] on RStudio[74]:

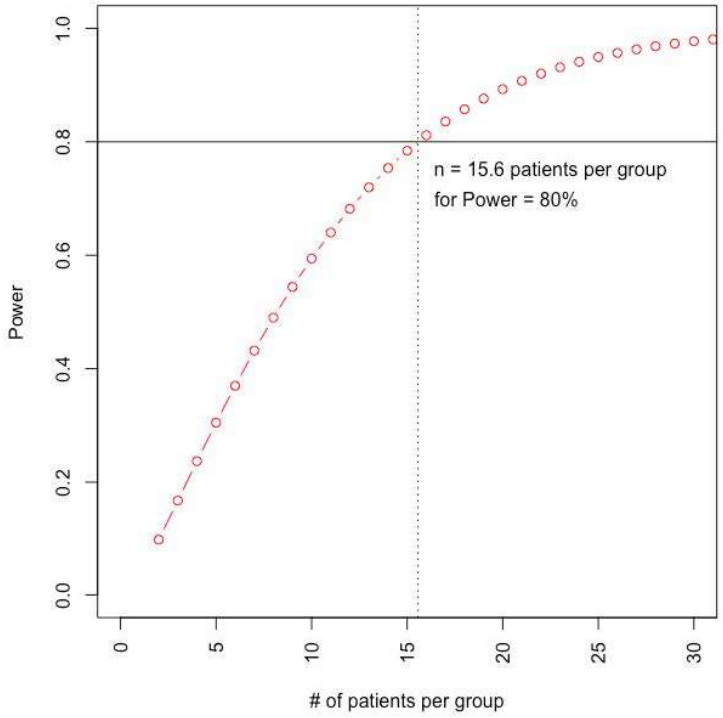


Figure 15 – Power calculation PLUG-2 trial

Based on this calculation, 16 patients per group would lead to an adequately powered study, which is similar to the previous calculation.

It is not known if the duration of chest tube drainage will be normally distributed in each group, and thus compared using two sample T test. If it is not, a nonparametric test will have to be used (Mann-Whitney U test). Increase of 15% of the sample size is recommended to maintain sufficient power if the sample size was calculated with the assumption of a normally distributed primary outcome when it was not[97]. Generally, endpoints in health care studies are more likely to be positively skewed (and therefore not normal). In addition, to account for a 10% loss of follow-up, further rise in the sample size is warranted. In summary, a sample size of 20 patients per group is considered as satisfactory.

Intention to treat and per protocol analyses will be applied. Mann-Whitney U test will be used to compare median DCTD between groups as mentioned above. Chi-squared/Fisher's exact test will be performed to examine proportion of patients with prolonged air leak ($\geq$ 5 days) between groups. Secondary outcomes will be evaluated using parametric and nonparametric statistical tests accordingly. Univariate and multivariate logistical and linear analyses to assess association between outcomes and baseline characteristics (sex, Charlson Comorbidity Index, type of resection, surgical approach, smoking status, air leak rate) will be conducted. An interim analysis assessing safety, efficacy, and possibly to adjust the volume of D50 to 200 mL will be performed when 50% of the sample size population is reached.

7.4 EXPECTED RESULTS AND SIGNIFICANCE

We propose an achievable sample size of 40 patients (20 per group) that should demonstrate a decrease in the DCTD with D50. We selected this endpoint as it is an objective patient-oriented outcome. We assume chest tubes are painful and patients do not like them. There has not been a validated instrument for QoL after oncological lung resection surgery – this is the closest endpoint there is. Based on our Phase I study, accrual could be completed in about 1 year if one additional centre participates.

We anticipate that D50 will replace talc as our pleurodesis agent of choice and become the new standard for sealing air leaks following lung resection surgery. Should we be successful in mitigating post-operative air leaks in patients undergoing lung resections, we will reduce their hospital length of stay. This intervention should improve patient outcomes by shortening the duration that a chest tube is required in the pleural space, minimizing post chest tube removal pneumothoraces, lessen chest tube-related pain, decrease the risk of post-operative infections, and health care costs. Should this simple, inexpensive, and novel therapy work to heal pulmonary air leaks, it will be a significant advancement in overcoming this long-standing “Achilles’ heel” in Thoracic Surgery.

7.5 LIMITATIONS

Accrual of patients may be slowed down by the ongoing COVID-19 pandemic and ORs shutdown. Additionally, accrual could be slow if thoracic surgeons are reluctant to consent patients for this study.

It took 9 months to accrue 12 patients in the present study in a single center. Involvement of at least another center will allow us to complete the study in a reasonable time frame.

Given the fact that we already obtained Health Canada approval to run this Phase I study, it is likely that we will be able to proceed with a Phase II study from a Research Ethics Board perspective.

Funding could be granted via a London Regional Cancer Program (LRCP) Catalyst grant as the patient population studied is mostly recovering from oncological surgery, or an Academic Medical Organization of Southwestern Ontario (AMOSO) grant.

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Appendix A

Schulich MEDICINE & DENTISTRY

Surgery

November 12, 2018

Dr. Richard Malthaner
Thoracic Surgery
[redacted]
LHSC/VH

Sent as PDF to: Richard.malthaner@lhsc.on.ca

Dear Dr. Malthaner

Your SIRF research grant entitled: **"Pleurodesis Using Glucose administration to treat post-operative air leaks following lung resection surgery (PLUG): Phase 1 and Phase 2 trials"** was reviewed by the members of the Department of Surgery Research Committee. **I am pleased to report that your grant was recommended for funding in the amount of $10,000 for the term December 1, 2018 to November 30, 2019.** Please find enclosed a summary of the review comments for your grant for your consideration to assist you with this grant as you go forward. At the completion of your grant you are required to complete an IRF End of Study Form or an IRF One Year Extension Request that you must return to the Department of Surgery Office.

You will need to apply for a research grant account through Western promptly. Please go to: New ROLA and submit a new ROLA. You will need to select the funding competition "UWO INTERNAL SURGERY" - "INTERNAL RESEARCH FUND-2018 OPEN FUNDING". **The deadline to activate your account is March 31, 2019.** If you require assistance, please contact Janice Sutherland (extension 64304) in the Department of Surgery Office. Please note that all internal research grants have a one-year limited time on expenditure of the funds.

Congratulations!

Yours Sincerely,

[redacted]

Alp Sener, MD, PhD, FRCSC
Chair
Department of Surgery Research Committee
Department of Surgery
Western University
Encls.

Cc: Dr. E. Schemitsch
Ms. D. Frank
Dr. C. Bailey
Dr. S. Jones
Research Development & Services (Western)

Schulich School of Medicine & Dentistry, Western University, SJHC, E3-117
London, ON, Canada N6A 4V2 t. 519.663.3349 www.schulich.uwo.ca/surgery

Western

Appendix B

Western Research

Date: 6 September 2019

To: Dr. Richard Malthaner

Project ID: 113906

Study Title: PLeurodesis Using hypertonic Glucose administration to treat post-operative air leaks following lung resection surgery (PLUG): Phase I trial.

Application Type: HSREB Initial Application

Review Type: Delegated

Meeting Date / Full Board Reporting Date: 17/Sep/2019

Date Approval Issued: 06/Sep/2019

REB Approval Expiry Date: 06/Sep/2020

Dear Dr. Richard Malthaner

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
HypertonicGlucoseToTreatPostop_DataDictionary_2019-09-05	Other Data Collection Instruments	05/Sep/2019	2
PLUG Letter of Consent 2019 09 05 v06	Written Consent/Assent	05/Sep/2019	6
PLUG-1 Procotol Health Canada v2.05 2019 07 11	Protocol	11/Jul/2019	2.05

Documents Acknowledged:

Document Name	Document Type	Document Date	Document Version
Dextrose50 Brochure	Investigator Brochure		
NOL229051	NOL/NOA	15/Jul/2019	1
WREM 2.6 References 2019 03 26	References		

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSRED , except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Patricia Sargeant, Ethics Officer (ext. 85990) on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Appendix C

ClinicalTrials.gov PRS
Protocol Registration and Results System

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: September 2, 2020

ClinicalTrials.gov ID: NCT03905408

Study Identification

Unique Protocol ID:	PLUG-I
Brief Title:	Pleurodesis Using Hypertonic Glucose to Treat Post-operative Air Leaks (PLUG-I)
Official Title:	PLeurodesis Using Hypertonic Glucose Administration to Treat Post-operative Air Leaks Following Lung Resection Surgery (PLUG-I): Phase 1
Secondary IDs:	

Study Status

Record Verification:	September 2020
Overall Status:	Recruiting
Study Start:	September 17, 2019 [Actual]
Primary Completion:	October 1, 2021 [Anticipated]
Study Completion:	October 1, 2021 [Anticipated]

Sponsor/Collaborators

Sponsor:	Lawson Health Research Institute
Responsible Party:	Principal Investigator Investigator: Richard Malthaner [rmalthaner] Official Title: MD, Chair/Chief Thoracic Surgery Affiliation: Lawson Health Research Institute
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	No
U.S. FDA-regulated Device:	No
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved Approval Number: 113906 Board Name: Western University HSREB Board Affiliation: Western University Phone [redacted] Email: Address:

[redacted]

Data Monitoring: No

FDA Regulated Intervention: No

Study Description

Brief Summary: The investigators will define the most appropriate safe dose of D50 to heal air leaks in patients that have undergone lung resection surgery

Detailed Description: The investigators will define the most appropriate safe dose of D50 to heal air leaks in patients that have undergone lung resection surgery (Phase I study). Air leaks from unhealed lung tissue are one of the most common complications after lung surgery including wedge resection, segmentectomy and lobectomy. Air leaks can lead to a delay in chest tube removal, prolonged pain, increased infections, prolonged hospital stay, and increased costs to the health care system. Different agents have been used to heal air leaks by creating a pleurodesis (adhesions to obliterate the pleural space between the visceral and parietal pleura). The success with these agents has been variable and come with the cost of complications that have restricted their use the post-operative period. There has been recent interest in the use of 50% hypertonic glucose (D50) to create pleurodesis with encouraging reports coming mostly from Asia. The investigators have performed a pilot study using 180 mL of D50 instilled through the chest tube for the management of post lobectomy air leak with very encouraging results. This preliminary study used strict inclusion criteria of only lobectomy patients and excluded all patients with known diabetes or any postoperative hyperglycemia. It is unknown if these patients would have benefitted from D50. Also, the optimal dose of D50 was chosen empirically and never clearly defined by previous work. It has been reported that high doses of D50 have been associated with acute lung injury. It is therefore critical that the optimal safe dose is clarified.

Conditions

Conditions: Postoperative Air Leak

Keywords: glucose
lung surgery
air leak
postoperative

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 1

Interventional Study Model: Sequential Assignment
Escalating dose:

Arm 1: 50 mL dextrose 50% Arm 2: 100 mL dextrose 50% Arm 3: 150 mL dextrose 50% Arm 4:, 200 mL dextrose 50%

Number of Arms: 4

Masking: None (Open Label)

Allocation: Non-Randomized

Enrollment: 12 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: 50 mL Dextrose 50 mL of 50% dextrose	Drug: 50 mL of 50% Glucose 1st dose Other Names: • Dextrose
Experimental: 100 mL Dextrose 100 mL of 50% dextrose	Drug: 100 mL of 50% Glucose 2nd dose Other Names: • Dextrose
Experimental: 150 mL Dextrose 150 mL of 50% dextrose	Drug: 150 mL of 50% Glucose 3rd dose Other Names: • Dextrose
Experimental: 200 mL Dextrose 200 mL of 50% dextrose	Drug: 200 mL of 50% Glucose 4th dose Other Names: • Dextrose

Outcome Measures

Primary Outcome Measure:

1. Occurrence of treatment related adverse events
   occurrence of treatment related adverse events (Grade 3 and more as assessed to the CTCAE v4.0) at any given dose of D50

   [Time Frame: 1 year]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

1. 18 years old or older
2. Lung resection is a wedge, segmentectomy, lobectomy or bilobectomy
3. Procedure performed by video-assisted thoracic surgery (VATS) or by Thoracotomy
4. Presence of an air leak on the digital draining system on postoperative day 2

Exclusion Criteria:

1. Large air leak arbitrarily defined as more than 1000 mL/min
2. Allergy to local anesthetics
3. Hemodynamic instability
4. Untreated coronary artery disease
5. Need for respiratory support
6. Any other early post-operative complication
7. Immunity disorder
8. Large pleural fluid output empirically defined as more than 500 mL in the last 12 hours
9. Inability to give consent
10. Fasting glucose ≥ 14 mmol/L the morning of the intervention (arbitrarily chosen cut-off in which patients' diabetes is considered very poorly controlled)
11. Endocrinology service not available to co-manage patients with either diabetes, or a fasting blood glucose ≥ 7 mmol/L, or HbA1c > 6.5%
12. Postoperative evidence of an active thoracic (lung or pleura) infection with systemic inflammatory response syndrome (2 or more of temperature > 38, heart rate > 90, respiratory rate > 20, white blood cell count > 12)

Contacts/Locations

Central Contact Person: Deb Lewis
Telephone: [redacted]
Email: [redacted]

Central Contact Backup: Mehdi Qiabi, MD
Telephone: [redacted]
Email: [redacted]

Study Officials:

Locations: **Canada, Ontario**
London Health Sciences Centre
[Recruiting]
London, Ontario, Canada, N6A 5W9
Contact: Mehdi Qiabi [redacted]
Contact: Deb Lewis

IPDSharing

Plan to Share IPD: No

References

Citations:

Links:

Available IPD/Information:

Appendix D

LAWSON FINAL APPROVAL NOTICE

LAWSON APPROVAL NUMBER: R-20-071

PROJECT TITLE: PLeurodesis Using hypertonic Glucose administration to treat post-operative air leaks following lung resection surgery (PLUG): Phase I trial.

PRINCIPAL INVESTIGATOR: Dr. Richard Malthaner

LAWSON APPROVAL DATE: 11/02/2020

ReDA ID: 7574

Overall Study Status: Active

Please be advised that the above project was reviewed by Lawson Administration and the project was approved.

Please provide your Lawson Approval Number (R#) to the appropriate contact(s) in supporting departments (eg. Lab Services, Diagnostic Imaging, etc.) to inform them that your study is starting. The Lawson Approval Number must be provided each time services are requested.

Dr. David Hill
V.P. Research
Lawson Health Research Institute

Appendix E

Health Canada / Santé Canada

Therapeutic Products Directorate
5th Floor, Holland Cross, Tower B
Address Locator # 3105A
OTTAWA, Ontario
K1A 0K9

JUL 15 2019

Dr. Richard Malthaner
c/o Mehdi Qiabi
Thoracic Surgery Resident
[redacted]

Your file / Votre référence
HC6-24-c229051
Our file / Notre référence

No Objection Letter RE: Protocol # MQRM711 (Version 2.05)

Dear Mehdi Qiabi :

I am pleased to inform you that the information and material to support your Clinical Trial Application for **DEXTROSE**, control number **229051**, received on July 3, 2019, have been reviewed and we have no objection to your proposed study. I would remind you of the necessity of complying with the *Food and Drug Regulations*, Division 5, in the sale of this product for clinical testing. In addition, the regulations impose record keeping responsibilities on those conducting clinical trials. You are also reminded that all clinical trials should be conducted in compliance with the Therapeutic Products Directorate's *Guideline for Good Clinical Practice*.

Please note that Health Canada has implemented electronic reporting of adverse drug reactions and is currently in pilots with some sponsors. Those sponsors who have an established electronic connection with Canada Vigilance Production stream should submit their reports using the distribution rules provided to them by Health Canada, and reporting to multiple directorates is no longer required. For the sponsors who have not yet established this connection, they should continue submitting their reports to the applicable directorate by fax or by courier. The following website provides further clarification on Health Canada's adverse drug reactions reporting requirements for clinical trials:
http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/ich/efficac/e2a_pre_notice_avis-eng.pdf

Consistent with Health Canada's Notice - *Registration and Disclosure of Clinical Trial Information* of November 30, 2007, sponsors are encouraged to register their clinical trials within 21 days of the trial's onset, using a publicly available registry that conforms with international standards for registries such as: Clinicaltrials.gov (www.clinicaltrials.gov); Current Controlled Trials (www.controlled-trials.com).

Should you have any questions concerning this letter, please contact the Office of Clinical Trials (613) 941-2132.

Yours sincerely,

[redacted]

Maurica Maher, MD, MSc., FRCPC
Clinical Manager
Office of Clinical Trials

MM/en

Canada

Appendix F

PLeurodesis Using hypertonic Glucose administration to treat post-operative air leaks following lung resection surgery (PLUG): Phase I trial.

Protocol Identifying Number: MQRM711

Principal Investigator: **Richard Malthaner, MD MSc FRCSC FACS**
Chair/Chief, Division of Thoracic Surgery
Director, Thoracic Surgery Research
Professor of Surgery, Epidemiology and Biostatistics
Schulich School of Medicine and Dentistry
Western University, Canada
Lawson Health Research Institute Scientist
London Health Sciences Centre

Funded by: UWO Internal Surgery – Internal Research Fund

Version Number: 2.05

11 July 2019

Table of Contents

LIST OF ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
CTCAE	Common Terminology Criteria for Adverse Events
D50	Dextrose 50%
DIN	Drug Identification Number
ICH E6	International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance
ICU	Intensive Care Unit
IRB	Investigational Review Board
N/A	Non applicable
OHRP	Office for Human Research Protections
POD	Post-operative day
SAE	Serious Adverse Event
TCPS 2	Tri-Council Policy Statement
UP	Unanticipated Problem
USP	United States Pharmacopeia
VATS	Video-assisted thoracic surgery

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS 2) training modules.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal investigator: _____
Print/Type name

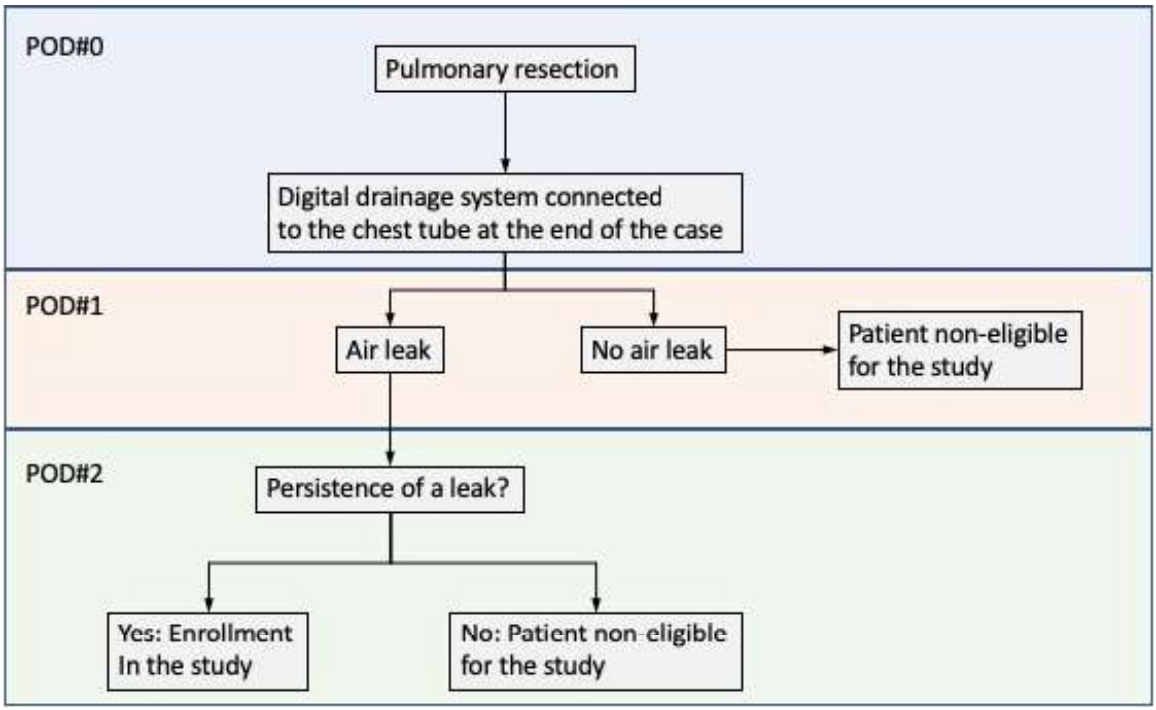
Signed: _____ Date: _____
Signature

PROTOCOL SUMMARY

Title:	**PL**eurodesis **U**sing hypertonic **G**lucose administration to treat post-operative air leaks following lung resection surgery (PLUG): Phase I trial.
Précis:	Patients with air leaks on postoperative day 2 following lung surgery will be invited to participate in the study. The precise definition of air leak is included in inclusion criteria. Dextrose 50% (D50) will be injected sterilely into the chest tube following the administration of 20 mL of 1% lidocaine. Twenty-four hours after the intervention, if there is an air leak cessation (defined elsewhere), chest tube removal will be considered by the surgical team. If an air leak is still present, no further intervention will be planned. The exact time of cessation of air leak, time of chest tube removal, date of discharge, and any adverse events will be prospectively recorded. The volume of D50 administered is incremental and will follow a rule-based escalation, 3+3 design: 3 patients will have a set dose, and if there are no dose-limiting toxicities or less than 2 moderate toxicity, the next group of 3 patients will go up one increment following review from the study safety committee to insure the acceptability of the treatment according to its side effects. The safety committee will meet every 4 weeks to review adverse events. The empiric increments will be 50 mL, 100 mL, 150 mL, and 200 mL. Therefore, a maximum of 12 patients will have to be enrolled.
Objectives:	The primary outcome is safety as defined by the lack of a grade 3, 4, or 5 adverse events at any given D50 volume according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute version 4.0. Secondary outcomes include the persistence of the air leak at 24h, 48h and 72h following the intervention, the pain score and point-of-care glucose measurement at 1h, 3h, 6h and 24h after the intervention, the pain level using a visual analog scale at 1h, 3h, 6h, and 24h after intervention, the output from the chest tube during the first 24h after the intervention, the length of hospital stay, the duration of chest tube drainage, the need to discharge the patient with a one-way valve, the need for an additional chest tube insertion, the increase in supplemental oxygen requirements, the air leak rate, and the post-operative morbidity. In addition, patient analgesia consumption will be monitored, including the type of analgesia and the

	route of administration until the earliest between discharge day versus post-operative day 5. Also, the need for an intervention to address hyperglycemia will be monitored, including what type of intervention (insulin administration?) and the length of intervention. All of the above outcomes will be measured until post-operative day 5, except for potential infectious complications which would be measured until post-operative day 14. The recurrence of an air leak at 60 days will also be monitored.
Population:	Total of 12 adult patients (18 years or older) following lung resection surgery with an active air leak on post-operative day 2 in London, Ontario.
Phase:	1
Sites:	1 – Victoria Hospital, London Health Sciences Centre, London, ON
Description of study agent:	Dextrose monohydrate injection USP 50% concentration (50 mg/mL). Volume of 50 mL, 100 mL, 150 mL, or 200 mL
Study duration:	Approximately 2 months
Participant duration:	Approximately 3 months

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

Richard Malthaner, MD MSc FRCSC FACS
Principal Investigator
Chair/Chief, Division of Thoracic Surgery
Director, Thoracic Surgery Research
Professor of Surgery, Epidemiology and Biostatistics
Schulich School of Medicine and Dentistry
Western University, Canada
Lawson Health Research Institute Scientist

[redacted]

Mehdi Qiabi, MD FRCSC
Co-investigator
Resident, Thoracic Surgery
Schulich School of Medicine and Dentistry
Western University, Canada

[redacted]

Deb Lewis, BSc CCRC
Research Coordinator, Thoracic Surgery
Program Administrator, Western University
London Health Sciences Centre, Victoria Hospital

[redacted]

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Pulmonary air leaks from unhealed lung tissue is one of the most common complications after lung surgery. This adverse event leads to a delay in chest tube removal, prolonged pain, increased infections, prolonged hospital stay, and increased costs to the health care system[1]. Different agents have been used to heal air leaks by pleurodesis but the success and safety profile of these agents has been variable. Instillation of a talc slurry into the pleural space is our current preferred method in stopping air leaks after lung resection. This technique can cause an acute lung injury and the long-term effects of talcosis remain a concern to some practitioners and some patients[2,58,98]. There has been recent interest in the use of hypertonic glucose (D50) to create pleurodesis from encouraging reports coming from Asia[6–8,49]. We have performed a pilot study using 180 mL of 50% hypertonic glucose instilled through the chest tube for the management of post lobectomy air leak and the results were encouraging[9].

Summary of all data

The search was completed on April 16, 2019 using the terms (dextrose OR glucose) AND pleurodesis on PubMed and Google Scholar. Abstracts, articles,and their bibliographies were reviewed to find more studies.

Articles where the intervention was intrapleural administration of any volume of hypertonic glucose were included. If the dextrose was administered concomitantly with another agent (such as talc), the study was rejected.

A total of 18 studies were found, covering 275 patients (Table 1). The concentration of Dextrose ranged from 20% to 50%. The volume of intrapleural dextrose during initial administration ranged from 60 mL to 500 mL. The maximal total volume administered was 1500 mL (3 times 500 mL over 3 days).

Author	Year	Study design	Location	n	Population	Intervention	Adverse events
Chen[34]	2010	case series	China	5	post-esophagectomy	50% glucose + 0.1% lidocaine (volume?) through the tube	self resolving dyspnea
Chung[49]	2008	cohort	South Korea	49	primary spontaneous pneumothorax	thoracoscopic procedure (bleb resection/bullectomy/electrocoagulation) + instillation of dextrose 20% 200 cc	rate of fever 22% (dextrose group) vs 10% (no dextrose group)
Tsukioka[7]	2013	cohort	Japan	20	secondary spontaneous pneumothorax	VATS bullectomy + mechanical abrasion + dextrose 50% (500 cc)	1 death[a] 24 days after the surgery from a pneumonia,1 prolonged air leak (15 days), 2 prolonged thoracic drainage, 1 "bacterial pleuritis", transient elevation of blood sugar
Hamada[10]	2017	case series	Japan	2	spontaneous pneumothorax	1- 200 mL of dextrose 50% 2- 400 mL of dextrose 50%	2 deaths[b]
Peng[50]	2002	case series	China	45	recurrent pneumothorax	60-80 mL of Dextrose 50% through the tube	7/45 had mild pain
Chee[44]	1992	case report	Singapore	1	spontaneous pneumothorax	50 mL dextrose 50%	pulmonary edema[c]
Fujino[6]	2016	cohort	Japan	46	35 post-lung resection patients with air leak and 11 patients with pneumothorax and prolonged air leak with a tube in place	200 mL of 50% glucose, between 1 and 3 doses, 7 patients had OK-432 after their 3rd dose for failure of the glucose to work	mild transient hyperglycemia in 20/46 patients
Takanashi[53]	2015	case report	Japan	1	spontaneous pneumothorax	50% glucose, 400 mL	ischemic colitis secondary to severe dehydratation (1960 mL/4 hours), prerenal acute renal failure
Togo[54]	2016	case series	Japan	29	14 pneumothorax, 11 post-lung resection air leak, 4 malignant pleural effusion	200 mL of 50% glucose (2 patients had 100 mL for « poor performance status »)	Mild transient hyperglycemia, chest pain and fever
Tsukioka[8]	2013	case series	Japan	13	spontaneous pneumothorax	200 - 500 mL 50% glucose through the tube, they often required more than one treatment	2 "bacterial pleuritis" (both of them required more than 1 treatment, and they had their tube 25 and 35 days, treated with antibiotics only), 1 aspiration pneumonia
Albargawi[9]	2016	cohort	Canada	10	post-lobectomy air leak	200 mL dextrose 50% with lidocaine, one or twice	mild increase in chest tube output, mild increase in blood sugar
Frick[45]	1990	case series	Germany	32	spontaneous pneumothorax	thoracoscopic pleurodesis with electrocoagulation of bullae, visceral/parietal pleurae cauterized, chemical pleurodesis with dextrose 50%	Horner syndrome (secondary to pleural cauterization)
Sumitomo[52]	2017	case series	Japan	13	post-lung resection air leak	200 mL glucose 50%, repeated as needed (2 patients had pleurodesis twice)	none
Kitagata[55]	2018	case report	Japan	1	leak post right lower lobectomy	glucose 50%	none
Yaginuma[56]	2016	case report	Japan	1	spontaneous pneumothorax on mechanical ventilation	pleurodesis with glucose 50% and minocycline	none
Kajikawa[57]	2017	case series	Japan	5	spontaneous pneumothorax	pleurodesis with 200 mL glucose 50%	transient hyperglycemia
Wei[99]	2016	case report	China	1	hydrothorax secondary to peritoneal dialysis catheter	diaphragm repaired, pleural effusion evacuated, and pleurodesis performed with dextrose 50%	?
Hennell[42]	1939	case report	US	1	Chronic pneumothorax	glucose 50% 50 mL, then 60% 67 mL	none

Table 1. List of all studies. VATS: video-assisted thoracic surgery, POD: post-operative day. [a,b,c] cf description of the events in the text

2.2 RATIONALE

Air leaks from unhealed lung tissue are one of the most common complications after lung surgery including wedge resection, segmentectomy and lobectomy. Air leaks can lead to a delay in chest tube removal, prolonged pain, increased infections, prolonged hospital stay, and increased costs to the health care system[1]. Different agents have been used to heal air leaks by creating a pleurodesis (adhesions to obliterate the pleural space between the visceral and parietal pleura). The success with these agents has been variable and come with the cost of complications that have restricted their use the post-operative period[2]. There has been recent interest in the use of D50 to create pleurodesis with encouraging reports coming mostly from Asia[6–8]. We have performed a pilot study using D50 instilled through the chest tube for the management of post lobectomy air leak with encouraging results[9]. This preliminary study used strict inclusion criteria of only lobectomy patients and excluded many other patients such as patients with diabetes or any postoperative hyperglycemia that may benefit from this intervention. Also, the optimal dose of D50 was chosen empirically and never clearly defined by previous work. It has been reported that high doses of D50 was associated to acute lung injury[10]. It is therefore critical that the optimal safe dose is clarified.

Objective: To define the most appropriate safe dose of D50 to heal air leaks in patients that have undergone lung resection surgery (Phase I study).

Hypothesis: In patients with a postoperative air leak following lung resection, the bedside administration of D50 into the pleural space on postoperative day 2 is safe (Phase I trial).

We predict that D50 will be found safe because no severe adverse events occurred with optimum dose found in the Phase I study. This will provide the motivation and data to proceed with a formal Phase II study to assess the effectiveness of the chosen dosage in reducing the length of stay and length of chest tube drainage, and then a Phase III randomized clinical trial.

We anticipate that D50 will replace talc as our pleurodesis agent of choice and become the new standard not only for sealing air leaks following lung resection surgery but also achieving pleurodesis for chronic pleural effusions. Should we be successful in reducing postoperative air leaks in patients undergoing lung resections, we will reduce their hospital length of stay. This intervention should improve patient outcomes by shortening the duration that a chest tube is required, reducing post chest tube removal pneumothoraces, decrease chest tube related pain, decrease the risk of postoperative infections, hospital length of stay, and health care costs. Should this simple, inexpensive, and novel therapy work to heal pulmonary air leaks, it will be a significant advancement in the overcoming this long standing “Achilles heel” in Thoracic Surgery.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

A literature review is summarized in the Table 1. In five papers[6,9,52,54,55], the population studied were post-lung resection patients with air leak (70 patients). In these 70 subjects, reported adverse events were as follow:

- mild transient hyperglycemia (n=26/70)
- mild transient chest pain
- mild transient fever
- mild increase in chest tube output

In these 70 patients, reported adverse events were mild. This population is similar to the population we plan to study. The concentration of dextrose was 50%. Except for one study[55] in which the data was not available, they all had administration of 200 mL, repeated up to 2 other times for a total of 600 mL over 3 days. There was no infectious complication.

In all 275 patients, infectious complications related to the intervention were rare. One study[7] where 20 patients underwent a bullectomy, mechanical abrasion and administration of 500 mL of Dextrose 50% in the operating room had one case of "bacterial pleuritis" as potential complication. The authors mentioned that "the period of thoracic drainage and the volume of air leakage may contribute to the development of a pleural infection". Another study[8] where 13 patients had spontaneous pneumothorax treated with a chest tube and then administration of between 200 to 500 mL of dextrose 50%, repeated up to a total of 3 times (500 mL administered 3 times over 3 days) reported 2 patients with "bacterial pleuritis". Both of them had their chest tubes in place for a prolonged period of time (25 and 35 days), and they both had repeated administration of 500 mL of dextrose 50% (one had a total of 2 doses and the other 3 doses). All these 3 patients were treated conservatively with antibiotics.

Ischemic colitis induced by dehydration was reported after the administration of 400 mL of Dextrose 50% on a 97 years old gentleman to induce pleurodesis after a spontaneous pneumothorax[53]. This was treated conservatively with rehydration and surgery was not required.

Chee[44] reported a case of dextrose pneumonitis. The 51 years old male with chronic obstructive airways disease complicated by cor pulmonale and hypercapnic respiratory failure had a spontaneous pneumothorax. He had a prolonged air leak for 41 days. Intrapleural instillation of 50 mL of Dextrose 50% was performed and the patient experience cardiorespiratory collapse requiring cardiopulmonary resuscitation. It was noted that copious amount of secretions was coming from the endotracheal tube, positive for glucose by a dipstick. The patient recovered well after that event and the leak stopped. It was postulated that osmotic pulmonary edema may have been caused by the high tonicity of the dextrose 50%.

Of the 275 patients who underwent intrapleural hypertonic dextrose administration for pleurodesis, a total of 3 deaths were reported.

4- In Tsukioka[7] paper, a 79 years old male with severe emphysema, unresectable lung cancer who recently had chemotherapy, underwent a bullectomy, mechanical abrasion of the pleura, and administration of 500 mL of dextrose 50% in the pleural cavity. Twenty-four days after his surgery, he passed away from a pneumonia. It is unclear whether his death is related to the administration of a sclerosing agent.

5- In Hamada[10] paper, a 72 years old male with a stage IV lung cancer and severe emphysema, presented with spontaneous pneumothorax. He was first treated with 5 rounds of OK-432 (sclerosing agent available in Japan to induce pleurodesis), but it did not work and the leak was still present. Then, 4 rounds of autologous blood and 200 mg of minocycline were injected into the pleural cavity via the chest tube, again without success. Finally, 200 mL of dextrose 50% was injected into the pleural space. The patient suffered from acute respiratory distress syndrome and had to be intubated. He eventually died from progression of respiratory failure. While there seems to be a temporal association, the causality is uncertain.

6- In Hamada[10] paper, a 84 years old male with idiopathic pulmonary fibrosis, on home oxygen and hypercapnic respiratory failure developed a spontaneous pneumothorax. A chest tube was inserted, and 400 mL of dextrose 50% administered into the pleural space. Immediate pain and respiratory failure occurred. It was recommended for the patient to be intubated, but the family refused. The patient died 1 week later from progression of respiratory failure.

In the case of Patient 1, the death seems to be related to a nosocomial pneumonia and not from the intervention. Patient 2 had multiple attempts at pleurodesis with various agents (OK-432, blood, minocycline) before dextrose was tried. This is not the type of intervention planned in the current proposed study. Patient 3 seemed to have an acute reaction to dextrose 50%. The volume administered is twice the maximum dose we are planning to use.

The potential safety concerns we will be ready to face are:

- acute respiratory distress
- dehydration
- pain
- hyperglycemia
- fever

It is hypothesized that the value of the information gained by performing this study will allow health care providers to have another option when comes the time to offer a

patient chemical pleurodesis (instead of offering talc, thoracic surgeons or respirologists will have the option of administering hypertonic glucose.

2.3.2 KNOWN POTENTIAL BENEFITS

After pulmonary resection, air leak is one of the most common complications arising from lung parenchyma at sites of division of adhesions, fissure dissection or lung retraction for exposure. A chest tube inserted at the end of the procedure will drain any ongoing air-leak allowing the underlying lung to re-expand.

Patients who have an air leak on post-operative day 2 typically are typically offered observation, hoping the air leak will seal by itself. However, previous work showed that a significant number of patients who still leak on POD2 will have a prolonged air leak (more than 5 days), and then will be typically offered one of 3 options:

1- waiting a longer period of time before removing the chest tube, with possibly discharging the patient home with a small one way valve if the lung stays well inflated, hoping the leak will have stopped at the next outpatient visit
2- injection of a sclerosing agent (such as talc) into the pleural space hoping the leak will stop
3- reoperation, hoping we can stop the leak

It is known in the thoracic surgery literature that the longer a leak persists, the more likely the patient may suffer from an infection of the pleural space. Other complications such as catheter-related discomfort, arrhythmia or deep vein thrombosis could potentially be attributed to prolonged length of stay.

Reports have shown some efficacy in inducing pleurodesis. Participants to the study will therefore potentially be able to be discharged home sooner, have their chest tube removed sooner (leading to pain relief), and because the leak would stop earlier, there is a hypothetic benefit in reducing the risk of post-operative infectious complications[18].

In addition, the worldwide current standard of practice to treat post-operative air leaks is typically to perform bedside chemical pleurodesis. A talc slurry is the most commonly used agent. A 2016 systematic review from Cochrane[33] revealed that a wide range of agents are used to induce pleurodesis, including tetracycline (antibiotic), doxycycline (antibiotic), mepacrine (anti-malarial drug), bleomycine (chemotherapy agent), doxorubicin (chemotherapy agent), proviodine (antiseptic agent), OK-432 (inactivated preparation of Streptococcus pyogenes), C. parvum (bacteria), interferon (immunomodulating agent), chlormethine (chemotherapy agent), mitoxantrone (chemotherapy agent), and triethylenethiophosphoramide (chemotherapy agent). They all have various risk of toxicity, and a simpler agent such as dextrose could possibly provide similar efficacy with a better safety profile.

3 OBJECTIVES AND PURPOSE

Objective: To define the most appropriate safe dose of D50 to heal air leaks in patients that have undergone lung resection surgery (Phase I study).

Hypothesis: In patients with a postoperative air leak following lung resection, the bedside administration of D50 into the pleural space on postoperative day 2 is safe (Phase I trial).

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

In this single-arm, phase I, single-center trial, patients with air leak on postoperative day 2 following lung surgery will be invited to participate in the study. The precise definition of air leak is found in 4.2.2. The solution to be used as pleurodesis agent will consist of sterile 50% Glucose to be injected into the chest tube following the administration of 20 mL of 1% lidocaine. The glucose solution is manufactured and marketed by Pfizer Canada ULC under “Dextrose Injection USP 50%”, DIN 02468514 (other DIN: 00037974) The agent comes in pre-filled 50 mL syringes (Ansyr™ II Syringe, product code 07517001), 25 g/50 mL.. Twenty-four hours after the intervention, if there is an air leak cessation (defined in 4.2.2), chest tube removal will be considered by the surgical team. However, if an air leak is still present, no further intervention will be planned. The exact time of cessation of air leak, time of chest tube removal, date of discharge, and any adverse events will be prospectively recorded. The volume of D50 administered is incremental and will follow a rule-based escalation, 3+3 design[63]: 3 patients will have a set dose, and if there are no dose-limiting toxicities (cf 6.1.7) or less than 2 moderate toxicties, the next group of 3 patients will go up one increment following review from the study safety committee to insure the acceptability of the treatment according to its side effects. The safety committee will meet on a monthly basis to review adverse events. The empiric increments will be 50 mL, 100 mL, 150 mL, and 200 mL. Therefore, a maximum of 12 patients will have to be enrolled.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINT

The primary outcome of the Phase I study will be safety as defined by the lack of a grade 3, 4, or 5 adverse event at any given D50 volume according to the CTCAE v4.0[64].

4.2.2 SECONDARY ENDPOINTS

Secondary outcomes include the persistence of the air leak at 24h, 48h and 72h following the intervention, the pain score and point-of-care glucose measurement at baseline, 1h, 3h, 6h and 24h after the intervention, the pain level using a visual analog

scale at 1h, 3h, 6h, and 24h after intervention, the output from the chest tube during the first 24h after the intervention, the length of hospital stay, the duration of chest tube drainage, the need to discharge the patient with a one-way valve, the need for an additional chest tube insertion, the increase in supplemental oxygen requirements, the air leak rate, and the post-operative morbidity. In addition, patient analgesia consumption will be monitored, including the type of analgesia and the route of administration until the earliest between discharge day versus post-operative day 5. Also, the need for an intervention to address hyperglycemia will be monitored, including what type of intervention (insulin administration?) and the length of intervention. All of the above outcomes will be measured until post-operative day 5, infectious adverse events will be recorded until 2 weeks post-op. The recurrence of an air leak at 60 days will also be monitored.

For the purpose of this study, “air leak” and “air leak cessation” are defined as follow:

Definition of air leak

The presence of an air leak using the Medela Thopaz™ digital system is defined as an air leak equal or more than 40 mL/min for at least 1 hour during the last 12 hours if the tube is on suction, or equal or more than 20 mL/min for at least 1 hour during the last 12 hours if the tube is on gravity mode.

Definition of cessation of air leak

An air leak has stopped if there was no record of sustained air leak (1 hour or more) of 40 mL/min or more for the last 12 hours if the tube is on suction, or equal or more than 20 mL/min for at least 1 hour during the last 12 hours if the tube is on gravity mode.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. 18 years old or older
2. Lung resection is a wedge, segmentectomy, lobectomy or bilobectomy
3. Procedure performed by video-assisted thoracic surgery, or by thoracocomy
4. Presence of an air leak on the digital draining system on POD#2

5.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Large air leak arbitrarily defined as more than 1000 mL/min

2. Allergy to local anesthetics
3. Hemodynamic instability
4. Untreated coronary artery disease
5. Need for respiratory support
6. Any other early post-operative complication
7. Immunity disorder
8. Large fluid output arbitrarily defined as more than 500 mL in the last 12 hours
9. Inability to give consent
10. Fasting glucose ≥14 mmol/L the morning of the intervention (arbitrarily chosen cut-off in which patients' diabetes is considered very poorly controlled)
11. Endocrinology service not available to co-manage patients with either diabetes, or a fasting blood glucose ≥ 7 mmol/L, or HbA1c > 6.5%
12. Postoperative evidence of an active thoracic (lung or pleura) infection with SIRS (2 or more of temperature > 38, heart rate > 90, respiratory rate > 20, WBC > 12)

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

On post-operative day 1, if the patient has an air leak as evaluated by the circle of care (thoracic surgery residents), s/he will be approached to assess whether s/he would be interested to participate in a study to treat air leaks. If the patient seems interested, the PI, co-investigator or the research coordinator will obtain consent.

All lung resections in London, Ontario are performed in Victoria Hospital, and all the members of the Division of Thoracic Surgery, along with residents/nurse practitioners will be made aware of the existence of this study and the details.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request. All data collected up until withdrawal of consent will be kept and analyzed, but future data won't be collected. An investigator may terminate participation in the study if:

- the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- if the patient meets criteria mentioned in sections 5.5 or 8.5

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

In this Phase I trial, we aim to capture adverse events, serious adverse events, and unanticipated problems. The intervention will happen only once and then the follow-up

is short (a few days). It would be unlikely to have participants withdrawing from the study or be terminated.

If the study is prematurely terminated, participants will not be replaced.

If the study is not prematurely terminated, but the participant voluntarily withdraws from participation in the study, this subject will be replaced by approaching the next available patient who would satisfy inclusion and exclusion criteria as outlined in sections 5.1 to 5.3.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

The study will be stopped entirely due to safety concern if any grade 4 or 5 (death) adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 occurs, or if the patient is transferred to the intensive care unit (ICU) for any condition thought to be secondary to the intervention, or if the patient experiences pain (8/10 or more on visual analog scale) immediately after the intervention not relieved by oral or subcutaneous analgesia.

6 STUDY AGENT

6.1 STUDY AGENT AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

The study agent is manufactured and marketed by Pfizer Canada ULC under “Dextrose Injection USP 50%”, DIN 02468514 (other DIN: 00037974) The agent comes in pre-filled 50 mL syringes (Ansyr™ II Syringe, product code 07517001), 25 g/50 mL. It will be acquired from the hospital pharmacy.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The agent comes in pre-filled 50 mL syringes (Ansyr™ II Syringe). The solution is clear.

Please refer to the product brochure.

6.1.3 PRODUCT STORAGE AND STABILITY

Product should be stored between 20 to 25°C. Protect from freezing and excessive heat.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

Do not use unless solution is clear and container or seal intact. Discard if it contains a precipitate. Single-use; discard unused portion.

Please refer to the product brochure.

6.1.4 PREPARATION

The drug comes in pre-filled syringe. There is no preparation needed. In cases of volume superior to 50 mL (i.e. 100 mL, 150 mL or 200 mL), multiple syringes may have to be used.

6.1.5 DOSING AND ADMINISTRATION

The volume of Dextrose 50% administered is incremental and will follow a rule-based escalation, 3+3 design: 3 patients will have a set dose, and if there are no dose-limiting toxicities or less than 2 moderate toxicities (cf. 6.1.7), the next group of 3 patients will go up one increment following review from the study safety committee to insure the acceptability of the treatment according to its side effects. The safety committee will meet on a monthly basis to review adverse events. The empiric increments will be 50 mL, 100 mL, 150 mL, and 200 mL. Therefore, a maximum of 12 patients will have to be enrolled.

6.1.6 ROUTE OF ADMINISTRATION

The route of administration will be intra-pleural through the chest tube already in place. The chest tube tubing will be disinfected, and then the solution injected into the tube. The tubing is kept elevated 50 cm above the chest of the patient in order to promote movement of the solution into the chest, and not into the digital drain device. The tube will not be clamped as there is an air leak, and clamping the tube may induce a tension pneumothorax (lung collapse).

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

Each participant will receive one dose only. The volume given will not be the same for all participants. We will start with 3 patients receiving 50 mL, then 3 other patients receiving each 100 mL, and so forth until reaching 200 mL after a total of 12 participants.

Dose limiting toxicities include any grade 4 or grade 5 (death) adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) v 4.0., in addition of the following:

1. Transfer to the ICU for any cause presumed to be related to the intervention
2. Pain score equal or more than 8/10 in visual analog scale not relieved by oral or subcutaneous analgesia

Moderate toxicities include all grade 3 toxicities presumed to be related to the intervention, in addition of the following:
1. Very high chest tube output, arbitrarily defined as > 1 L/12 hours

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

Adjustments or modifications of dose is not anticipated.

6.1.9 DURATION OF THERAPY

Data will be recorded and tracked until post-operative day 5 or until discharge. A follow-up visit will happen at post-operative day 14 to monitor for infectious adverse events.

6.1.10 TRACKING OF DOSE

The dose is administered by the circle of care (thoracic surgery residents). It will also be listed in the MAR (Medication Administration Record).

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

The study agent will be sent to the Thoracic Surgery Ward as for any other drug. Upon reception to the ward, it will be administered.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

If a participant is enrolled into this trial, s/he will require the following study procedures:

- Point of care glycemia evaluation before the intervention, 1 hour after the intervention, 3 hours after the intervention, 6 hours after the intervention, and 24 hours after the intervention

Should the glycemia rises above 11 mmol/L, co-management from an endocrinologist and monitoring will be requested.

7.1.2 STANDARD OF CARE STUDY PROCEDURES

If a participant is enrolled into this trial, s/he will not require any other standard of care procedure.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

The only laboratory evaluation required as part of this study is point-of-care glycemia.

7.2.2 OTHER ASSAYS OR PROCEDURES

N/A

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

N/A

7.2.4 SPECIMEN SHIPMENT

N/A

7.3 STUDY SCHEDULE

7.3.1 SCREENING

On post-operative day 1, if the patient has an air leak as evaluated by the circle of care (thoracic surgery residents), s/he will be approached to assess whether s/he would be interested to participate in a study to treat air leaks. If the patient seems interested, the PI, co-investigator or the research coordinator will obtain consent.

POD#1

- During morning rounds, the thoracic surgery residents assess whether there is an active air leak or not
- The circle of care will evaluate all inclusion and exclusion criteria, and, if appropriate, will approach the patient to enquire if he would be interested in participating in a study to treat post-operative air leaks
- if the patient is interested, either the PI, a co-investigator or the study coordinator will approach the patient, will explain the study and answer questions

7.3.2 ENROLLMENT/BASELINE

POD#2

- If there is still an air leak during morning rounds, informed consent will be obtained from the investigators if the patient is still interested with pursuing with the trial

- a baseline point-of-care glycemia will be performed at that time

7.3.3 FOLLOW-UP

All participants are hospitalized. They are followed up at least twice daily if inpatients. All the outcomes are recorded until post-operative day 5 (or 72 hours after the intervention), with the exception of infectious adverse events that can arise on a delayed fashion. Patients will therefore be evaluated on POD#14 for that reason in an outpatient setting (Thoracic Surgery clinic).

7.3.4 FINAL STUDY VISIT

The final study visit will be POD#14 (+/- 2 days to accommodate for statutory holidays/weekends). Adverse events will be recorded.

7.3.5 EARLY TERMINATION VISIT

Evaluation of adverse events are performed if there is an early termination visit (although unlikely).

7.3.6 UNSCHEDULED VISIT

The patients are instructed prior to discharge to let the Thoracic Surgery team know if any adverse event occur. They are given instructions as to where/who to call during weekdays hours and after-hours.

7.3.7 SCHEDULE OF EVENTS TABLE

	Surgery	**POD#1 (screening)**	**POD#2**	**Discharge from hospital**	**POD#14 (final study visit)**
Informed consent			X		
Administration of D50			X		
Adverse events evaluation			X	X	X

7.4 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

N/A

7.5 JUSTIFICATION FOR SENSITIVE PROCEDURES

N/A

7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

N/A

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

N/A

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Intrapleural lidocaïne 1%, 20 mL will be administered before hypertonic dextrose administration

7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

Pain, if any, will be managed as part of our standard post-operative order set (analgesics).

Fever, if any, will be investigated. Fever, defined as an oral temperature equal or superior to 38 degrees Celsius, will require performance of blood and pleural fluid cultures. Acetaminophen administration will be avoided in order to not mask an underlying infection. Acetaminophen will be administered only if absolutely necessary. The reason for administration, the start time and date, the stop time and date, and the total dose of acetaminophen administered will be recorded.

Hyperglycemia, if any, will be managed as part of our standard post-operative order set (insulin scale if needed).

Desaturation, if any, will be managed as part of our standard post-operative order set (supplemental oxygen).

If the air leak fails to heal despite dextrose administration, the study participant will not be receiving more dextrose. It will be up to the Most Responsible Physician to use his/her clinical judgement and perform one of these 3 options:

1. inject another intra-pleural agent such as talc (agent currently used in clinical practice)
2. wait a few more days, and possibly discharge the patient home with a tube still in place connected to a one-way valve
3. on very rare circumstances, patients may have to be re-operated to surgically address the leak

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

N/A

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Serious adverse event or serious suspected adverse reaction. An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UP.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild –** Events require minimal or no treatment and do not interfere with the participant's daily activities.

- **Moderate –** Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Severe –** Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 RELATIONSHIP TO STUDY AGENT

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related –** There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related –** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal

(dechallenge). Rechallenge information is not required to fulfill this definition.

- **Possibly Related –** There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

- **Unlikely to be related –** A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related –** The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 EXPECTEDNESS

An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent. For example, it is expected for intrapleural hypertonic glucose to produce some degree of chest discomfort, low grade fever, and sometimes self-resolving dyspnea.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate data report form. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's

condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 60 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

Study adverse events will be logged into the institutional data collection program (REDCap). They will be disclosed to the Data Safety Monitoring Board on a monthly basis.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the study sponsor and DSMB within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship, will be submitted to the study sponsor and DSMB within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying Health Canada of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

8.4.3 UNANTICIPATED PROBLEM REPORTING

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator’s responsibility to report UPs

to their IRB and to the study sponsor and DSMB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the study sponsor and DSMB within 72 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB, to the study sponsor and to the DSMB within 7 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 7 days of the IRB's receipt of the report of the problem from the investigator.

8.4.4 EVENTS OF SPECIAL INTEREST

N/A

8.4.5 REPORTING OF PREGNANCY

N/A

8.5 STUDY HALTING RULES

Administration of study agent will be halted if on a single patient 2 grade 3 AEs determined to be "probably related" are reported to the Data Coordinating Center, or if 1 grade 4 or grade 5 (SAE) is reported. The Data Coordinating Center will notify the study sponsor and investigators immediately and enrollment screens will stop accepting new study participants. The study sponsor will inform the DSMB members within 24 hours of this occurrence and will provide the DSMB with AE listing reports. The DSMB will convene an ad hoc meeting by teleconference or in writing as soon as possible. The DSMB will provide recommendations for proceeding with the study to the study sponsor/Health Canada. The study sponsor will inform Health Canada of the temporary halt and the disposition of the study.

8.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, including lung and pleural physiology. Such individuals would be physicians specialized in thoracic surgery, anesthesiology, respirology and endocrinology. The DSMB will be independent from the study investigators. The DSMB will meet at least monthly to assess safety data on the study. The first meeting will take place before the first patient is enrolled. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the principal investigator and co-investigator.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), and with applicable regulatory requirement(s).

- One of the DSMB member will conduct a single, on-site, random monitoring evaluation
- Independent audits will not be conducted
- Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

There will not be a formal statistical and analytical plan as our data will be mostly descriptive in nature.

10.2 STATISTICAL HYPOTHESES

N/A

10.3 ANALYSIS DATASETS

N/A

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

Our data will be mostly descriptive in nature. Data will be presented using percentages, means (with standard deviations), median, range.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

We do not anticipate any missing data. The data will be descriptive.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

We do not anticipate any missing data. The data will be descriptive. Cf Section 10.4.11, Exploratory Analyses.

10.4.4 SAFETY ANALYSES

The adverse events are graded using the CTCAE v.4.0. Information reported about each AE are:

- start time and date
- stop time and date
- severity
- relationship
- duration

AEs will be PI reported.

All grade 4 or grade 5 AEs are considered SAEs.

10.4.5 ADHERENCE AND RETENTION ANALYSES

N/A

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Planned descriptive statistics include means and rate for demographics (age, gender, comorbidities), ASA, conversion to thoracotomy, VATS/thoracotomy, type of lung resection, presence of an air leak pre-op, mean glycemia increase over time, mean pain increase over time, rate of resolution of air leak 24 hours, 48 hours and 72 hours after the intervention, mean length of stay, mean chest tube output over 24 hours after the intervention, mean duration of chest tube drainage, rate of patients needing to be discharged on a one-way valve, rate of patients requiring insertion of another tube, need for an increase in oxygen requirements after the intervention, rate of patients being discharged with home oxygen, mean air leak rate 24 hours, 48 hours, and 72 hours post-intervention.

10.4.7 PLANNED INTERIM ANALYSES

10.4.7.1 SAFETY REVIEW

Please refer to Section 5.5, Premature Termination or Suspension of Study, and to Section 8.5 Study Halting Rules.

No statistical analyses will be required for safety review.

10.4.7.2 EFFICACY REVIEW

N/A

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

Because of the relatively small sample size, no sub-group analyses will be performed.

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

N/A

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

N/A

10.4.11 EXPLORATORY ANALYSES

If dramatic absolute differences are noted between different volumes of D50, we may perform exploratory analyses (comparison between mean chest tube output at 24 hours for instance between participants who received 50 mL versus 200 mL).

10.5 SAMPLE SIZE

For this phase I trial, we did not calculate a simple size as we will use a rule-based escalation, 3+3 design[63]. We will have 3 patients receiving each one administration of the following volume of D50: 50 mL, 100 mL, 150 mL, 200 mL. We will require a total of 12 patients.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLEMENT/RANDOMIZATION/MASKING PROCEDURES

The research coordinator will obtain consent and our nurse practitioner or physician assistant will administer the dextrose. Assessment of adverse events will be performed by the residents working in the thoracic surgery team and be logged in an institutional secured database (REDCap). These residents are not investigators. The investigators will therefore be blinded, thus reducing potential bias.

Ultimately, we are planning to perform a Phase III which would be blinded to avoid observer bias.

We will reduce selection bias by considering everyone for the study and approaching them to participate.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

We will ask members of the team if they knew what dose if any the patient received.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

N/A

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Data collected pertaining to the study will be stored on our institutional database (REDCap), approved by Lawson Health Research Institute.

The principal investigator, co-investigators, research coordinator, Western University Health Sciences Research Ethics Board, and Lawson Quality Assurance and Education Program will have access to this data.

12 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control procedures will be implemented beginning with the data entry system and data quality control checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated for clarification/resolution.

The monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The following consent materials are submitted with this protocol:

- Letter of information & Consent

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor. This confidentiality is extended to cover the clinical information

relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations. A master linking log with identifiers will be stored separately from the study data.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be kept at the study center. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENTS OR DATA

- Storage: Access to stored data will be limited using access to selected individuals and password protected. Data will be stored using codes assigned by the investigators. Data will be kept in password-protected institutional database. Only investigators will have access to the data.
- Data will be tracked using by logging who electronically access them
    - Disposition at the completion of the study: All stored consent forms will be sent to "Command Services" (repository).

13.5 FUTURE USE OF STORED SPECIMENS

N/A

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections the original entry will be crossed out with a single line, and initialed and date of the change will be recorded.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

14.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 25 years. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations must be reported to Health Canada. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

14.4 PUBLICATION AND DATA SHARING POLICY

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. The ICMJE does not review specific studies to determine whether registration

is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The Study Team will govern the conduct of the study. The Study Team will be composed of the principal investigator, co-investigator and research coordinator.

16 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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APPENDIX

Version	Date	Significant Revisions
2.02	03 July 2019	Clarification of Sections 5.4.1, 5.4.2 and 7.8
2.03	07 July 2019	Clarification of Sections 2.1, 4.2.2, 5.2, 7.1.1, 7.8, 8.3
2.04	10 July 2019	Clarification of Sections 7.8 and 8.6
2.05	11 July 2019	Clarification of Sections 7.8 and 8.6

Appendix G

Letter of Information & Consent

Project Title: **PL**eurodesis **U**sing hypertonic **G**lucose administration to treat post-operative air leaks following lung resection surgery (PLUG): Phase I trial.

Principal Investigator: **Richard Malthaner, MD MSc FRCSC FACS**
Research Director, Division of Thoracic Surgery
London Health Sciences Centre
[redacted]

Co-Investigators: **Mehdi Qiabi, MD FRCSC**

Funded by: UWO Internal Surgery – Internal Research Fund

Introduction:

In this Consent document, "you" always refers to the study participant. You are being invited to participate in a research study. You are being asked to participate because you had a lung resection, and you are experiencing an air leak following your surgery. Before you decide to participate, it is important for you to understand why this study is being **done what it will involve**. Please take time to read the following information carefully and discuss it with your family and friends and/or **your family doctor if you wish**. There may be words of statements **that you do not understand**. Ask your study doctor or staff to explain anything that is not clear or if you would like more information. Take time to decide whether **or not you wish to take part**.

Before agreeing to participate in this study, it is important you know about the study. This document describes the purpose, procedures, benefits, discomforts and risks associated with this study, as well as your rights if you decide to participate in this study.

Purpose of Study:

Many patients experience air leaks after having a lung resection. This may cause you to stay in the hospital for longer while this leak stops.

This clinical study will evaluate the feasibility and effectiveness of using a concentrated glucose (sugar) solution injected into the space between your chest wall and your lungs, to stop the leak.

Number of Participants:

A total of 12 patients will be recruited.

Participation Eligibility:

You are eligible for the study if you have an air leak following your lung resection. That air leak needs to be persistent for 2 days after your surgery. Note that you will only be included if you have given your written consent to partake in the study.

Voluntary Participation:

Participation in this study is voluntary. You may refuse or agree to participate in the study. You may withdraw from the study at any moment without any effect on your future care. If you decide to withdraw from the study, the information that was collected before you leave the study will still be used to help answer the research question. No new information will be collected without your permission.

If you are not interested in participating in this study:

The standard of care is to wait until the leak stops on its own. It may take several days to several weeks. Sometimes, we let patients go home with their chest tube still in place attached to a one-way valve, and we reevaluate them in the clinic on a weekly basis. Unfortunately, there are patients whose leak does not heal on its own. It is hard to predict the duration of an air leak. In the case of a persistent air leak that does not heal on its own, we normally inject a product through the tube going into the chest called talc to create an inflammatory reaction and hope that it will stop the air leak. The longer the duration of air leak, the higher the risk of infection. It is therefore hoped that the leak is stopped as soon as possible. Rarely, patients may require a second surgery to address and stop the air leak.

Goal of the study:

The research procedure offered to you is to inject a solution with high concentration of sugar into the chest tube 2 days after the surgery if there is an air leak, hoping that the leak stops quickly. We are therefore offering you an intervention sooner than we usually would have. This intervention may or may not work.

You may choose not to participate in this study. This requires to keep the chest tube until the leak stops.

Your study doctor can tell you more about your condition and the possible benefits of the available treatments.

Be reassured that should you decide to refuse to participate in this study, the care you will receive will be unaffected.

Study Procedure:

If you choose to take part in this study, between 50 millilitres and 200 millilitres of a solution of 50% glucose will be injected into your pleural space (the space between your chest wall and your lungs) the second day after the surgery. This is done after injecting a local anesthetic to numb your chest cavity (lidocaine). The injection will be administered through your chest tube, which is already in place. There will be no injection of talc.

Some studies have already shown that a volume between 180 milliliters and 200 milliliters seem to be effective and appears safe. However, these volumes were chosen arbitrarily. The aim of this study is to be confident that the dose administered to patients is safe. Each participant will receive only one injection of glucose at a defined volume. We will start with a smaller amount (50 milliliters), and an independent group of physicians will analyze the data and potential associated adverse events. They have a list of criteria. If the dose is considered safe, we will increase the volume to 100 milliliters for the next group of participants. The same process will repeat until we reach a maximum volume of 200 milliliters.

If you choose to take part in this study, you will be followed by a researcher who will monitor you for the duration of your air leak, the duration of chest drainage, the length of hospitalization, and the occurrence of complications or discomfort.

Potential benefits associated with participation in this study:

If you agree to take part in this study, there may or may not be direct medical benefit to you. Your hospital stay and how long you require a chest tube may be reduced by this treatment. It may also prevent further air leak or lung collapse, decrease chest tube pain, and decrease post-operative complications.

Potential risks associated with participation in this study:

If you agree to participate in this trial, you may be at risk of potential side effects. You should discuss these with the study doctor. There are some side effects that cannot be predicted. These side effects are unlikely to happen.

- Temporary increase in the blood sugar level (hyperglycemia), a condition that is generally easily treated with no long-term consequences if monitored and treated appropriately
- Inflammation of the lung (pneumonitis) caused by the sugar-rich solution injected, which is a serious but rare complication
- Pain
- Infection

All the information collected during the research project will remain strictly confidential to the extent provided by law although confidentiality cannot be guaranteed as there is a risk of breach of privacy.

Should you become injured or ill as a result of participating in the study, all medical care will be provided to you at no cost.

Confidentiality:

The study investigators are committed to respecting your privacy. Any documents containing identifiable information will be stored in a locked cabinet at Victoria Hospital, accessible only to the research team. A unique study number will be assigned to your data. A list linking your study number with your initials and hospital identification number will stored on a password-protected computer on a secure network behind institutional firewalls at Victoria Hospital. All documentation will be destroyed 15 years after the closure of study as required per Lawson's data retention policy. De-identified data will be entered in an institutional database protected by a firewall.

Qualified representatives of the following organizations may look at your medical/clinical study records at the site where these records are held, for quality assurance (to check that the information collected for the study is correct and follows proper laws and guidelines).

- Representatives of Lawson Quality Assurance Education Program
- Representatives of the University of Western Ontario Health Sciences Research Ethics Board that oversees the ethical conduct of this study

Compensation and Costs:

You will not be reimbursed for your participation in this study. There is no compensation to you in relation to this research study.

Rights as a Participant:

You do not waive any legal right by signing this consent form.

If you have any questions about your rights as a research participant or the conduct of this study, you may contact the Patient Experience Office at LHSC at [redacted] or access the online form at: [redacted]

Questions about the Study:

If you have questions about the study contact the principal investigator, Dr. Richard Malthaner at [redacted] or Deb Lewis, study coordinator at [redacted].

A copy of this letter of information & consent is for you to keep.

Consent Form

This study has been explained to me and any questions I had have been answered. I know that I may leave the study at any time. I agree to participate in the study.

_____	_____	_____
Print Name of Participant	Signature of Participant	Date

My signature means that I have explained the study to the participant named above. I have answered all questions.

_____	_____	_____
Print Name of Person Obtaining Consent	Signature	Date

Was the participant assisted during the consent process? ☐ **YES** ☐ **NO**

If **YES**, please check the relevant box and complete the signature space below:

☐ The person signing below acted as a translator for the participant during the consent process and attests that the study as set out in this form was accurately translated and has had any questions answered.

_____	_____	_____
Print Name of Translator	Signature	Date

_____
Language

☐ The consent form was read to the participant. The person signing below attests that the study as set out in this form was accurately explained to, and has had any questions answered.

_____	_____	_____
Print Name of Witness	Signature	Date

_____
Relationship to Participant

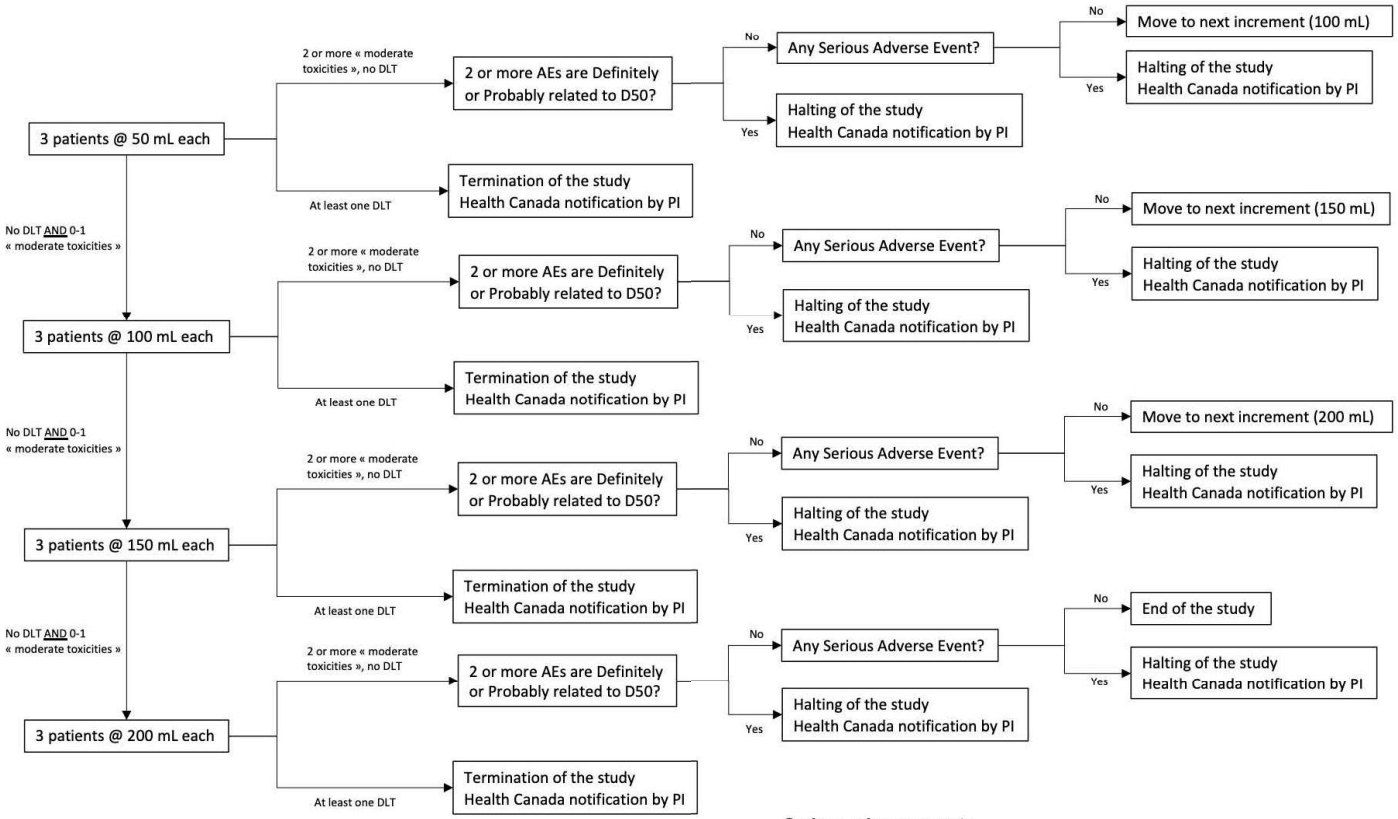
Appendix H

Data and Safety Monitoring Board – Study Halting Rules

Dr Richard Inculet, Thoracic Surgeon
Dr Nathan Ludwig, Anesthesiologist
Dr Amanda Berberich, Endocrinologist
Dr Michael Mitchell, Respirologist

Pleurodesis Using hypertonic Glucose administration to treat post-operative air leaks following lung resection surgery (PLUG): Phase I trial.

Dr Richard Malthaner and Dr Mehdi Qiabi



DLT (Dose-limiting toxicity)

- Any grade 4 or grade 5 adverse event according to CTCAE v4.0
- Transfer to the ICU definitely or probably related to D50
- Inability to relieve patient pain (> 8/10) after D50

Moderate toxicities

- Any grade 3 adverse event according to CTCAE v4.0
- Chest tube output > 1L/12 hours following D50 administration

Serious adverse events

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

• **Definitely Related** - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

• **Probably Related** - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

• **Possibly Related** - There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

• **Unlikely to be related** - A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

• **Not Related** - The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Appendix I

PRESCRIBING INFORMATION

Dextrose Injection USP

(Concentrated Dextrose for Intravenous Administration)

50%
(500 mg/mL)

Fluid and Nutrient Replenisher

Pfizer Canada Inc.
17300 Trans-Canada Highway
Kirkland, Québec
H9J 2M5

Date of Revision:
September 21, 2017

Control #: 205097

WARNINGS

Dextrose Injection USP is hypertonic and may cause phlebitis and thrombosis at the site of injection. Significant hyperglycemia and possible hyperosmolar syndrome may result from a too rapid administration. The physician should be aware of the symptoms of hyper-osmolar syndrome, such as mental confusion and loss of consciousness, especially in patients with chronic uremia and those with known carbohydrate intolerance.

The intravenous administration of this solution can cause fluid and/or solute overloading resulting in dilution of serum electrolytes, overhydration, congested states or pulmonary edema.

The risk of dilutional states is inversely proportional to electrolyte concentrations of administered parenteral solutions.

Care should be taken to avoid hyperglycemia in patients with acute ischemic strokes, as hyperglycemia has been implicated in increasing cerebral ischemic brain damage and in impairing recovery.

Additives may be incompatible. Consult with a pharmacist, if available. When introducing additives, use aseptic technique, mix thoroughly and do not store.

Peripheral Vein Administration

The solution should be given slowly, preferably through a small bore needle into a large vein, to minimize venous irritation.

Central Venous Administration

Concentrated dextrose should be administered via central vein only after suitable dilution.

PRECAUTIONS

Electrolyte deficits, particularly in serum potassium and phosphate, may occur during prolonged use of concentrated dextrose solutions. Blood electrolyte monitoring is essential, and fluid and electrolyte imbalances should be corrected. Essential vitamins and minerals should also be provided as needed.

Hyperglycemia and consequently glycosuria may occur with excessive administration. To minimize hyperglycemia and consequent glycosuria, it is desirable to monitor blood and urine glucose and, if necessary, add insulin.

When concentrated dextrose infusion is abruptly withdrawn, it is advisable to follow with the administration of 5% or 10% dextrose injection to avoid rebound hypoglycemia.

Solutions containing dextrose should be used with caution in patients with known subclinical or overt diabetes mellitus.

Care should be exercised to insure that the needle is well within the lumen of the vein and that extravasation does not occur. If thrombosis should occur during administration, the injection should be stopped and corrective measures instituted.

Concentrated dextrose solutions should not be administered subcutaneously or intramuscularly.

Pregnancy

Animal reproduction studies have not been conducted with dextrose. It is also not known whether dextrose can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Dextrose should be given to a pregnant woman only if the benefits outweigh the risks.

ADVERSE REACTIONS

Hyperosmolar syndrome, resulting from excessively rapid administration of concentrated dextrose, may cause mental confusion and/or loss of consciousness (see **WARNINGS).**

Reactions, which may occur because of the solution or the technique of administration, include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation and hypervolemia.

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of the fluid for examination if deemed necessary.

OVERDOSAGE

In the event of overhydration or solute overload during therapy, re-evaluate the patient and institute appropriate corrective measures. See **WARNINGS** and **PRECAUTIONS.**

DOSAGE AND ADMINISTRATION

Peripheral Vein Administration

Injection of the solution should be made **slowly.**

The maximum rate at which dextrose can be infused without producing glycosuria is 0.5 g/kg of body weight/hour. About 95% of the dextrose is retained when infused at a rate of 0.8 g/kg/hr.

In insulin-induced hypoglycemia, intravenous injection of 10 to 25 g of dextrose (20 to 50 mL of 50% dextrose) is usually adequate. Repeated doses and supportive treatment may be required in severe cases. A specimen for blood glucose determination should be taken before injecting the dextrose. In such emergencies, dextrose should be administered promptly without awaiting pretreatment test results.

Central Venous Administration

For total parenteral nutrition 50%, Dextrose Injection USP is administered by slow intravenous infusion: (a) After admixture with amino acid solutions via indwelling catheter with the tip positioned in a large

central vein, preferably the superior vena cava, or (b) After dilution with sterile water for injection. Dosage should be adjusted to meet individual patient requirements.

Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations and acid-base balance during prolonged parenteral therapy or whenever the condition of the patient warrants such evaluation.

The maximum rate of dextrose administration which does not result in glycosuria is the same as cited above.

STORAGE RECOMMENDATIONS

Product should be stored between 20 to 25°C. Protect from freezing and excessive heat.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

Do not use unless solution is clear and container or seal intact. Discard if it contains a precipitate.

Single-use; discard unused portion.

AVAILABILITY

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Do not use unless the solution is clear and seal is intact. Discard unused portion.

Dextrose Injection USP is a sterile nonpyrogenic, hypertonic solution of dextrose in water for injection for intravenous injection as a fluid and nutrient replenisher.

Each 100 mL of fluid contains 50 g of dextrose hydrous which delivers 3.4 kcal/g. The solution has an osmolarity of 2526 mOsm/L (calc.), an approximate pH of 4.2 and may contain sodium hydroxide and hydrochloric acid for pH adjustment.The solution contains no bacteriostat, antimicrobial agent or added buffer (except for pH adjustment) and is intended only for use as a single-use injection. When smaller doses are required, the unused portion should be discarded with the entire unit.

Dextrose Injection USP, 50%, is supplied in single-use containers as follows:

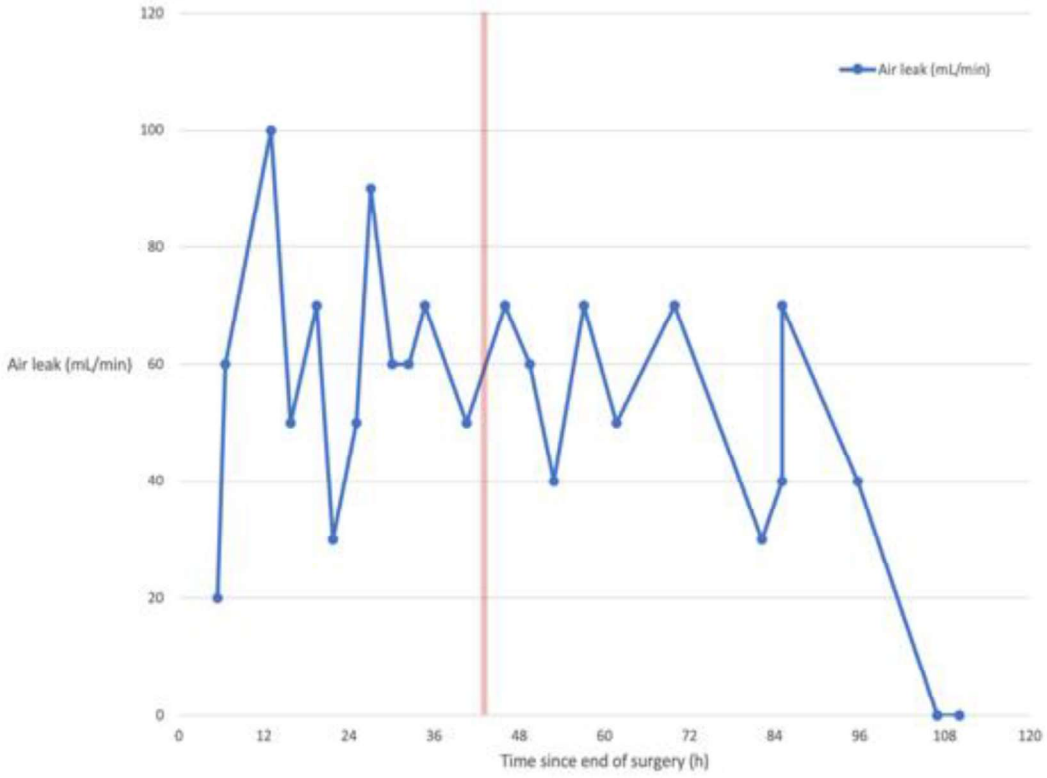
Container	Size
50 mL Fliptop Vial	25 g in 50 mL
LifeShield ™ Abboject ™ Syringe[1]	25 g in 50 mL
Ansyr ™ II Syringe[2]	25 g in 50 mL

1: LifeShield ™ Abboject ™ syringes: Flexible and reliable, the ready-to-use LifeShield™ Abboject™ syringe minimizes errors and protects caregivers and patients alike. It can be used for needle-free or shrouded needle access. The design features

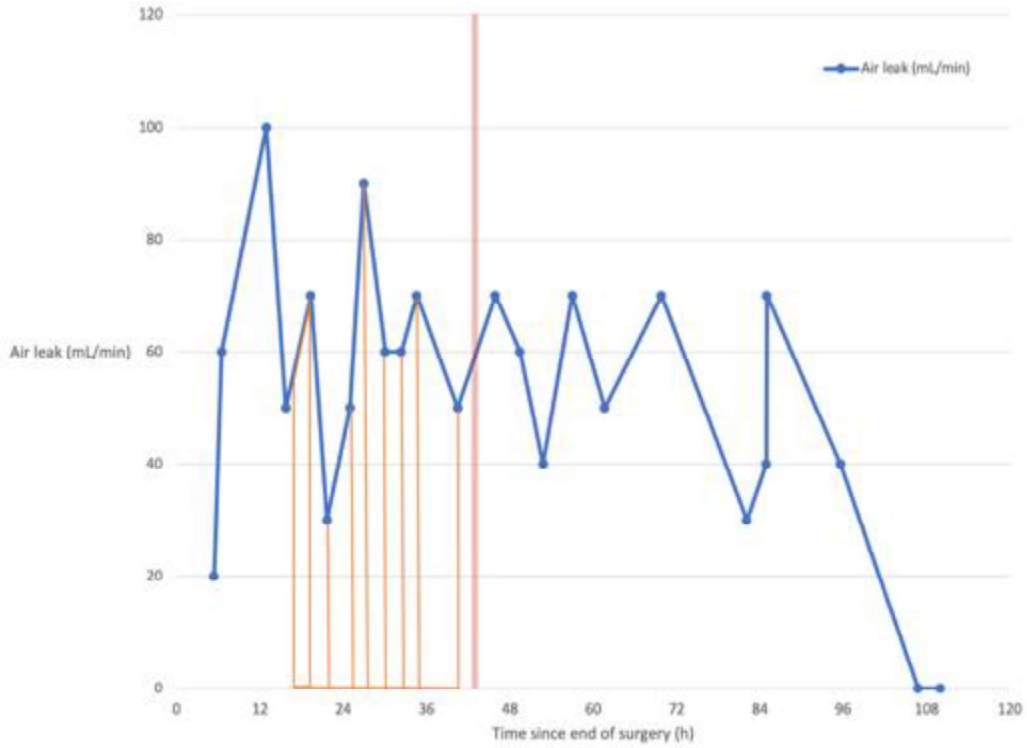
two pieces — a calibrated glass drug vial and a matching plastic syringe barrel with integral injector needle. Medication, fluid path and needle are sterile and nonpyrogenic if caps and needle cover are undisturbed and package intact.

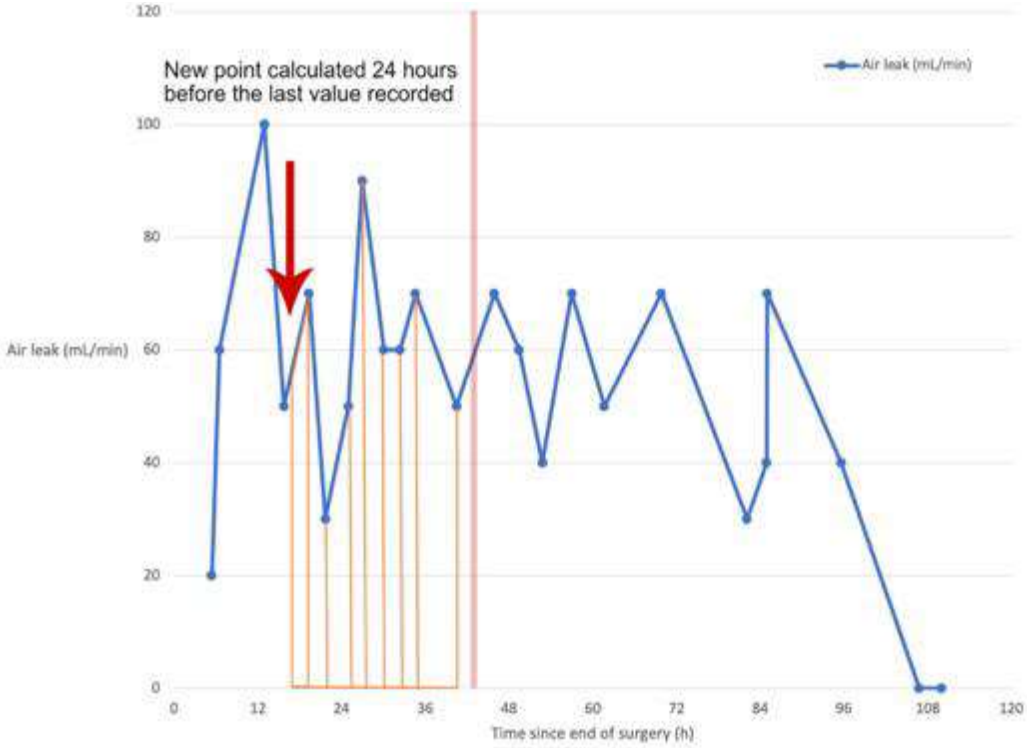
2:Ansyr ™ **II Syringe**: The Ansyr™ II syringe is a proprietary delivery option offering the combination of drugs and an innovative delivery systems with syringe and barrel detached, polypropylene plastic construction with a needle-free male luer lock adapter. Ansyr™ II syringes are available prefilled with a wide range of emergency medications. Graduated markings on the syringe barrel conform to ISO standards and clearly show any drug remaining. Medication and fluid path are sterile and nonpyrogenic if protective cover is undisturbed and package intact.

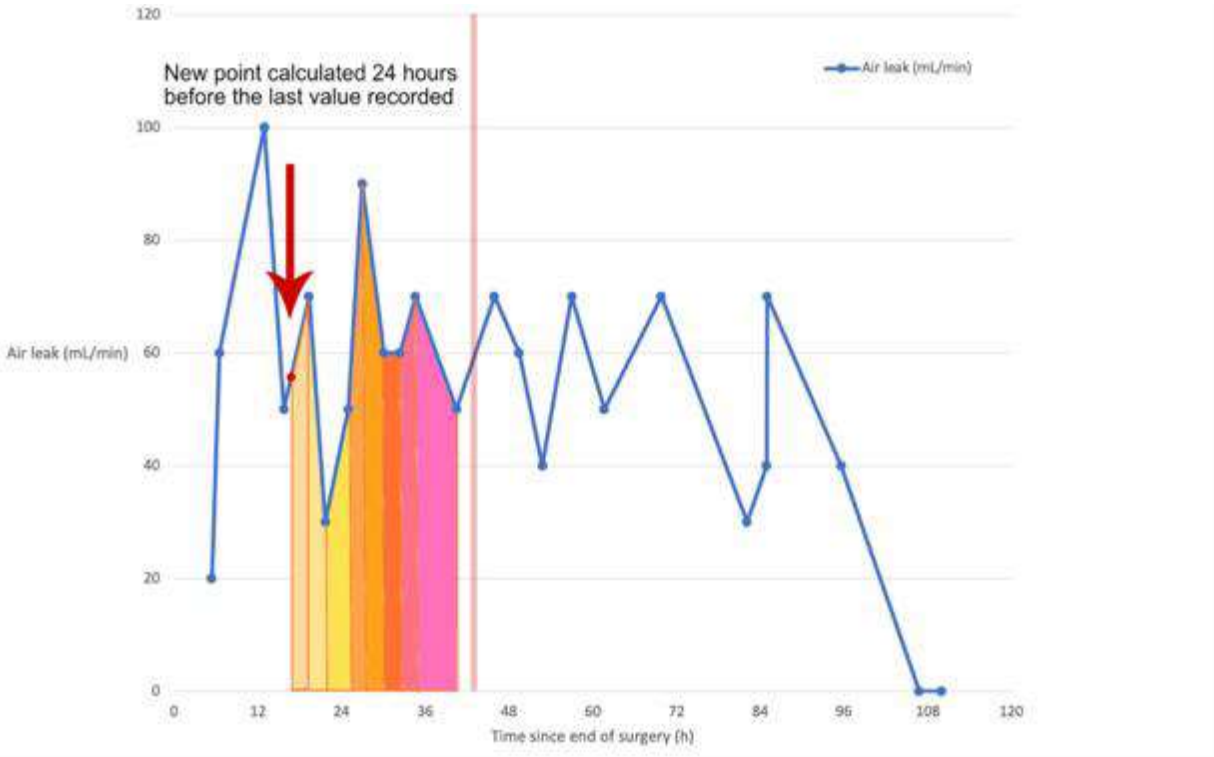
Appendix J



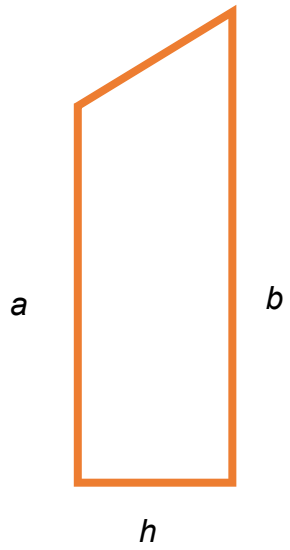
This is Patient #1 from Figure 5-A. Red line denotes when D50 was administered (43 hours here). There are various points recorded with time in hours in the X-axis, and air leak rate in mL/min in the Y-axis. The area under the curve represents the volume of air. We can calculate this area under the curve by using the trapezoidal rule. The area of interest is chosen, here it is between the last recorded value before the red line (41 hours) up since the 17 hours mark, so the volume of the preceding 24 hours is calculated. In this situation, there is no recorded flow at 17 hours, but the air leak rate at 16 and 19 hours are known. It is therefore possible to approximate the air flow rate at 17 hours.


Air leak (mL/min)
120
100
80
60
40
20
0
0
12
24
36
48
60
72
84
96
108
120
Time since end of surgery (h)
Air leak (mL/min)


New point calculated 24 hours before the last value recorded
Air leak (mL/min)
120
100
80
60
40
20
0
0
12
24
36
48
60
72
84
96
108
120
Time since end of surgery (h)
Air leak (mL/min)



The area under the curve is segmented in several trapezia. Each trapezius surface area (TSA) is calculated using the formula TSA = $h(a + b)/2$. The sum of each trapezius surface area provides the volume of air leaked in that time frame.



Appendix K

(edited to remove surgeon and dates)

Patient Information

Patient ID	1
Age (years)	72
Gender	⊗ Female
Height (m)	1.57
Weight (kg)	78
BMI	31.64428577224228

Patient Comorbidities (CCI)

Comorbidities	
Comorbidity (Choose all that are present)	☒ Metastatic solid tumor (+6)
Age	⊗ 70 - 79 (+3)
Total points:	9
Additional Comorbidities	☒ Any Previous Cancer in Last 5 Years ☒ Hypertension ☒ Ex-Smoker (quit >1 month ago)
Patient on Home O2?	⊗ No

Admission

Admission Information	
Admission Date	
Surgeon	⊗ Surgeon C
Diagnosis Group	⊗ Probable Cancer
Diagnosis	⊗ Lung Metastases
Pre-Op Therapy	⊗ None (within last 3 months)
PFTs	
FEV1% Pre	95
FEV1 Actual Pre (L)	1.96
DLCO % Pre	81
pO2 (mmHg)	117
pCO2 (mmHg)	25
Surgical Information	
Surgery Date	
Emergency Case	⊗ No
Side	⊗ Right
Chest Incision	⊗ Thoracotomy
Primary Surgery	⊗ Lobectomy
Lobe	☒ RUL
Number of Chest Tubes?	1
ASA	⊗ 4
Air leak pre-op?	⊗ No
Procedure Start	
Procedure Stop	

Total Surgery Time (minutes)	197 (Total Time in Surgery)
Date of Discharge	

Intervention

Intervention	
Date and Time of Administration	
Volume of D50 (mL)	⊗ 50 (ml)
Gucose	
Fasting Blood Glucose	5.4
POC Glucose pre-D50	7.5
POC Glucose 1 hr post-D50	6.1
POC Glucose 3 hrs post-D50	6.7
POC Glucose 6 hrs post-D50	7.9
POC Glucose 24 hrs post-D50	7.0
Pain	
Pain level pre-D50 (/10)	1
Pain level 1 hr post-D50 (/10)	0
Pain level 3 hrs post-D50 (/10)	2.0
Pain level 6 hrs post-D50 (/10)	4
Pain level 24 hrs post-D50 (/10)	4
Air Leak	
Air Leak Rate pre-D50 (mL/min)	50
Air leak 24 hrs post-D50?	⊗ Yes
Air Leak Rate 24 hrs post-D50 (mL/min)	70
Air leak 48 hrs post-D50?	⊗ Yes
Air Leak Rate 48 hrs post-D50 (mL/min)	70
Air leak 72 hrs post-D50?	⊗ No
O2 Requirements	

O2 Requirements Pre-D50 (L/min)	2.0
O2 Requirements 1 hr post-D50 (L/min)	2.0
O2 Requirements 3 hrs post-D50 (L/min)	2.0
O2 Requirements 6 hrs post-D50 (L/min)	2.0
O2 Requirements 24 hrs post-D50 (L/min)	3.0
O2 Requirements 48 hrs post-D50 (L/min)	3.0
O2 Requirements 72 hrs post-D50 (L/min)	2.0
Total Chest Tube Output during 24 hrs post-D50 (mL)	325
Hyperglycemia	
Hyperglycemia requiring any additional treatment?	⊗ No
At Discharge	
Insertion of Another Chest Tube post-D50?	⊗ No
Discharged on Home O2?	⊗ No
Date and Time of Chest Tube Removal	
Discharged with a Heimlich valve?	⊗ Yes
14 Day Follow-up	
Readmission within 14 days of discharge?	⊗ No
Air leak recurrence within 14 days of discharge (if applicable)?	⊗ N/A

Adverse Events

AE Reference Guide [Attachment: "2018-07-01 AE Reference Guide.pdf"]	
Adverse Events	
DSMB	
Additional notes (description of each adverse event for the DSMB to assess)	Patient had no adverse event other than the air leak post-op. This patient was administered acetaminophen by the nursing team despite the acetaminophen order being discontinued. Then, resident reordered it during morning round.
Any AE fits the definition of Serious Adverse Event?	⊗ N/A
Patient reviewed by the DSMB?	⊗ Yes

Definition of Serious Adverse Events
An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
- death
- a life-threatening adverse even
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The study sponsor will be responsible for notifying Health Canada of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

Relationship to the study agent
For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

• Definitely Related - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

• Probably Related - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

• Possibly Related - There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

• Unlikely to be related - A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

• Not Related - The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Analgesia Post-D50

0 - 24 hrs (POD1)	
Hydromorphone S/C (mg)	⊗ Yes
Total Hydromorphone S/C (mg)	1
Hydromorphone PO (mg)	⊗ No
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ Yes
Total Tramacet PO (mg)	225
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Analgesia Post-D50

24 - 48 hrs (POD2)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ No
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ Yes
Total Acetaminophen PO (mg)	650
Ibuprofen PO (mg)	⊗ Yes
Total Ibuprofen PO (mg)	400
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Analgesia Post-D50

48 - 72 hrs (POD3)	
Hydromorphone S/C (mg)	⊗ Yes
Total Hydromorphone S/C (mg)	1
Hydromorphone PO (mg)	⊗ No
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ Yes
Total Acetaminophen PO (mg)	1950
Ibuprofen PO (mg)	⊗ Yes
Total Ibuprofen PO (mg)	1200
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Patient Information

Patient ID	2
Age (years)	66
Gender	⊗ Male
Height (m)	1.72
Weight (kg)	92
BMI	31.09789075175771

Patient Comorbidities (CCI)

Comorbidities	
Comorbidity (Choose all that are present)	☒ Metastatic solid tumor (+6)
Age	⊗ 60 - 69 (+2)
Total points:	8
Additional Comorbidities	☒ Hypertension ☒ Hypercholesterolemia ☒ Non-Smoker
Patient on Home O2?	⊗ No

Admission

Admission Information	
Admission Date	
Surgeon	⊗ Surgeon A
Diagnosis Group	⊗ Probable Cancer
Diagnosis	⊗ Lung Metastases
Pre-Op Therapy	⊗ None (within last 3 months)
PFTs	
FEV1% Pre	96
FEV1 Actual Pre (L)	2.81
DLCO % Pre	110
pO2 (mmHg)	76
pCO2 (mmHg)	37
Surgical Information	
Surgery Date	
Emergency Case	⊗ No
Side	⊗ Right
Chest Incision	⊗ Thoracotomy
Primary Surgery	⊗ Lobectomy
Secondary Surgery	⊗ Wedge Resection
Lobe	☒ LLL ☒ RUL
Number of Chest Tubes?	1
ASA	⊗ 3
Air leak pre-op?	⊗ No
Procedure Start	

Procedure Stop	
Total Surgery Time (minutes)	235 (Total Time in Surgery)
Date of Discharge	

Intervention

Intervention	
Date and Time of Administration	
Volume of D50 (mL)	⊗ 50 (ml)
Gucose	
Fasting Blood Glucose	5.6
POC Glucose pre-D50	7.2
POC Glucose 1 hr post-D50	5.9
POC Glucose 3 hrs post-D50	5.8
POC Glucose 6 hrs post-D50	5.4
POC Glucose 24 hrs post-D50	6.6
Pain	
Pain level pre-D50 (/10)	0
Pain level 1 hr post-D50 (/10)	1
Pain level 3 hrs post-D50 (/10)	1.0
Pain level 6 hrs post-D50 (/10)	0
Pain level 24 hrs post-D50 (/10)	2
Air Leak	
Air Leak Rate pre-D50 (mL/min)	30
Air leak 24 hrs post-D50?	⊗ Yes
Air Leak Rate 24 hrs post-D50 (mL/min)	10
Air leak 48 hrs post-D50?	⊗ Yes
Air Leak Rate 48 hrs post-D50 (mL/min)	30
Air leak 72 hrs post-D50?	⊗ No
O2 Requirements	

O2 Requirements Pre-D50 (L/min)	2.0
O2 Requirements 1 hr post-D50 (L/min)	2.0
O2 Requirements 3 hrs post-D50 (L/min)	2.0
O2 Requirements 6 hrs post-D50 (L/min)	1.0
O2 Requirements 24 hrs post-D50 (L/min)	0.0
O2 Requirements 48 hrs post-D50 (L/min)	0.0
O2 Requirements 72 hrs post-D50 (L/min)	0.0
Total Chest Tube Output during 24 hrs post-D50 (mL)	300
Hyperglycemia	
Hyperglycemia requiring any additional treatment?	⊗ No
At Discharge	
Insertion of Another Chest Tube post-D50?	⊗ No
Discharged on Home O2?	⊗ No
Date and Time of Chest Tube Removal	
Discharged with a Heimlich valve?	⊗ No
14 Day Follow-up	
Readmission within 14 days of discharge?	⊗ No
Air leak recurrence within 14 days of discharge (if applicable)?	⊗ No

Adverse Events

AE Reference Guide

[Attachment: "2018-07-01 AE Reference Guide.pdf"]

Adverse Events

Infection	
Infection 1	⊗ Cellulitis or Skin Infection
Grade	⊗ 2
Relationship	⊗ Not Related
DSMB	
Additional notes (description of each adverse event for the DSMB to assess)	Patient had a right knee cellulitis before his surgery. The investigators were not notified. Patient was enrolled for the trial. The day after dextrose administration, the medical team started antibiotics to treat the cellulitis.
Any AE fits the definition of Serious Adverse Event?	⊗ No
Patient reviewed by the DSMB?	⊗ Yes

Definition of Serious Adverse Events
An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
- death
- a life-threatening adverse even
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The study sponsor will be responsible for notifying Health Canada of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

Relationship to the study agent
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• Definitely Related - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

• Probably Related - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

• Possibly Related - There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

• Unlikely to be related - A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

• Not Related - The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Analgesia Post-D50

0 - 24 hrs (POD1)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	2
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Analgesia Post-D50

24 - 48 hrs (POD2)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	12
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Analgesia Post-D50

48 - 72 hrs (POD3)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	8
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Patient Information

Patient ID	3
Age (years)	66
Gender	⊗ Male
Height (m)	1.82
Weight (kg)	55.5
BMI	16.755222799178842

Patient Comorbidities (CCI)

Comorbidities	
Comorbidity (Choose all that are present)	☒ Chronic pulmonary disease (+1) ☒ Solid tumor (non metastatic) (+2)
Age	⊗ 60 - 69 (+2)
Total points:	5
Additional Comorbidities	☒ Hypertension ☒ Smoker
Patient on Home O2?	⊗ No

Admission

Admission Information	
Admission Date	
Surgeon	⊗ Surgeon B
Diagnosis Group	⊗ Probable Cancer
Diagnosis	⊗ Lung Nodule
Pre-Op Therapy	⊗ None (within last 3 months)
PFTs	
FEV1% Pre	73
FEV1 Actual Pre (L)	2.44
DLCO % Pre	44
pO2 (mmHg)	72
pCO2 (mmHg)	33
Surgical Information	
Surgery Date	
Emergency Case	⊗ No
Side	⊗ Right
Chest Incision	⊗ VATS
Primary Surgery	⊗ Wedge Resection
Lobe	☒ RUL
Number of Chest Tubes?	1
ASA	⊗ 3
Air leak pre-op?	⊗ No
Procedure Start	
Procedure Stop	

Total Surgery Time (minutes)	108 (Total Time in Surgery)
Date of Discharge	

Intervention

Intervention	
Date and Time of Administration	
Volume of D50 (mL)	⊗ 50 (ml)
Gucose	
Fasting Blood Glucose	6.4
POC Glucose pre-D50	6.3
POC Glucose 1 hr post-D50	7.3
POC Glucose 3 hrs post-D50	5.9
POC Glucose 6 hrs post-D50	5.4
POC Glucose 24 hrs post-D50	9.3
Pain	
Pain level pre-D50 (/10)	4
Pain level 1 hr post-D50 (/10)	3
Pain level 3 hrs post-D50 (/10)	2.0
Pain level 6 hrs post-D50 (/10)	3
Pain level 24 hrs post-D50 (/10)	2
Air Leak	
Air Leak Rate pre-D50 (mL/min)	400
Air leak 24 hrs post-D50?	⊗ No
Air leak 48 hrs post-D50?	⊗ No
Air leak 72 hrs post-D50?	⊗ Yes
Air Leak Rate 72 hrs post-D50 (mL/min)	1
O2 Requirements	
O2 Requirements Pre-D50 (L/min)	0.0

O2 Requirements 1 hr post-D50 (L/min)	0.0
O2 Requirements 3 hrs post-D50 (L/min)	0.0
O2 Requirements 6 hrs post-D50 (L/min)	0.0
O2 Requirements 24 hrs post-D50 (L/min)	0.0
O2 Requirements 48 hrs post-D50 (L/min)	0.0
O2 Requirements 72 hrs post-D50 (L/min)	0.0
Total Chest Tube Output during 24 hrs post-D50 (mL)	0
Hyperglycemia	
Hyperglycemia requiring any additional treatment?	⊗ No
At Discharge	
Insertion of Another Chest Tube post-D50?	⊗ Yes
Discharged on Home O2?	⊗ No
Date and Time of Chest Tube Removal	
Discharged with a Heimlich valve?	⊗ Yes
14 Day Follow-up	
Readmission within 14 days of discharge?	⊗ No
Air leak recurrence within 14 days of discharge (if applicable)?	⊗ N/A

Adverse Events

AE Reference Guide [Attachment: "2018-07-01 AE Reference Guide.pdf"]	
Adverse Events	
GI	
Gastrointestinal 1	⊗ Diarrhea - C diff
Grade	⊗ 1
Relationship	⊗ Not Related
Infection	
Infection 1	⊗ Lung Infection or Pneumonia
Grade	⊗ 3
Relationship	⊗ Not Related
DSMB	
Additional notes (description of each adverse event for the DSMB to assess)	Patient was offered the intervention without the investigators being aware that a sputum sample was sent on POD#2 in the AM, prior to the intervention. The sputum sample was positive for Haemophilus influenzae and Moraxella catarrhalis and the patient was placed on IV antibiotics. Therefore the pneumonia is not related to the intervention. Furthermore, 3 days after initiation of the antibiotics, patient had diarrhea and was found to be positive to C. difficile. He was treated with oral vancomycin. This was not related to the intervention. An additional chest tube was placed on POD#3, or 22 hours after the intervention. The original chest tube was deemed to be very positional. There was significant variation in the air leak rate depending on the position of the patient. The patient developed subcutaneous emphysema immediately post-operatively. It is not felt from the team that the need of an additional chest tube was due to the administration of glucose.
Any AE fits the definition of Serious Adverse Event?	⊗ No
Patient reviewed by the DSMB?	⊗ Yes

Definition of Serious Adverse Events
An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
- death
- a life-threatening adverse even
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The study sponsor will be responsible for notifying Health Canada of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

Relationship to the study agent
For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

• Definitely Related - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

• Probably Related - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

• Possibly Related - There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

• Unlikely to be related - A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

• Not Related - The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Analgesia Post-D50

0 - 24 hrs (POD1)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	18
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Analgesia Post-D50

24 - 48 hrs (POD2)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	18
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Analgesia Post-D50

48 - 72 hrs (POD3)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	18
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ Yes
Total Ibuprofen PO (mg)	400
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Patient Information

Patient ID	4
Age (years)	63
Gender	⊗ Male
Height (m)	1.78
Weight (kg)	72.1
BMI	22.755965155914655

Patient Comorbidities (CCI)

Comorbidities	
Comorbidity (Choose all that are present)	☒ Peripheral vascular disease (+1) ☒ Chronic pulmonary disease (+1) ☒ Solid tumor (non metastatic) (+2)
Age	⊗ 60 - 69 (+2)
Total points:	6
Additional Comorbidities	☒ Smoker
HbA1c level (%)	5.8
Date of HbA1c	
Patient on Home O2?	⊗ No

Admission

Admission Information	
Admission Date	
Surgeon	⊗ Surgeon A
Diagnosis Group	⊗ Cancer
Diagnosis	⊗ Lung Cancer Recurrence
Pre-Op Therapy	⊗ None (within last 3 months)
PFTs	
FEV1% Pre	47
FEV1 Actual Pre (L)	1.46
DLCO % Pre	49
Surgical Information	
Surgery Date	
Emergency Case	⊗ No
Side	⊗ Right
Chest Incision	⊗ Thoracotomy
Primary Surgery	⊗ Lobectomy
Lobe	☒ RUL
Number of Chest Tubes?	2
ASA	⊗ 4
Air leak pre-op?	⊗ No
Procedure Start	
Procedure Stop	
Total Surgery Time (minutes)	113 (Total Time in Surgery)

Date of Discharge

Intervention

Intervention	
Date and Time of Administration	
Volume of D50 (mL)	⊗ 100 (ml)
Gucose	
Fasting Blood Glucose	6.7
POC Glucose pre-D50	9.0
POC Glucose 1 hr post-D50	10.4
POC Glucose 3 hrs post-D50	8.5
POC Glucose 6 hrs post-D50	5.3
POC Glucose 24 hrs post-D50	9.2
Pain	
Pain level pre-D50 (/10)	7
Pain level 1 hr post-D50 (/10)	5
Pain level 3 hrs post-D50 (/10)	8.0
Pain level 6 hrs post-D50 (/10)	8
Pain level 24 hrs post-D50 (/10)	3
Air Leak	
Air Leak Rate pre-D50 (mL/min)	110
Air leak 24 hrs post-D50?	⊗ Yes
Air Leak Rate 24 hrs post-D50 (mL/min)	70
Air leak 48 hrs post-D50?	⊗ No
Air leak 72 hrs post-D50?	⊗ No
O2 Requirements	
O2 Requirements Pre-D50 (L/min)	3.0

O2 Requirements 1 hr post-D50 (L/min)	3.0
O2 Requirements 3 hrs post-D50 (L/min)	3.0
O2 Requirements 6 hrs post-D50 (L/min)	2.0
O2 Requirements 24 hrs post-D50 (L/min)	1.0
O2 Requirements 48 hrs post-D50 (L/min)	0.0
O2 Requirements 72 hrs post-D50 (L/min)	2.0
Total Chest Tube Output during 24 hrs post-D50 (mL)	600
Hyperglycemia	
Hyperglycemia requiring any additional treatment?	⊗ No
At Discharge	
Insertion of Another Chest Tube post-D50?	⊗ No
Discharged on Home O2?	⊗ No
Date and Time of Chest Tube Removal	
Discharged with a Heimlich valve?	⊗ No
14 Day Follow-up	
Readmission within 14 days of discharge?	⊗ No
Air leak recurrence within 14 days of discharge (if applicable)?	⊗ No

Adverse Events

AE Reference Guide [Attachment: "2018-07-01 AE Reference Guide.pdf"]	
Adverse Events	
DSMB	
Additional notes (description of each adverse event for the DSMB to assess)	No adverse events. Patient with chronic pain (spinal stenosis) and had to use increased amount of narcotics. Epidural discontinued on POD#1 as it was not working.
Any AE fits the definition of Serious Adverse Event?	⊗ N/A
Patient reviewed by the DSMB?	⊗ Yes

Definition of Serious Adverse Events
An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
- death
- a life-threatening adverse even
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect.

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• Probably Related - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

• Possibly Related - There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

• Unlikely to be related - A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

• Not Related - The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Analgesia Post-D50

0 - 24 hrs (POD1)	
Hydromorphone S/C (mg)	⊗ Yes
Total Hydromorphone S/C (mg)	2
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	8
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ Yes
Total Ibuprofen PO (mg)	600
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Analgesia Post-D50

24 - 48 hrs (POD2)	
Hydromorphone S/C (mg)	⊗ Yes
Total Hydromorphone S/C (mg)	1
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	10
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ Yes
Total Ibuprofen PO (mg)	1000
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Analgesia Post-D50

48 - 72 hrs (POD3)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	10
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ Yes
Total Ibuprofen PO (mg)	400
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ Yes
Total Gabapentin PO (mg)	300

Patient Information

Patient ID	5
Age (years)	74
Gender	⊗ Female
Height (m)	1.57
Weight (kg)	67
BMI	27.18163008641324

Patient Comorbidities (CCI)

Comorbidities	
Comorbidity (Choose all that are present)	☒ Chronic pulmonary disease (+1) ☒ Solid tumor (non metastatic) (+2)
Age	⊗ 70 - 79 (+3)
Total points:	6
Additional Comorbidities	☒ Any Previous Cancer in Last 5 Years ☒ Hypertension ☒ Hypercholesterolemia ☒ Ex-Smoker (quit >1 month ago)
HbA1c level (%)	6.2
Date of HbA1c	
Patient on Home O2?	⊗ No

Admission

Admission Information	
Admission Date	
Surgeon	⊗ Surgeon A
Diagnosis Group	⊗ Cancer
Diagnosis	⊗ Lung Cancer
Pre-Op Therapy	⊗ None (within last 3 months)
PFTs	
FEV1% Pre	87
FEV1 Actual Pre (L)	1.69
DLCO % Pre	79
Surgical Information	
Surgery Date	
Emergency Case	⊗ No
Side	⊗ Right
Chest Incision	⊗ Thoracotomy
Primary Surgery	⊗ Lobectomy
Lobe	☒ RUL
Number of Chest Tubes?	2
ASA	⊗ 3
Air leak pre-op?	⊗ No
Procedure Start	
Procedure Stop	
Total Surgery Time (minutes)	161 (Total Time in Surgery)

Surgery Comments	Bleeding from the PA, controlled with sutures Epidural placed, discontinued prior Dextrose administration as it was not working
Date of Discharge	

Intervention

Intervention	
Date and Time of Administration	
Volume of D50 (mL)	⊗ 100 (ml)
Gucose	
Fasting Blood Glucose	7.7
POC Glucose pre-D50	12.6
POC Glucose 1 hr post-D50	14.5
POC Glucose 3 hrs post-D50	13.8
POC Glucose 6 hrs post-D50	9.0
POC Glucose 24 hrs post-D50	6.0
Pain	
Pain level pre-D50 (/10)	3
Pain level 1 hr post-D50 (/10)	1
Pain level 3 hrs post-D50 (/10)	0.0
Pain level 6 hrs post-D50 (/10)	6
Pain level 24 hrs post-D50 (/10)	5
Air Leak	
Air Leak Rate pre-D50 (mL/min)	120
Air leak 24 hrs post-D50?	⊗ No
Air leak 48 hrs post-D50?	⊗ No
Air leak 72 hrs post-D50?	⊗ No
O2 Requirements	
O2 Requirements Pre-D50 (L/min)	1.0
O2 Requirements 1 hr post-D50 (L/min)	1.0

O2 Requirements 3 hrs post-D50 (L/min)	1.0
O2 Requirements 6 hrs post-D50 (L/min)	1.0
O2 Requirements 24 hrs post-D50 (L/min)	1.0
O2 Requirements 48 hrs post-D50 (L/min)	0.0
O2 Requirements 72 hrs post-D50 (L/min)	0.0
Total Chest Tube Output during 24 hrs post-D50 (mL)	325
Hyperglycemia	
Hyperglycemia requiring any additional treatment?	⊗ Yes
Insulin required for insulin naive patients?	⊗ Yes
Increase of insulin requirements?	⊗ N/A
At Discharge	
Insertion of Another Chest Tube post-D50?	⊗ No
Discharged on Home O2?	⊗ No
Date and Time of Chest Tube Removal	
Discharged with a Heimlich valve?	⊗ No
14 Day Follow-up	
Readmission within 14 days of discharge?	⊗ No
Air leak recurrence within 14 days of discharge (if applicable)?	⊗ No

Adverse Events

AE Reference Guide

[Attachment: "2018-07-01 AE Reference Guide.pdf"]

Adverse Events

Cardiac	
Cardiovasc 1	⊗ Supraventricular Arrhythmia or A Fib
Grade	⊗ 2
Relationship	⊗ Unlikely to be Related
DSMB	
Additional notes (description of each adverse event for the DSMB to assess)	- Patient was prescribed Tramacet by NP (contains acetaminophen) on POD#4 (2 days after administration of Dextrose) for pain. Patient had pain from the thoracotomy incision prior to the Dextrose administration. Patient never was febrile or subfebrile prior or after Tramacet administration, making it unlikely to have masked an infectious complication. - Patient developed Atrial fibrillation on POD#4 easily controlled by metoprolol 12.5 mg oral. She was asymptomatic and picked up on monitor. It was deemed to be "Unlikely to be related" to the Dextrose administration. - Patient had an elevated fasting glucose, and higher than normal HbA1c. Endocrinology was consulted, and classified her as pre-existing pre-diabetes/mild T2DM. They elected to prescribe a sliding scale as patient pre-dextrose glycemia was 12.6. Recommendation was for a follow-up with the GP in regards to her diabetes.
Any AE fits the definition of Serious Adverse Event?	⊗ No
Patient reviewed by the DSMB?	⊗ Yes

Definition of Serious Adverse Events
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- death
- a life-threatening adverse even
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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Relationship to the study agent
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• Definitely Related - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

• Probably Related - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

• Possibly Related - There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

• Unlikely to be related - A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

• Not Related - The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Analgesia Post-D50

0 - 24 hrs (POD1)	
Hydromorphone S/C (mg)	⊗ Yes
Total Hydromorphone S/C (mg)	3
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	2
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Analgesia Post-D50

24 - 48 hrs (POD2)	
Hydromorphone S/C (mg)	⊗ Yes
Total Hydromorphone S/C (mg)	4
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	2
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ Yes
Total Tramacet PO (mg)	650
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Analgesia Post-D50

48 - 72 hrs (POD3)	
Hydromorphone S/C (mg)	⊗ Yes
Total Hydromorphone S/C (mg)	1.5
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	2
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ Yes
Total Tramacet PO (mg)	1300
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Patient Information

Patient ID	6
Age (years)	71
Gender	⊗ Male
Height (m)	1.77
Weight (kg)	86.3
BMI	27.546362794854605

Patient Comorbidities (CCI)

Comorbidities	
Comorbidity (Choose all that are present)	☒ Solid tumor (non metastatic) (+2)
Age	⊗ 70 - 79 (+3)
Total points:	5
Additional Comorbidities	☒ Hypertension ☒ Smoker
Patient on Home O2?	⊗ No

Admission

Admission Information	
Admission Date	
Surgeon	⊗ Surgeon C
Diagnosis Group	⊗ Probable Cancer
Diagnosis	⊗ Lung Cancer
Pre-Op Therapy	⊗ None (within last 3 months)
PFTs	
Surgical Information	
Surgery Date	
Emergency Case	⊗ No
Side	⊗ Right
Chest Incision	⊗ VATS
Primary Surgery	⊗ Lobectomy
Lobe	☒ RLL
Number of Chest Tubes?	1
ASA	⊗ 4
Air leak pre-op?	⊗ No
Procedure Start	
Procedure Stop	
Total Surgery Time (minutes)	305 (Total Time in Surgery)
Date of Discharge	

Intervention

Intervention	
Date and Time of Administration	
Volume of D50 (mL)	⊗ 100 (ml)
Gucose	
Fasting Blood Glucose	6.7
POC Glucose pre-D50	7.3
POC Glucose 1 hr post-D50	11.9
POC Glucose 3 hrs post-D50	7.0
POC Glucose 6 hrs post-D50	5.7
POC Glucose 24 hrs post-D50	8.3
Pain	
Pain level pre-D50 (/10)	5
Pain level 1 hr post-D50 (/10)	8
Pain level 6 hrs post-D50 (/10)	5.0
Pain level 24 hrs post-D50 (/10)	3
Air Leak	
Air Leak Rate pre-D50 (mL/min)	190
Air leak 24 hrs post-D50?	⊗ No
Air leak 48 hrs post-D50?	⊗ No
Air leak 72 hrs post-D50?	⊗ No
O2 Requirements	
O2 Requirements Pre-D50 (L/min)	2.0
O2 Requirements 1 hr post-D50 (L/min)	2.0
O2 Requirements 3 hrs post-D50 (L/min)	2.0

O2 Requirements 6 hrs post-D50 (L/min)	2.0
O2 Requirements 24 hrs post-D50 (L/min)	0.0
O2 Requirements 48 hrs post-D50 (L/min)	0.0
O2 Requirements 72 hrs post-D50 (L/min)	0.0
Total Chest Tube Output during 24 hrs post-D50 (mL)	500
Hyperglycemia	
Hyperglycemia requiring any additional treatment?	⊗ No
At Discharge	
Insertion of Another Chest Tube post-D50?	⊗ No
Discharged on Home O2?	⊗ No
Date and Time of Chest Tube Removal	
Discharged with a Heimlich valve?	⊗ No
14 Day Follow-up	
Readmission within 14 days of discharge?	⊗ No
Air leak recurrence within 14 days of discharge (if applicable)?	⊗ No

Adverse Events

AE Reference Guide [Attachment: "2018-07-01 AE Reference Guide.pdf"]	
Adverse Events	
DSMB	
Additional notes (description of each adverse event for the DSMB to assess)	No adverse event noted
Any AE fits the definition of Serious Adverse Event?	⊗ N/A
Patient reviewed by the DSMB?	⊗ Yes

Definition of Serious Adverse Events
An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
- death
- a life-threatening adverse even
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The study sponsor will be responsible for notifying Health Canada of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

Relationship to the study agent
For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

• Definitely Related - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

• Probably Related - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

• Possibly Related - There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

• Unlikely to be related - A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

• Not Related - The AE is completely independent of study drug administration, and/or evidence exists that

is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Analgesia Post-D50

0 - 24 hrs (POD1)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ No
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ Yes
Total Ibuprofen PO (mg)	1600
Tramacet PO (mg)	⊗ Yes
Total Tramacet PO (mg)	200
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ Yes
Total Gabapentin PO (mg)	600

Analgesia Post-D50

24 - 48 hrs (POD2)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ No
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ Yes
Total Ibuprofen PO (mg)	1600
Tramacet PO (mg)	⊗ Yes
Total Tramacet PO (mg)	150
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ Yes
Total Gabapentin PO (mg)	600

Patient Information

Patient ID	7
Age (years)	81
Gender	⊗ Female
Height (m)	1.68
Weight (kg)	59
BMI	20.904195011337873

Patient Comorbidities (CCI)

Comorbidities	
Comorbidity (Choose all that are present)	☒ Peripheral vascular disease (+1) ☒ Cerebrovascular disease (except hemiplegia) (+1) ☒ Solid tumor (non metastatic) (+2)
Age	⊗ 80 - 89 (+4)
Total points:	8
Additional Comorbidities	☒ Ex-Smoker (quit >1 month ago) ☒ Stroke
Patient on Home O2?	⊗ No

Admission

Admission Information	
Admission Date	
Surgeon	⊗ Surgeon B
Diagnosis Group	⊗ Cancer
Diagnosis	⊗ Lung Cancer
Pre-Op Therapy	⊗ None (within last 3 months)
PFTs	
FEV1% Pre	112
FEV1 Actual Pre (L)	2.37
pO2 (mmHg)	80
pCO2 (mmHg)	38
Surgical Information	
Surgery Date	
Emergency Case	⊗ No
Side	⊗ Right
Chest Incision	⊗ Thoracotomy
Primary Surgery	⊗ Lobectomy
Lobe	☒ RUL
Number of Chest Tubes?	2
ASA	⊗ 4
Air leak pre-op?	⊗ No
Procedure Start	
Procedure Stop	

Total Surgery Time (minutes)	198 (Total Time in Surgery)
Surgery Comments	Epidural discontinued prior to glucose administration
Date of Discharge	

Intervention

Intervention	
Date and Time of Administration	
Volume of D50 (mL)	⊗ 150 (ml)
Gucose	
Fasting Blood Glucose	6.2
POC Glucose pre-D50	6.7
POC Glucose 1 hr post-D50	14.9
POC Glucose 3 hrs post-D50	10.2
POC Glucose 6 hrs post-D50	10.8
POC Glucose 24 hrs post-D50	8.2
Pain	
Pain level pre-D50 (/10)	2
Pain level 1 hr post-D50 (/10)	2.0
Pain level 3 hrs post-D50 (/10)	4.0
Pain level 6 hrs post-D50 (/10)	7.0
Pain level 24 hrs post-D50 (/10)	4.0
Air Leak	
Air Leak Rate pre-D50 (mL/min)	490
Air leak 24 hrs post-D50?	⊗ No
Air leak 48 hrs post-D50?	⊗ No
Air leak 72 hrs post-D50?	⊗ No
O2 Requirements	
O2 Requirements Pre-D50 (L/min)	0.0
O2 Requirements 1 hr post-D50 (L/min)	0.0

O2 Requirements 3 hrs post-D50 (L/min)	0.0
O2 Requirements 6 hrs post-D50 (L/min)	0.0
O2 Requirements 24 hrs post-D50 (L/min)	0.0
O2 Requirements 48 hrs post-D50 (L/min)	0.0
O2 Requirements 72 hrs post-D50 (L/min)	0.0
Total Chest Tube Output during 24 hrs post-D50 (mL)	775
Hyperglycemia	
Hyperglycemia requiring any additional treatment?	⊗ No
At Discharge	
Insertion of Another Chest Tube post-D50?	⊗ Yes
Discharged on Home O2?	⊗ No
Date and Time of Chest Tube Removal	
Discharged with a Heimlich valve?	⊗ No
14 Day Follow-up	
Readmission within 14 days of discharge?	⊗ No
Air leak recurrence within 14 days of discharge (if applicable)?	⊗ No

Adverse Events

AE Reference Guide [Attachment: "2018-07-01 AE Reference Guide.pdf"]	
Adverse Events	
DSMB	
Additional notes (description of each adverse event for the DSMB to assess)	There were no adverse events
Any AE fits the definition of Serious Adverse Event?	⊗ No
Patient reviewed by the DSMB?	⊗ Yes

Definition of Serious Adverse Events
An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
- death
- a life-threatening adverse even
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The study sponsor will be responsible for notifying Health Canada of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

Relationship to the study agent
For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

• Definitely Related - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

• Probably Related - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

• Possibly Related - There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

• Unlikely to be related - A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

• Not Related - The AE is completely independent of study drug administration, and/or evidence exists that [illegible]

is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Analgesia Post-D50

0 - 24 hrs (POD1)	
Hydromorphone S/C (mg)	⊗ Yes
Total Hydromorphone S/C (mg)	1
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	2
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ Yes
Total Tramacet PO (mg)	50
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Analgesia Post-D50

24 - 48 hrs (POD2)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ No
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ Yes
Total Tramacet PO (mg)	150
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Analgesia Post-D50

48 - 72 hrs (POD3)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ No
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ Yes
Total Tramacet PO (mg)	200
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Patient Information

Patient ID	8
Age (years)	72
Gender	⊗ Male
Height (m)	1.78
Weight (kg)	84
BMI	26.511804065143288

Patient Comorbidities (CCI)

Comorbidities	
Comorbidity (Choose all that are present)	☒ Solid tumor (non metastatic) (+2)
Age	⊗ 70 - 79 (+3)
Total points:	5
Patient on Home O2?	⊗ No

Admission

Admission Information	
Admission Date	
Surgeon	⊗ Surgeon B
Diagnosis Group	⊗ Probable Cancer
Diagnosis	⊗ Lung Nodule
Pre-Op Therapy	⊗ None (within last 3 months)
PFTs	
FEV1% Pre	125
FEV1 Actual Pre (L)	2.98
DLCO % Pre	125
pO2 (mmHg)	87
pCO2 (mmHg)	31
Surgical Information	
Surgery Date	
Emergency Case	⊗ No
Side	⊗ Right
Chest Incision	⊗ Thoracotomy
Primary Surgery	⊗ Wedge Resection
Lobe	☒ RUL
Number of Chest Tubes?	1
ASA	⊗ 4
Air leak pre-op?	⊗ No
Procedure Start	
Procedure Stop	

Total Surgery Time (minutes)	73 (Total Time in Surgery)
Date of Discharge	

Intervention

Intervention	
Date and Time of Administration	
Volume of D50 (mL)	⊗ 150 (ml)
Gucose	
POC Glucose pre-D50	7.8
POC Glucose 1 hr post-D50	9.2
POC Glucose 3 hrs post-D50	6.7
POC Glucose 6 hrs post-D50	6.5
POC Glucose 24 hrs post-D50	6.9
Pain	
Pain level pre-D50 (/10)	3
Pain level 1 hr post-D50 (/10)	3
Pain level 3 hrs post-D50 (/10)	3.0
Pain level 6 hrs post-D50 (/10)	2.0
Pain level 24 hrs post-D50 (/10)	3.0
Air Leak	
Air Leak Rate pre-D50 (mL/min)	310
Air leak 24 hrs post-D50?	⊗ No
Air leak 48 hrs post-D50?	⊗ Yes
Air Leak Rate 48 hrs post-D50 (mL/min)	140
Air leak 72 hrs post-D50?	⊗ Yes
Air Leak Rate 72 hrs post-D50 (mL/min)	150
O2 Requirements	
O2 Requirements Pre-D50 (L/min)	0.0

O2 Requirements 1 hr post-D50 (L/min)	0.0
O2 Requirements 3 hrs post-D50 (L/min)	0.0
O2 Requirements 6 hrs post-D50 (L/min)	0.0
O2 Requirements 24 hrs post-D50 (L/min)	0.0
O2 Requirements 48 hrs post-D50 (L/min)	0.0
O2 Requirements 72 hrs post-D50 (L/min)	0.0
Total Chest Tube Output during 24 hrs post-D50 (mL)	400
Hyperglycemia	
Hyperglycemia requiring any additional treatment?	⊗ No
At Discharge	
Insertion of Another Chest Tube post-D50?	⊗ No
Discharged on Home O2?	⊗ No
Date and Time of Chest Tube Removal	
Discharged with a Heimlich valve?	⊗ Yes
14 Day Follow-up	
Readmission within 14 days of discharge?	⊗ No
Air leak recurrence within 14 days of discharge (if applicable)?	⊗ N/A

Adverse Events

AE Reference Guide [Attachment: "2018-07-01 AE Reference Guide.pdf"]	
Adverse Events	
DSMB	
Additional notes (description of each adverse event for the DSMB to assess)	Patient tripped on chest tube, and it came apart. The air leak was down to 10 mL/min. After the chest tube was reconnected, air leak became 170 mL/min.
Any AE fits the definition of Serious Adverse Event?	⊗ No
Patient reviewed by the DSMB?	⊗ Yes

Definition of Serious Adverse Events
An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
- death
- a life-threatening adverse even
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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Relationship to the study agent
For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

• Definitely Related - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

• Probably Related - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

• Possibly Related - There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

• Unlikely to be related - A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

• Not Related - The AE is completely independent of study drug administration, and/or evidence exists that the AE is [illegible]

is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Analgesia Post-D50

0 - 24 hrs (POD1)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	10
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Analgesia Post-D50

24 - 48 hrs (POD2)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	8
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Analgesia Post-D50

48 - 72 hrs (POD3)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	10
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Patient Information

Patient ID	9
Age (years)	69
Gender	⊗ Female
Height (m)	1.70
Weight (kg)	64.7
BMI	22.387543252595158

Patient Comorbidities (CCI)

Comorbidities	
Comorbidity (Choose all that are present)	☒ Chronic pulmonary disease (+1) ☒ Solid tumor (non metastatic) (+2)
Age	⊗ 60 - 69 (+2)
Total points:	5
Additional Comorbidities	☒ Ex-Smoker (quit >1 month ago)
Patient on Home O2?	⊗ No

Admission

Admission Information	
Admission Date	
Surgeon	⊗ Surgeon C
Diagnosis Group	⊗ Cancer
Diagnosis	⊗ Lung Nodule
PFTs	
FEV1% Pre	73
FEV1 Actual Pre (L)	1.74
DLCO % Pre	49
pO2 (mmHg)	68
pCO2 (mmHg)	37
Surgical Information	
Surgery Date	
Emergency Case	⊗ No
Side	⊗ Right
Chest Incision	⊗ Thoracotomy
Primary Surgery	⊗ Wedge Resection
Lobe	☒ RLL
Number of Chest Tubes?	2
ASA	⊗ 4
Air leak pre-op?	⊗ No
Procedure Start	
Procedure Stop	
Total Surgery Time (minutes)	115 (Total Time in Surgery)

Date of Discharge

Intervention

Intervention	
Date and Time of Administration	
Volume of D50 (mL)	⊗ 150 (ml)
Gucose	
Fasting Blood Glucose	6.4
POC Glucose pre-D50	6.1
POC Glucose 1 hr post-D50	11.4
POC Glucose 3 hrs post-D50	7.0
POC Glucose 6 hrs post-D50	7.7
POC Glucose 24 hrs post-D50	6.7
Pain	
Pain level pre-D50 (/10)	7
Pain level 1 hr post-D50 (/10)	8
Pain level 3 hrs post-D50 (/10)	5.0
Pain level 6 hrs post-D50 (/10)	4.0
Pain level 24 hrs post-D50 (/10)	6
Air Leak	
Air Leak Rate pre-D50 (mL/min)	590
Air leak 24 hrs post-D50?	⊗ No
Air leak 48 hrs post-D50?	⊗ No
Air leak 72 hrs post-D50?	⊗ No
O2 Requirements	
O2 Requirements Pre-D50 (L/min)	1.0
O2 Requirements 1 hr post-D50 (L/min)	1.0

O2 Requirements 3 hrs post-D50 (L/min)	1.0
O2 Requirements 6 hrs post-D50 (L/min)	1.0
O2 Requirements 24 hrs post-D50 (L/min)	1.0
O2 Requirements 48 hrs post-D50 (L/min)	1.0
O2 Requirements 72 hrs post-D50 (L/min)	0.0
Total Chest Tube Output during 24 hrs post-D50 (mL)	200
Hyperglycemia	
Hyperglycemia requiring any additional treatment?	⊗ No
At Discharge	
Insertion of Another Chest Tube post-D50?	⊗ No
Discharged on Home O2?	⊗ No
Date and Time of Chest Tube Removal	
Discharged with a Heimlich valve?	⊗ Yes
14 Day Follow-up	
Readmission within 14 days of discharge?	⊗ No
Air leak recurrence within 14 days of discharge (if applicable)?	⊗ N/A

Adverse Events

AE Reference Guide [Attachment: "2018-07-01 AE Reference Guide.pdf"]	
Adverse Events	
DSMB	
Additional notes (description of each adverse event for the DSMB to assess)	No adverse events
Any AE fits the definition of Serious Adverse Event?	⊗ No
Patient reviewed by the DSMB?	⊗ Yes

Definition of Serious Adverse Events
An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
- death
- a life-threatening adverse even
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The study sponsor will be responsible for notifying Health Canada of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

Relationship to the study agent
For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

• Definitely Related - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

• Probably Related - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

• Possibly Related - There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

• Unlikely to be related - A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

• Not Related - The AE is completely independent of study drug administration, and/or evidence exists that the AE is [illegible]

is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Analgesia Post-D50

0 - 24 hrs (POD1)	
Hydromorphone S/C (mg)	⊗ Yes
Total Hydromorphone S/C (mg)	0.5
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	4
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ Yes
Total Ibuprofen PO (mg)	400
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Analgesia Post-D50

24 - 48 hrs (POD2)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	12
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ Yes
Total Ibuprofen PO (mg)	400
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Analgesia Post-D50

48 - 72 hrs (POD3)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	10
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Patient Information

Patient ID	10
Age (years)	69
Gender	⊗ Female
Height (m)	1.67
Weight (kg)	57.8
BMI	20.725017031804654

Patient Comorbidities (CCI)

Comorbidities	
Comorbidity (Choose all that are present)	☒ Solid tumor (non metastatic) (+2)
Age	⊗ 60 - 69 (+2)
Total points:	4
Additional Comorbidities	☒ Any Previous Cancer in Last 5 Years ☒ Hypercholesterolemia ☒ Ex-Smoker (quit >1 month ago)
Patient on Home O2?	⊗ No

Admission

Admission Information	
Admission Date	
Surgeon	⊗ Surgeon B
Diagnosis Group	⊗ Probable Cancer
Diagnosis	⊗ Lung Cancer Recurrence
Pre-Op Therapy	⊗ None (within last 3 months)
PFTs	
FEV1% Pre	77
FEV1 Actual Pre (L)	1.81
DLCO % Pre	54
Surgical Information	
Surgery Date	
Emergency Case	⊗ No
Side	⊗ Right
Chest Incision	⊗ Thoracotomy
Primary Surgery	⊗ Lobectomy
Lobe	☒ RUL
Number of Chest Tubes?	2
ASA	⊗ 3
Air leak pre-op?	⊗ No
Procedure Start	
Procedure Stop	
Total Surgery Time (minutes)	169 (Total Time in Surgery)

Date of Discharge

Intervention

Intervention	
Date and Time of Administration	
Volume of D50 (mL)	⊗ 200 (ml)
Gucose	
Fasting Blood Glucose	5.5
POC Glucose pre-D50	6.4
Pain	
Pain level pre-D50 (/10)	5
Pain level 1 hr post-D50 (/10)	5
Pain level 3 hrs post-D50 (/10)	2.0
Pain level 6 hrs post-D50 (/10)	3
Pain level 24 hrs post-D50 (/10)	1
Air Leak	
Air Leak Rate pre-D50 (mL/min)	50
Air leak 24 hrs post-D50?	⊗ No
Air leak 48 hrs post-D50?	⊗ No
Air leak 72 hrs post-D50?	⊗ No
O2 Requirements	
O2 Requirements Pre-D50 (L/min)	2.0
O2 Requirements 1 hr post-D50 (L/min)	2.0
O2 Requirements 3 hrs post-D50 (L/min)	2.0
O2 Requirements 6 hrs post-D50 (L/min)	2.0
O2 Requirements 24 hrs post-D50 (L/min)	2.0
O2 Requirements 48 hrs post-D50 (L/min)	2.0

O2 Requirements 72 hrs post-D50 (L/min)	0.0
Total Chest Tube Output during 24 hrs post-D50 (mL)	100
Hyperglycemia	
Hyperglycemia requiring any additional treatment?	⊗ No
At Discharge	
Insertion of Another Chest Tube post-D50?	⊗ No
Discharged on Home O2?	⊗ No
Date and Time of Chest Tube Removal	
Discharged with a Heimlich valve?	⊗ No
14 Day Follow-up	
Readmission within 14 days of discharge?	⊗
Air leak recurrence within 14 days of discharge (if applicable)?	⊗

Adverse Events

AE Reference Guide

[Attachment: "2018-07-01 AE Reference Guide.pdf"]

Adverse Events

Other	
Misc	⊗ Chest wall pain
Grade	⊗ 3
Relationship	⊗ Definitely Related
DSMB	
Additional notes (description of each adverse event for the DSMB to assess)	Severe pain was noted during administration of the dextrose. Only 10 mL were administered, and then the patient expressed that the pain was up to 9/10. The pain resolved completely immediately after the tube was placed on suction and the glucose evacuated from the pleural space.
Any AE fits the definition of Serious Adverse Event?	⊗ No
Patient reviewed by the DSMB?	⊗ Yes

Definition of Serious Adverse Events
An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
- death
- a life-threatening adverse even
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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Relationship to the study agent
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• Definitely Related - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

• Probably Related - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

• Possibly Related - There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

• Unlikely to be related - A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

• Not Related - The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Analgesia Post-D50

0 - 24 hrs (POD1)	
Hydromorphone S/C (mg)	⊗ Yes
Total Hydromorphone S/C (mg)	1
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	4
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ Yes
Total Acetaminophen PO (mg)	650
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Analgesia Post-D50

24 - 48 hrs (POD2)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	6
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Analgesia Post-D50

48 - 72 hrs (POD3)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	2
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ Yes
Total Tramacet PO (mg)	100
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Patient Information

Patient ID	11
Age (years)	72
Gender	⊗ Female
Height (m)	1.59
Weight (kg)	85.6
BMI	33.859420117875075

Patient Comorbidities (CCI)

Comorbidities	
Comorbidity (Choose all that are present)	☒ Metastatic solid tumor (+6)
Age	⊗ 70 - 79 (+3)
Total points:	9
Additional Comorbidities	☒ Any Previous Cancer in Last 5 Years ☒ Hypertension ☒ Ex-Smoker (quit >1 month ago)
Patient on Home O2?	⊗ No

Admission

Admission Information	
Admission Date	
Surgeon	⊗ Surgeon C
Diagnosis Group	⊗ Probable Cancer
Diagnosis	⊗ Lung Metastases
Pre-Op Therapy	⊗ None (within last 3 months)
PFTs	
Surgical Information	
Surgery Date	
Emergency Case	⊗ No
Side	⊗ Right
Chest Incision	⊗ VATS
Primary Surgery	⊗ Wedge Resection
Lobe	☒ RML ☒ RLL
Number of Chest Tubes?	2
ASA	⊗ 4
Air leak pre-op?	⊗ No
Procedure Start	
Procedure Stop	
Total Surgery Time (minutes)	129 (Total Time in Surgery)
Date of Discharge	

Intervention

Intervention	
Date and Time of Administration	
Volume of D50 (mL)	⊗ 200 (ml)
Gucose	
Fasting Blood Glucose	5.4
POC Glucose pre-D50	6.0
POC Glucose 1 hr post-D50	6.1
POC Glucose 3 hrs post-D50	7.3
POC Glucose 6 hrs post-D50	7.0
Pain	
Pain level pre-D50 (/10)	6
Pain level 1 hr post-D50 (/10)	6
Pain level 3 hrs post-D50 (/10)	7.0
Pain level 6 hrs post-D50 (/10)	6.0
Pain level 24 hrs post-D50 (/10)	3.0
Air Leak	
Air Leak Rate pre-D50 (mL/min)	100
Air leak 24 hrs post-D50?	⊗ No
Air leak 48 hrs post-D50?	⊗ No
Air leak 72 hrs post-D50?	⊗ No
O2 Requirements	
O2 Requirements Pre-D50 (L/min)	1.0
O2 Requirements 1 hr post-D50 (L/min)	1.0
O2 Requirements 3 hrs post-D50 (L/min)	1.0

O2 Requirements 6 hrs post-D50 (L/min)	1.0
O2 Requirements 24 hrs post-D50 (L/min)	0.0
O2 Requirements 48 hrs post-D50 (L/min)	0.0
O2 Requirements 72 hrs post-D50 (L/min)	0.0
Total Chest Tube Output during 24 hrs post-D50 (mL)	125
Hyperglycemia	
Hyperglycemia requiring any additional treatment?	⊗ No
At Discharge	
Insertion of Another Chest Tube post-D50?	⊗ No
Discharged on Home O2?	⊗ No
Date and Time of Chest Tube Removal	
Discharged with a Heimlich valve?	⊗ No
14 Day Follow-up	
Readmission within 14 days of discharge?	⊗ No
Air leak recurrence within 14 days of discharge (if applicable)?	⊗ No

Adverse Events

AE Reference Guide

[Attachment: "2018-07-01 AE Reference Guide.pdf"]

Adverse Events

Other	
Misc	⊗ Cough
Grade	⊗ 1
Relationship	⊗ Definitely Related
DSMB	
Additional notes (description of each adverse event for the DSMB to assess)	Patient did experience mild to moderate cough after administration of an initial volume of 20 mL of hypertonic glucose. The investigator paused and resumed injection of another 15 mL when the administration was stopped completely for fear that too much of the hypertonic solution may enter the lung parenchyma. The patient was able to taste sugar in her mouth. The chest tube was kept above the patient for the usual 2 hours, and then placed back on the ground and on suction. She did well without any issue afterwards. This coughing episode lasted a few minutes.
Any AE fits the definition of Serious Adverse Event?	⊗ No
Patient reviewed by the DSMB?	⊗ Yes

Definition of Serious Adverse Events
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- death
- a life-threatening adverse even
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect.

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• Probably Related - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

• Possibly Related - There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

• Unlikely to be related - A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

• Not Related - The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Analgesia Post-D50

0 - 24 hrs (POD1)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	2
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ No
Tramacet PO (mg)	⊗ Yes
Total Tramacet PO (mg)	50
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Patient Information

Patient ID	12
Age (years)	62
Gender	⊗ Female
Height (m)	1.63
Weight (kg)	59.4
BMI	22.356882080620274

Patient Comorbidities (CCI)

Comorbidities	
Comorbidity (Choose all that are present)	☒ Solid tumor (non metastatic) (+2)
Age	⊗ 60 - 69 (+2)
Total points:	4
Additional Comorbidities	☒ Ex-Smoker (quit >1 month ago)
Patient on Home O2?	⊗ No

Admission

Admission Information	
Admission Date	
Surgeon	⊗ Surgeon B
Diagnosis Group	⊗ Probable Cancer
Diagnosis	⊗ Lung Cancer
Pre-Op Therapy	⊗ None (within last 3 months)
PFTs	
FEV1% Pre	76
FEV1 Actual Pre (L)	1.75
DLCO % Pre	66
Surgical Information	
Surgery Date	
Emergency Case	⊗ No
Side	⊗ Left
Chest Incision	⊗ Thoracotomy
Primary Surgery	⊗ Lobectomy
Lobe	☒ LUL
Number of Chest Tubes?	1
ASA	⊗ 3
Air leak pre-op?	⊗ No
Procedure Start	
Procedure Stop	
Total Surgery Time (minutes)	172 (Total Time in Surgery)

Date of Discharge

Intervention

Intervention	
Date and Time of Administration	
Volume of D50 (mL)	⊗ 200 (ml)
Gucose	
Fasting Blood Glucose	5.2
POC Glucose pre-D50	5.3
POC Glucose 1 hr post-D50	12.7
POC Glucose 3 hrs post-D50	8.0
POC Glucose 6 hrs post-D50	10.5
POC Glucose 24 hrs post-D50	7.5
Pain	
Pain level pre-D50 (/10)	2
Pain level 1 hr post-D50 (/10)	2
Pain level 3 hrs post-D50 (/10)	2.0
Pain level 6 hrs post-D50 (/10)	2.0
Pain level 24 hrs post-D50 (/10)	4.0
Air Leak	
Air Leak Rate pre-D50 (mL/min)	40
Air leak 24 hrs post-D50?	⊗ No
Air leak 48 hrs post-D50?	⊗ No
Air leak 72 hrs post-D50?	⊗ No
O2 Requirements	
O2 Requirements Pre-D50 (L/min)	2.0
O2 Requirements 1 hr post-D50 (L/min)	2.0

O2 Requirements 3 hrs post-D50 (L/min)	2.0
O2 Requirements 6 hrs post-D50 (L/min)	2.0
O2 Requirements 24 hrs post-D50 (L/min)	1.0
O2 Requirements 48 hrs post-D50 (L/min)	1.0
O2 Requirements 72 hrs post-D50 (L/min)	1.0
Total Chest Tube Output during 24 hrs post-D50 (mL)	725
Hyperglycemia	
Hyperglycemia requiring any additional treatment?	⊗ No
At Discharge	
Insertion of Another Chest Tube post-D50?	⊗ No
Discharged on Home O2?	⊗ No
Date and Time of Chest Tube Removal	
Discharged with a Heimlich valve?	⊗ No
14 Day Follow-up	
Readmission within 14 days of discharge?	⊗ No
Air leak recurrence within 14 days of discharge (if applicable)?	⊗ No

Adverse Events

AE Reference Guide

[Attachment: "2018-07-01 AE Reference Guide.pdf"]

Adverse Events

Cardiac	
Cardiovasc 1	⊗ Supraventricular Arrhythmia or A Fib
Grade	⊗ 2
Relationship	⊗ Unlikely to be Related
DSMB	
Any AE fits the definition of Serious Adverse Event?	⊗ No
Patient reviewed by the DSMB?	⊗ Yes

Definition of Serious Adverse Events
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- death
- a life-threatening adverse even
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The study sponsor will be responsible for notifying Health Canada of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

Relationship to the study agent
For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

• Definitely Related - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

• Probably Related - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

• Possibly Related - There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

• Unlikely to be related - A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

• Not Related - The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Analgesia Post-D50

0 - 24 hrs (POD1)	
Hydromorphone S/C (mg)	⊗ Yes
Total Hydromorphone S/C (mg)	1
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	4
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ Yes
Total Ibuprofen PO (mg)	800
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ No

Analgesia Post-D50

24 - 48 hrs (POD2)	
Hydromorphone S/C (mg)	⊗ No
Hydromorphone PO (mg)	⊗ Yes
Total Hydromorphone PO (mg)	12
Hydromorphone IV (mg)	⊗ No
Tylenol 3 (tabs)	⊗ No
Codeine PO (mg)	⊗ No
Acetaminophen PO (mg)	⊗ No
Ibuprofen PO (mg)	⊗ Yes
Total Ibuprofen PO (mg)	400
Tramacet PO (mg)	⊗ No
Fentanyl IV (mg)	⊗ No
Oxycodone PO (mg)	⊗ No
Naprosyn PO (mg)	⊗ No
Ketorolac PO (mg)	⊗ No
Ketorolac IV (mg)	⊗ No
Gabapentin PO (mg)	⊗ Yes
Total Gabapentin PO (mg)	400

Appendix L

Example of RStudio code used to create the segmented regressions/interrupted time series (p-value associated with the immediate impact of D50 is circled in red)

Patient #6:

```
##pt 6 ITS all data points
read.csv("test pt 6 ITS.csv")
dat6 <- read.csv("test pt 6 ITS.csv")
library(arm)
library(dplyr)
results <- lm(air.leak.flow ~ hourspostop + D50 + hourspostD50, data=dat6)
summary(results)
mypar(1,1)
ggplot(dat6, aes(x = hourspostop, y = air.leak.flow)) +
  geom_point(data = subset(dat6, hourspostop < 46.35), size=2, color ="#5f9be3") +
  geom_point(data = subset(dat6, hourspostop >= 46.35), size=2, color ="#c43541") +
  geom_smooth(data = subset(dat6, hourspostop < 46.35), method="lm", se=T, color="#5f9be3") +
  geom_smooth(data = subset(dat6, hourspostop >= 46.35), method="lm", se=T, color="#c43541") +
  theme_bw() + labs(colour="") +
  geom_vline(xintercept = 46.35, linetype="dashed") +
  labs(title = "Impact of D50 on the air leak rate all data points",
       subtitle = "Patient #6" ,
       y = "Air leak rate (mL/min)", x= "Hours post-op") +
  coord_fixed(ratio = .15) +
  theme(plot.caption = element_text(lineheight=.5)) +
  scale_x_continuous(limit = c(0,90)) +
  scale_y_continuous(limit = c(-50, 450))
```

```
Call:
lm(formula = air.leak.flow ~ hourspostop + D50 + hourspostD50,
    data = dat6)

Residuals:
     Min       1Q   Median       3Q      Max
-121.106  -15.543    1.107   12.857  186.489

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  405.3703    21.7630  18.627  < 2e-16 ***
hourspostop   -9.3528     0.9041 -10.345 1.32e-12 ***
D50           34.8765    35.8092   0.974    0.336
hourspostD50   8.9521     1.3677   6.545 1.02e-07 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 56.77 on 38 degrees of freedom
  (11 observations deleted due to missingness)
Multiple R-squared:  0.8599,    Adjusted R-squared:  0.8488
F-statistic: 77.75 on 3 and 38 DF,  p-value: 2.825e-16
```

Patient #7

```
##pt 7 ITS
read.csv("test pt 7 ITS.csv")
dat7 <- read.csv("test pt 7 ITS.csv")
dat7before80 <- filter(dat7, hourspostop<=80)
library(arm)
library(dplyr)
results <- lm(air.leak.flow ~ hourspostop + D50 + hourspostD50, data=dat7before80)
summary(results)
mypar(1,1)
ggplot(dat7before80, aes(x = hourspostop, y = air.leak.flow)) +
  geom_point(data = subset(dat7before80, hourspostop < 46.6), size=2, color ="#5f9be3") +
  geom_point(data = subset(dat7before80, hourspostop >= 46.6), size=2, color ="#c43541") +
  geom_smooth(data = subset(dat7before80, hourspostop < 46.6), method="lm", se=T, color="#5f9be3") +
  geom_smooth(data = subset(dat7before80, hourspostop >= 46.6), method="lm", se=T, color="#c43541") +
  theme_bw() + labs(colour="") +
  geom_vline(xintercept = 46.6, linetype="dashed") +
  labs(title = "Impact of D50 on the air leak rate",
       subtitle = "Patient #7" ,
       y = "Air leak rate (mL/min)", x= "Hours post-op") +
  coord_fixed(ratio = .06) +
  theme(plot.caption = element_text(lineheight=.5)) +
  scale_x_continuous(limit = c(18,80))
```

```
Call:
lm(formula = air.leak.flow ~ hourspostop + D50 + hourspostD50,
    data = dat7before80)

Residuals:
    Min      1Q  Median      3Q     Max
-343.77  -17.78    3.46   25.34  257.34

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)   545.9968    98.8869   5.521 6.68e-06 ***
hourspostop    -2.2532     3.0726  -0.733    0.469
D50          -387.3805    67.0660  -5.776 3.35e-06 ***
hourspostD50    0.7539     3.9840   0.189    0.851
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 95.45 on 28 degrees of freedom
  (15 observations deleted due to missingness)
Multiple R-squared:  0.8602,    Adjusted R-squared:  0.8453
F-statistic: 57.45 on 3 and 28 DF,  p-value: 4.383e-12
```

Appendix M

The terms (Glucose OR dextrose OR Glucose Solution, Hypertonic) AND (Pleurodesis OR pneumothorax OR pneumothoraces) were used on PubMed, Google Scholar and SCOPUS. Cochrane database was searched for the term “Pleurodesis” (all text). Web of Science database was searched using “ALL=((Glucose OR dextrose) AND (Pleurodesis OR pneumothorax OR pneumothoraces))” as search strategy. There was no restriction on publication date range. Mr. David Le Sauvage, librarian at Western University, assisted with this search strategy. Two authors (M Qiabi, A Ednie) worked independently and screened available studies. The references of all relevant studies were manually assessed to avoid missing any available paper.

Schulich School of Medicine & Dentistry
Professional Curriculum Vitae
DECEMBER 24, 2020
2016 JANUARY - 2020 DECEMBER

DR. MEHDI QIABI

MD, FRCSC

Assistant Professor - Department of Surgery
Assistant Professor - Department of Oncology

PERSONAL SUMMARY

Name	Mehdi Qiabi
Languages	English, Understood, Spoken, Read, Written French, Understood, Spoken, Read, Written

EDUCATION AND QUALIFICATIONS

Degrees and Diplomas

2017 - 2019	Resident, Western University, Surgery, Thoracic Surgery, London, Ontario, Canada
2012 - 2017	Resident, Université de Sherbrooke, Chirurgie, Chirurgie générale, Sherbrooke, Quebec, Canada

Research Training

2019 - 2020	MSc in Surgery, Western University, Surgery, Pleurodesis Using hypertonic Glucose administration to treat post-operative air leaks following lung resection surgery (PLUG): Phase I trial. Supervisor: Dr. Richard Malthaner, London, Ontario, Canada

Specialized Training

2019	POEM / ESD training, The Foundation for Surgical Innovation & Education, Foregut Surgery, POEM / ESD training, Portland, Oregon, United States
2019	Interventional GI Endoscopy Advanced Course, IRCAD, Foregut Surgery, POEM / ESD training, Strasbourg, Bas-Rhin, France

APPOINTMENTS

Academic Appointments

2019 - present	Assistant Professor, Department of Surgery, Division of Thoracic Surgery, Schulich School of Medicine & Dentistry, The University of Western Ontario
2019 - present	Assistant Professor, Department of Oncology, Division of Surgical Oncology, Schulich School of Medicine & Dentistry, The University of Western Ontario

Clinical Appointments

2019 - present	Thoracic Surgeon, London Health Sciences Centre, Department of Surgery, Division of Thoracic Surgery

POSITIONS HELD & LEADERSHIP EXPERIENCE

Academic Positions

2020 - present	Program Director - Thoracic Surgery, Western University, Schulich School of Medicine & Dentistry, Surgery, London, Ontario, Canada
2019 - present	Surgery Clerkship Specialty Director - Thoracic Surgery, Western University, Schulich School of Medicine & Dentistry, Surgery, London, Ontario, Canada
2019 - present	Simulation Director - Thoracic Surgery, Western University, Schulich School of Medicine & Dentistry, Surgery, London, Ontario, Canada
2019 - 2020	Assistant Program Director - Thoracic Surgery, Western University, Schulich School of Medicine & Dentistry, Surgery, London, Ontario, Canada
2017 - present	Western Surgical Bootcamp instructor – Chest tube insertion
2017 - 2018	Chief resident – Thoracic Surgery, London Health Science Centre
2015 - 2016	Resident-representative of Fleurimont Hospital for General, Pediatric, Vascular and Thoracic Surgery

SERVICE AND ADMINISTRATION

Professional Affiliations and Activities

Professional Associations

2017 - 2030	Member, Canadian Association of Thoracic Surgeons
2017 - 2030	Member, Society of Thoracic Surgeons
2017 - 2030	Member, Royal College of Physician and Surgeons of Canada

RESEARCH AND SCHOLARLY ACTIVITIES

Research Endeavours

2020	Education strategies to teach chest tube insertion - A systematic review, What are the existing methods in literature for teaching chest tube insertion to the undergraduate and post-graduate medical learners and surgical residents
2019 - 2020	Pleurodesis using hypertonic glucose administration to treat post-operative air leaks following lung resection surgery - A systematic review, Systematic review on the intrapleural administration of hypertonic glucose to treat post-operative air leaks

Grants

Peer Reviewed

Active Grants

2020 Dec - 2021 Dec **Role:** Principal Investigator	**Title:** Extended Reality Applications in Surgical Education **Co-Investigators:** Ge Shi, Richard Malthaner, Michael Ott, Elvis Chen, Terry Peters **Funding Source:** Western University DoS Resident Research Grant
Principal Investigator: Mehdi Qiabi	
Grant Total: $5,000 **Industry Grant:** N	

Past Grants

2018 Dec - 2019 Nov **Role:** Co-Investigator	**Title:** Pleurodesis Using Glucose administration to treat post-operative air leaks following lung resection surgery (PLUG): Phase 1 and Phase 2 trials ($10,000) **Co-Investigators: Qiabi M**, Inculet R, Fortin D **Funding Source:** Western University DoS Internal Research Fund
Principal Investigator: Malthaner R	
Grant Total: $10,000 **Industry Grant:** N	

Other Professional Activities

Education - Graduate

2019 - 2020 Facilitator, Thoracic Surgery Crises Simulation, Western University, Research Project, In situ simulation sessions for Thoracic Surgery fellows, senior residents in Anesthesia and Cardiac Surgery and nurses, Collaborators: Dr Richard Malthaner

PUBLICATIONS

Peer Reviewed Publications

Journal Article

Published

1. Dwyer CD, **Qiabi M**, Fortin D, Inculet RI, Nichols AC, MacNeil SD, Malthaner R, Yoo J, Fung K. Idiopathic Subglottic Stenosis: An Institutional Review of Outcomes With a Multimodality Surgical Approach. Otolaryngol Head Neck Surg. Online ahead of print. 2020 Oct 13: 194599820966978, **Coauthor**, DOI: 10.1177/0194599820966978.

Submitted

1. McDonald A, **Qiabi M**, Leeper R, Fortin D, Inculet R, Malthaner R. Thoracic Surgery Crisis Simulation During the COVID-19 Pandemic. Canadian Journal of Surgery, 2020 Sep 25, **Coauthor**
2. Shi G, Calvin C, Taheri K, Aziz R, Lai M, Duan N, Rothman Z, Darras K, Schlachta C, Malthaner R, **Qiabi M**, Pennefather P, Krebs C, Blair G. Extended Reality Applications in Surgery. 2020 May 25, **Collaborator**
3. **Qiabi M**, Inculet R, DaSilva W, Bierer J, Malthaner A, Warner A, Fortin D, Malthaner R. Robotic-Assisted Giant Paraesophageal Hernia Repair Compared to Traditional Approaches. Annals of Thoracic Surgery, 2020 Feb 17, **Principal Author**
4. **Qiabi M**, Dwyer C, Yoo J, Fortin D, Malthaner R, Fung K, Inculet R. Resection of Upper Tracheal Stenoses With Laryngeal Mask Airway Ventilation: Long Term Results. Annals of Thoracic Surgery, 2019 Jul 15, **Principal Author**

Book Chapter / Review Article

Published

1. Butter A, Rieder S, **Qiabi M**, Fréchette É. Chapter 116, Congenital Diaphragmatic Malformations. Pearson's Thoracic and Esophageal Surgery. 4th edition.; 2020, **Coauthor**

ABSTRACTS

Abstracts Published

Peer Reviewed

Published

1. Alexandra McDonald. Thoracic surgery crisis simulation during the COVID-19 pandemic. Canadian Conference for the Advancement of Surgical Education: Abstracts. Can J Surg; 2020. p. S61-S78. **Coauthor**. DOI: 10.1503/cjs.021920

Abstracts Presented

1. **Qiabi M**, Hetu J, Comeau E. Prevalence of staging laparoscopy among eligible gastric cancer patients at the CHUS: 10 years experience. 2016, CHUS Surgical Department annual research day, Sherbrooke, Quebec, Canada, **Presenter**

Posters Presented

1. **Qiabi M**, Dwyer C, Yoo J, Fortin D, Malthaner RA, Fung K, Inculet RI. Subglottic and Cervical Tracheal Stenoses With Laryngeal Mask Airway Ventilation: Long Term Surgical Results. 2019, 55th Annual Meeting of the Society of Thoracic Surgeons (STS), San Diego, California, United States, **Presenter**

PRESENTATIONS

Conference Presentation

International

1. **Presenter**, Robotic-Assisted Giant Paraesophageal Hernia Repair Compared to Traditional Approaches. 56th Annual Meeting of the Society of Thoracic Surgeons (STS)s, Presenters: **Qiabi M**, Inculet R, DaSilva W, Bierer J, Malthaner A, Warner A, Fortin D, Malthaner R, 2020 Jan 28, New Orleans, Louisiana, United States, Scientific Presentation

TEACHING ACTIVITIES

Curriculum Development

Undergraduate

2019 - 2020 Medical and Educational Director, Thoracic Surgery Clerkship Virtual Curriculum created at the request of the Western Surgery Clerkship Director (Dr A Butter) in response to the Global Pandemic. Undergraduate, Thoracic Surgery Clerkship Virtual Curriculum, Western University, Schulich School of Medicine & Dentistry, Department of Surgery, Division of Thoracic Surgery, Hours: 40, London, Ontario, Canada

Postgraduate

2019 - 2020 Course Director, Development of a Thoracic Surgery Difficult Surgical Exposure Course (TS-DISEC) in collaboration with Dr Tyler Beveridge (Department of Anatomy & Cell Biology), inaugural session was held Feb 25, 2020. Postgraduate, TS-DISEC, Western University, Schulich School of Medicine & Dentistry, Department of Surgery, Division of Thoracic Surgery, Hours: 12, 2, London, Ontario, Canada

2019 - 2020 Medical and Educational Director, Renewed and revamped education curriculum for Thoracic Surgery fellows with updated monthly mock examinations. Postgraduate, Western Thoracic Surgery Fellowship renewed educational curriculum - practice written examinations, Western University, Schulich School of Medicine & Dentistry, Department of Surgery, Division of Thoracic Surgery, Hours: 60, 2, London, Ontario, Canada

OTHER ACTIVITIES

Areas of Interest

Clinical	Research	Teaching
Endoscopy	Image-guided therapies	Curriculum design
Minimally Invasive Surgery	Patient-oriented outcomes	Video-based assessments
Oncology	Simulation in Thoracic Surgery	