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Rapid Rhino vs. Merocel: A retrospective analysis of patients with anterior epistaxis visiting emergency rooms in London, Ontario

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Abstract

When patients present to an emergency room (ER) with a nosebleed, one technique that physicians employ is the application of nasal packing. Merocel is a common nasal pack utilized in ER because of their low cost. Rapid Rhino is a nasal packing that is more comfortable for patients but is more costly than Merocel. Costing for epistaxis treatment is more than initial treatment costs and needs to consider rebleed rates. Using a retrospective cohort study design with covariates adjusted by propensity scores, we compared the costs associated with Merocel, and Rapid Rhino from the hospital and provincial healthcare perspectives. Merocel had a 26/62 (42%) total rebleed rate contrasted to Rapid Rhino's 4/17 (24%). For both the hospital and provincial perspectives, our sample did not provide evidence that there was difference in costs between Merocel and Rapid Rhino.

Keywords

Epistaxis, Rapid Rhino, Merocel, Nasal Pack, nosebleed, cost analysis, Ontario, Canada

Summary for Lay Audience

When epistaxis occurs, the bleed is often self-limited. However, in some cases the bleeding does not stop, and the patient requires additional medical intervention. Emergency room physicians will typically attempt further conservative management, like applying pressure to the nose and decongestion before consideration of invasive methods. Nasal packing is one option when these conservative methods fail. Merocel is a commonly utilized nasal pack in the ER as the direct material costs for these packs are relatively cheaper to other options. In comparison, other nasal packs like Rapid Rhino are more expensive but more comfortable for patients.

However, costs associated with nasal packing are more than just direct material costs. A major contributor to costs is rebleeds. If patients experience a greater rate of rebleed using one pack, they return to the ER again incurring additional costs. Unfortunately, there are few studies comparing rebleed rates of Merocel to Rapid Rhino directly, and even fewer cost-analysis that include rebleed rates for both nasal packs.

A retrospective review of medical charts for adult anterior epistaxis patients during the year 2018 presenting at University and Victoria hospital ERs was conducted. Patients were followed-up for two weeks to assess rebleed rates. Total costs were assessed using both inverse probability weight and covariate balancing propensity score weighting for the hospital and provincial health care perspectives.

The sample size for Rapid Rhino was 17, while the Merocel sample size was 62. Our total rate of rebleeds in Merocel was 42% (26/62) compared to 24% (4/17) in Rapid Rhino. Patients receiving Rapid Rhino have statistically non-significant difference in costs per patient ($61.61, 95% CI: -$127.84 to $251.05) for the hospital perspective as well as the provincial health care perspective ($78.14, 95% CI: -$89.54 to $245.83). Our sample did not suggest differences in costs for using Merocel and Rapid Rhino in treatment of epistaxis in the emergency room.

Co-Authorship Statement

This work was a collaborative effort of a team. Dr. Sowerby reviewed patients' electronic charts if further information was required for certain patients, provided consultation during the ethics approval process as well as during analyses of results. Dr. Sisira Sarma and Dr. Guangyong Zou provided consultation on categorizing and analyzing case-costing for patients. Various Lawson staff members helped with compiling a list of epistaxis patients presenting to the ER and provided details about case-costing for patient visits. Dhatri Shukla, was the principal contributor who wrote out the research proposal for ethics approval, retrieved patient information from their medical charts, coded information onto a database, calculated costs for patients and analyzed the results.

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List of Abbreviations

ATE	Average Treatment Effect
ATET	Average Treatment Effect on the Treated
BIPP	Bismuth Iodoform Paraffin Paste
CBPS	Covariate Balancing Propensity Score
CHF	Cardiac Heart Failure
COPD	Chronic Obstructive Pulmonary Diseases
CI	Confidence Interval
ENT	Ear, Nose, Throat
ER	Emergency Room
GLM	Generalized Linear Model
ICER	Incremental Cost-Effectiveness Ratio
IPWRA	Inverse Probability Weighted Regression Adjustment
IPTW	Inverse Probability of Treatment Weighting
IQR	Interquartile Range
LHSC	London Health Science Center
OHIP	Ontario Health Insurance Plan
QALY	Quality Adjusted Life-Year
RCT	Randomized Clinical Trial
REDCap	Research Electronic Data Capture
SMD	Standardized Mean Difference

Chapter 1

1 Introduction

1.1 Epistaxis

Epistaxis occurs when small vessels within the nasal cavity rupture. Evidence suggests that approximately 60% of the population experiences epistaxis at least once in their lifetime.[1] There are two types of epistaxis: posterior and anterior. Posterior epistaxis occurs when bleeding is located at the back of the nasal cavity. This form of epistaxis is rare, but often more serious and requires immediate medical attention.[2] Comparatively, anterior epistaxis occurs along the nasal septum at the front of the nose. Fortunately, anterior epistaxis comprises the majority of cases for both children and adults. Nasal trauma and mucosal dehydration are the most common causes of anterior epistaxis. In adults, hypertension and anticoagulation can also increase risk of epistaxis.[3]

In the United States, 6% of the population sees a healthcare professional for epistaxis in their lifetime; of these, about 90% are anterior epistaxis.[1] Application of pressure for 15 - 20 minutes is recommended prior to seeking medical attention.[4] There are exceptions to this rule: if excessive bleeding or light-headedness occurs, patients are recommended to seek medical help immediately.[4] Although no step-by-step procedure for stopping anterior epistaxis in the emergency room (ER) exists, there are many permutations and nuances to effective management. Each case is different and may require a combination of interventions. Certain interventions are also more comfortable for patients and easier to perform for physicians. These interventions have different costs and effectiveness associated with them.

1.2 Risk Factors

Risk factors such as hypertension and use of anticoagulants are known to be associated with higher risks of refractory anterior epistaxis. A recent meta-analysis and systematic review found an association between hypertension and epistaxis. Min *et al*. reported an odds ratio of 1.53 [95% CI: 1.18-1.99], indicating a significant increase in the risk of epistaxis for individuals with hypertension compared to a control group with no hypertension.[5] Similarly, a retrospective review compared the occurrence of epistaxis in 35,749 patients with hypertension to 35,749 patients without hypertension.[6] They concluded that hypertension was associated with an increased risk of epistaxis and more ER visits.[6] It is important to note that the current clinical guidelines highlight an association rather then a causal link between hypertension and epistaxis.[7]

Anticoagulants or blood-thinner medications reduce the risk of blood clotting in patients with atrial fibrillation but may increase the chance of epistaxis. Chaaban *et al*.[8] reviewed older patient's charts (>75 years of age) to determine the increase of patient visits to the ER for patients with a history of pulmonary embolism, atrial fibrillation, or a heart valve (defined as the "anticoagulant group"). In the "anticoagulant group", patients who also had congestive heart failure (CHF) and chronic obstructive pulmonary diseases (COPD) visited the ER more frequently for epistaxis ($p < 0.05$) compared to patients without these comorbidities.[8] However, the patients were not confirmed to have utilized anticoagulants and this increased rate in epistaxis seem to be attributed to CHF and COPD. A prospective study of 290 ER patients with epistaxis shows an association between anticoagulation use and epistaxis and demonstrates how patients on anticoagulants make up a large portion of in-patient ER admission rates.[9] In this study, 119 patients required an otolaryngologist to assess the patient, and 74 (62%) of those patients were on anticoagulants.[9]

Goljo *et al.* conducted a retrospective cross-sectional study in the United States using a national hospital inpatient sample assessed occurrence of epistaxis in 16,828 patients.[10] These patients had a mean age of 68 with 52% being male. In this study, out of the 16,828 patients that were admitted to a hospital with epistaxis as a diagnosis, approximately 3,494 (21%) of those patients were on long-term anticoagulants.[10] Furthermore, Newton *et al.*[11] conducted a retrospective study for anterior epistaxis in the ER using patient medical charts. Of the 353 patients, 49% were female and 51% male. In this study, 56% of these patients had hypertension and 61% were on an anticoagulant.[11] The majority of patients in this study ranged from 60-70 years of age.[11]

The use of certain anticoagulants appears to be associated with a higher risk of epistaxis.[12] For example, a recent retrospective cohort study included 2098 patients that received apixaban, 474 patients on dabigatran, 3106 patients on rivaroxaban, and 1403 patients receiving warfarin from 2014 to 2019.[12] They followed patients to assess risk of epistaxis and used inverse probability weighting to adjust for confounders. The confounders they included into this study were age, sex, hypertension, bleeding disorders and all the variables in the Charlson comorbidity index (except AIDS), prior history of venous thromboembolic events, prior gastrointestinal bleeding and epistaxis events requiring hospital admission, treatment indication, region of residence, and concomitant use of anti-histamines, antihypertensives, antiplatelets, corticosteroids, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, selective serotonin receptor inhibitors, and statins.[12] The study concluded that warfarin had higher rates of epistaxis compared to apixaban, dabigatran and rivaroxaban at the 5% significance level.[12]

A variety of comorbidities affect epistaxis management and costs. For example, there are recommendations in the literature for patients to stop smoking in order to lower their chances of epistaxis recurrence.[2] Furthermore, a prospective longitudinal study from March 2006 to March 2007 noted that out of the 54 patients discharged with nasal packing, 48% were smokers and 55% of patients with recurrence of epistaxis were also

smokers.[13] Some literature on clinical guidelines in managing epistaxis note that patients who abuse drugs or have blood clotting disorders tend to experience a higher rate of epistaxis.[1-2] Goljo *et al.* found that patients with alcohol abuse, sinonasal disease, renal disease had an increased length of stay in the hospital and higher costs associated with them.[10] Chaaban *et al.* also found that patients with congestive heart failure, diabetes mellitus, and obstructive sleep apnea had higher rates of recurrent ER epistaxis visits compared to patients without these comorbidities.[8]

1.3 Guidelines in Managing Epistaxis

Although there are general recommendations in the literature for treating epistaxis, there is no consensus on the exact steps to follow to stop an active nosebleed. The first recommendation is to apply pressure to the nose which indirectly compresses the anterior septum. Patients can apply pressure by themselves or use a nasal compression clip. The amount of time to apply pressure is not consistent between studies, but 10 minutes is often used based on coagulation physiology and consensus.[14,15] However, knowledge of epistaxis management in healthcare professionals can be relatively poor. One study found that less than 1/3 of ER physicians, nurses, and residents knew proper first-aid measures for epistaxis.[16] Simple education for patients regarding the appropriate first-aid measures for epistaxis have been shown to reduce re-visits to the ER by more than 50%.[17]

If bleeding continues, and an obvious source of active bleeding is visible, then cauterization is the second step. Topical silver nitrate is the most common type of cautery for anterior epistaxis, but electrocautery or thermal cautery can also be used. When silver nitrate encounters water (or blood), a chemical reaction occurs to form nitric acid and silver oxide. Nitric acid provides a chemical burn to the area of application, while silver ions obstruct any bleeding vessels.[18] After cauterizing the bleed, a gel is recommended to allow for the nose to heal.[19] Medications such as oxymetazoline, topical epinephrine, and

tranexamic acid can all be used in conjunction or as alternatives to cautery to stop epistaxis.[20-22]

If a health practitioner cannot visualise the area of the bleed or the patient is continuing to bleed after the above-mentioned methods have failed, they may consider packing the nose with dissolvable or non-dissolvable material.[7] It is estimated that around 20% of all epistaxis patients required nasal packing.[23] Two common non-dissolvable nasal packs include Merocel and Rapid Rhino.[24] Other non-dissolvable packs include Vaseline gauze, Epistat, Rhino Rockets, and Bismuth Iodoform Paraffin Paste (BIPP) gauze. Dissolvable packing material can also be used but acts more as a hemostatic matrix rather than applying tamponading pressure to the site of bleeding.[15] A popular dissolvable pack is Floseal which is a topical gelfoam and thrombin slurry. Much like with applying clamps or pressure, there is no standard wait time to stop the bleeding for nasal packs. Some of the literature recommend a 10-minute wait time while others state 10 to 30 minutes.[14,15,25] If successful, nasal packs are removed from the nose at home or at a follow-up visit in the ER 1-2 days after placement. However, if bleeding continues, the next step is to consult with an Otolaryngologist - Head and Neck Surgeon (also commonly known as ENT).[7] There are certain cases where nasal packing will not be sufficient to stop the bleed, and the patient may need surgery. Although these methods are outlined in the literature, healthcare practitioners may navigate through the algorithm in variable routes to control the bleed prior to referring to a specialist.

1.4 Nasal Packs

Historically, the original non-dissolvable nasal packing was Vaseline gauze. Gauze strips impregnated with Vaseline are layered into the nasal cavity to apply pressure to the site of bleeding. There is no expansile property to the gauze, and this frequently resulted in additional trauma to the nasal cavity. Over the last century, different types of nasal packs have been introduced that are much easier to insert/remove and are much more

comfortable for the patient. The best type of nasal packing is heavily debated in the literature. A myriad of different shapes, sizes and materials have been used for non-dissolvable nasal packs. Choosing the best nasal pack requires comparisons on efficacy, patient comfort and cost-effectiveness.

1.4.1 Rapid Rhino and Merocel

Merocel is a popular brand of non-dissolvable nasal pack made up of polyvinyl acetate. This pack is essentially a compressed sponge, which increases in size when inserted in the nose. The pressure of the expanded Merocel in the nose is used to stop a bleed and prevent the occurrence of a new rebleed. Merocel is one of the more popular nasal packs to utilize in hospitals. It is not only effective, but also relatively cheaper.

Rapid Rhino (non-dissolvable pack) is an inflatable balloon designed with self-lubricating properties and a carboxymethylcellulose covering for clot stabilization. It is available in four different sizes both with and without a breathing port for adults experiencing anterior epistaxis. The Rapid Rhino is a high volume and low-pressure combination that is designed to allow for more comfort for patients and to better contour to patient anatomy. A 2017 systematic review comparing 27 articles related to non-dissolvable nasal packing in both anterior and posterior epistaxis patients found Rapid Rhino to be the most comfortable for patients.[26]

1.5 Thesis Objective

While Rapid Rhino appears to be more comfortable for patients, Merocel is still used in many hospitals. One of the main reasons Merocel is a popular choice of nasal packing in the hospitals is because it costs less than Rapid Rhino. However, there are very few studies that examine the economic impact of nasal pack choice.[26] Other variables that add costs to hospital care and ER visits are often not thoroughly examined.

One important variable influencing the economic cost of nasal packing is rebleed rates. While the upfront costs of Merocel may be cheaper than Rapid Rhino it is difficult to conclude that Merocel is less costly compared to Rapid Rhino. Rebleeds cause patients to return to the ER more frequently which incurs costs for the hospital through costs for labour, costs for removing nasal packs and costs for preventing the new bleed. The current literature looking at rebleed rates for Merocel and Rapid Rhino tend to have a very small sample size and no clear follow-up times.[26-39] The small sample size makes it difficult to conclude which nasal pack is more effective in terms of preventing a bleed. There is some heterogeneity in follow-up times, these can range from management of initial bleed in the ER or up until three months after the initial bleed.[11,26-39] This makes it difficult to combine data from different studies to conduct a meta-analysis. There are only six studies that include both Merocel and Rapid Rhino. Four of these studies only measure initial management of a bleed or right after a scheduled removal of a nasal pack, and two studies do not state how many patients received Merocel vs. Rapid Rhino.[32,35-39] Based on limited data in the literature, Merocel tend to have a higher rate of rebleeds resulting in higher overall costs. Only one study compares Rapid Rhino and Merocel directly to each other in terms of costs, and this study focus on inpatient admission costs for epistaxis in Ireland.[32]

The primary objective of this study is to compare total costs of Merocel and Rapid Rhino in the ER setting using a two-week follow-up period. The hypothesis is that Rapid Rhino may have reduced total costs, due to a lower rate of rebleeds. Rapid Rhino is more comfortable for patients and has properties that help with clot stabilization. Both these factors should contribute to preventing patients returning to ER with a rebleed event.

To test our hypothesis a retrospective study was conducted for the year 2018 using adult patient medical charts from the emergency rooms in London Health Sciences Centre (LHSC) -- Victoria and University Hospitals in London, Ontario. Both hospitals currently utilize Merocel as their nasal pack of choice. In 2018, Rapid Rhino was under evaluation

at University Hospital for a trial period for the first six months of the year. Merocel was utilized in both University and Victoria hospitals year-round. Therefore, for the first six months at University hospital, physicians could choose between utilizing Merocel or Rapid Rhino. Costing analysis was undertaken from two perspectives: LHSC hospitals and provincial health care system. The hospital perspective captures the burden of paying for costs of hospital employees, material costs, costs for the overhead and costs related to upkeep for the hospital. One limitation of the hospital perspective is that it excludes physician billings, which are paid by the Ontario Ministry of Health. The provincial health care perspective captures costs incurred by hospitals and physician billing costs. A two-week follow-up was chosen as rebleeds outside of this timeframe are uncommon and would not be considered a failure of the initial management strategy; indeed, a recent study assessing rebleed rates for Merocel based in Ottawa, used a similar timeframe.[11] This analysis will contribute information to the hospital's management team on whether to change the nasal packs to Rapid Rhino. Even if there is no difference between the costs of Merocel and Rapid Rhino after accounting for the rebleed events, the hospital may still decide to switch to Rapid Rhino for an improved patient experience.

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Chapter 2

2 Literature Review

2.1 Epistaxis

Epistaxis is one of more frequent reasons behind otolaryngology emergencies.[1] When a patient presents to the ER with a nosebleed, physicians ideally attempt conservative management first. This includes, if the bleeding site can be visualized, silver nitrate to chemically cauterize the area of bleed.[2] Other interventions such as tranexamic acid, epinephrine can be used as either an alternative to silver nitrate or in conjunction with it to manage a bleed.[3-4] These interventions should be ideally attempted first but are not always before the more invasive method of nasal packing is considered. Nasal packs can be dissolvable, (e.g., Surgifoam, Surgicel, and Floseal) or non-dissolvable (e.g., BIPP packs, Rhino Rockets, Merocel or Rapid Rhino).[5] Merocel is popular in many hospitals due to their low cost when compared to other nasal packs. Rapid Rhino is a newer nasal pack that is designed to be more comfortable for patients, but it is also more expensive than Merocel. However, the overall costs associated with nasal packing is more than just the direct cost of the pack itself. Rebleeds increase patient visits to the ER, thereby incurring additional costs. Furthermore, when recommending a nasal pack, patient's comfort needs to be taken into consideration as well. To fully understand the impact of nasal packs, efficacy on preventing rebleeds, comfort level for patients when utilizing these nasal packs and its economic impact to be analyzed. A systematic review from 2017 concluded that Rapid Rhino appeared to be the most comfortable non-dissolvable nasal pack, yet Merocel is routinely used in hospitals due to its low price.[5] Therefore, the primary focus of the literature review will be to assess the current evidence on efficacy and costs of the two nasal packing materials: Rapid Rhino and Merocel.

2.1.1 Search Strategy

EMBASE and PubMed were used to search using the keywords ((epistaxis) AND (human)) AND (tampons) OR ((epistaxis) AND (hospital costs)) OR ((epistaxis) AND (emergency department)) to provide a comprehensive list of studies on Merocel and Rapid Rhino. Figure 2.1 describes the search strategy for these databases. References from these articles were searched for additional articles and google scholar was used to identify any missing articles.

The inclusion criteria were:

1) The nasal pack Rapid Rhino, Merocel or both must be part of the study
2) Adult anterior epistaxis patients should be included in the study
3) The study must measure one or a combination of the following.
    a. Patient's discomfort
    b. Rate of rebleeding
    c. Previous data on patients' discomfort or rebleed rates were used to conduct a cost-analysis.
4) Randomized and non-randomized studies were both included

The exclusion criteria were

1) The full text of the article cannot be found
2) If the language the text was written in was non-English
3) The paper was descriptive commentary only
4) The focus on the study was post-operative patients

This search was conducted from June 2021 to September 2021. Initially there were 1416 articles found, out of those 1395 articles were removed due to duplicates, and application of the inclusion/exclusion criteria to the abstracts. After 21 remained, and for 2 of these articles the full text could not be found. One article was a descriptive commentary from a textbook on the current state of epistaxis management. Five articles were excluded because on full-text review the patients had not received Rapid Rhino or Merocel or it

was unclear if any patients received either nasal pack. This left this review with thirteen articles. From these articles, the references were checked to find other relevant articles. Two articles were found from checking the references and two articles were found from searching google scholar citations. At the end there were seventeen articles available for the review. Since the literature review was conducted last year, this review was updated by searching PubMed and EMBASE on October 2022, using the same key words as the initial search, while restricting the dates of the articles published since the initial search. Google scholar was also utilized. Appendix A contains the breakdown of the updated search. From this review two new articles that met the criteria of this study have been published on the topic by October 2022, resulting in a total of 19 articles for review.

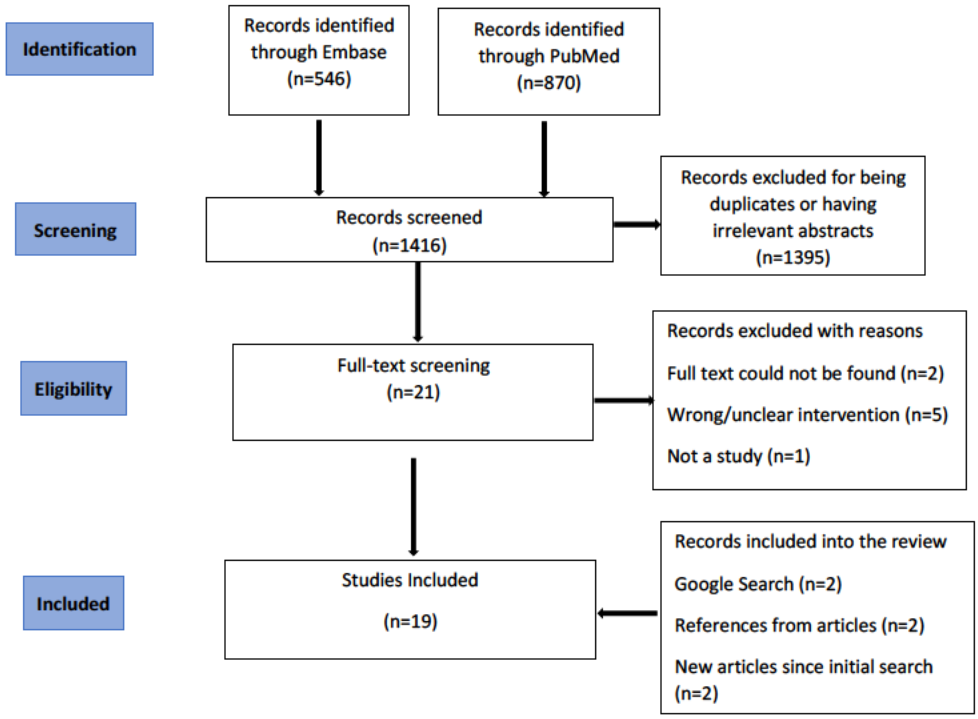

Figure 2.1: Literature Review inclusion and exclusion criteria

2.2 Rebleed Rates

2.2.1 Merocel

Van Wyk *et al.* conducted a retrospective review of a 2004 ER protocol implemented in ERs in the United Kingdom.[6] In this study, 62 patients were packed with Merocel initially. Out of these 62 patients, 16 (26%) required admission into the hospital during initial visits and 46 patients were discharged with Merocel inserted.[6] The study found that about 15% (7/46) of patients discharged with Merocel experienced a rebleed within 3 days after packing.[6] This study had no comparable interventions to Merocel. In Ottawa, Newton *et al.* conducted a retrospective review of medical charts from January 2012 to May 2014 in an ER at the Ottawa Hospital.[7] They were interested in evaluating patient rebleed rate within 2 weeks after discharge from the hospital.[7] Patients using Merocel had a 26% (24/92) rebleed rate. The comparison group in this study was silver nitrate, no treatment, other packing, "other" and nasal clips. Out of all these interventions only "other packing" may be comparable to Merocel, since nasal packing is generally utilized after no treatment, silver nitrate, "other" interventions and nasal clips have failed. The "other" packing group was most comprised of Vaseline with a mixture of other non-dissolvable nasal packs. Patients using "other nasal pack" had about a 42% (19/45) rebleed rate.[7] While there was no "control" group in this study silver nitrate was directly compared to Merocel. This resulted in the study concluding that silver nitrate had lower rates of rebleed with a odds ratio of 0.694 (95% CI: 0.364–1.322). This difference was significant with a p-value = 0.27.[7]

A retrospective review of hospital admissions in the UK in from March 1994 to March 1995 found that Merocel successfully controlled 92% (76/83) of bleeding during the initial visit.[8] However, this study did not have a comparison group or follow-up data to study rebleed events. Murray *et al.* conducted a randomized control trial from July 1, 2015 to July 1. 2017 at University of Alberta Hospital and Royal Alexandra Hospital. They focused on patients with persistent epistaxis and compared Floseal (a topical

gelfoam and thrombin slurry) to a control group comprising of Merocel and Vaseline gauze.[9] Floseal as mentioned before is a dissolvable packing material that acts more as a hemostatic matrix rather the applying tamponading pressure like Merocel. While they are both nasal packs, they are not exactly comparable. Persistent epistaxis was defined as the failure of a physician to manage previous epistaxis, but the patient had to have a failed management for longer than 48 hours.[9] This study only included patients that were not on anticoagulants (except for aspirin). Out of the 26 total participants, 13 were treated with Floseal and the 13 treated with the controls (Merocel and Vaseline gauze).[9] Out of the 13 patients in the control group 10 received Merocel, however, it is unclear how many of the rebleeds reported were in patients packed with Merocel.[9] Initially about 77% (10/13) of patients treated with Floseal and 85% (11/13) of patients treated with Merocel, or Vaseline gauze had a rebleed right after the treatment. There were 15% (2/13) of patients requiring admission into the hospital from the Floseal group, and 46% (6/13) of patients required admission in the Merocel and Vaseline gauze group.[9] For re-occurrence of bleeding at 48 hours, 77% (10/13) of patients treated with Floseal had a rebleed and 69% (9/13) of patients treated with Merocel and Vaseline gauze had a rebleed.[9] Finally there was a 15% (2/13) recurrence of rebleeds for the Floseal group and 46% (6/13) recurrence for the Merocel and Vaseline gauze group within 30 days after initial packing.[9]

The oldest randomized control trial measuring patient's rebleed rates for Merocel was conducted between March 1, 1994 to July 14, 1994 at Northwick Park Hospital in Middlesex, UK.[10] This trial compared Merocel to Bismuth subnitrate and Iodoform paste (BIPP).[10] There were 49 patients total and the authors counted each side as nasal cavity packed. There were 27 nasal cavities packed with Merocel and 28 nasal cavities packed with BIPP. Out of the 27 nasal cavities packed by Merocel, 25 (93%) were successfully controlled with nasal packs initially.[10] For BIPP, 24 were packed successfully out of the 28 (86%) nasal cavities.[10] Akkan *et al.* conducted a randomized control trial in one hospital ER from May to August 2018.[11] They had 3 treatment groups, tranexamic acid

with compression (TXA), nasal compression and Merocel packing.[11] There were 45 patients in each group. The study measured cessation of a bleed within 15 minutes of the intervention being used and any follow-up bleeds at 24 hours.[11] Merocel was successful in stopping about 93% (42/45) patients bleed within 15 minutes of application. After 24 hours Merocel was successful in preventing a rebleed for 73% (33/45) of patients.[11] Simply applying pressure and utilizing TXA cannot be compared to Merocel, as stated before Merocel is nasal pack and is therefore often used after initial inventions like pressure and TXA have failed. However, the authors reported the rate of rebleeds for patients that received TXA and nasal compression (summarized in Appendix B).

Mehanna *et al*. conducted a prospective study with a 24 hour-follow up after pack removal.[12] A total of 50 patients were included in the study, if they needed nasal packing and were admitted into the otolaryngology ward. Of these patients, 25 received Merocel, 17 received Vaseline gauze, 2 had BIPP inserted, and 6 packs were not recorded.[12] In this study, 10 patients had recurrent epistaxis after pack removal, but the study did not specify which nasal pack the patients had received before rebleeding.[12]

Abdelkhalek *et al.* conducted a prospective trial with patients that presented with epistaxis at the emergency or ENT departments of Al-Azhar university hospitals between April 2021 to January 2022.[13] They measured if bleeding was stopped initially and monitored patients weekly for 3 months for signs of rebleeds.[13] In this study 30 patients received Merocel and 30 patients received a Merocel/Surgical wrap. Initially 24/30 (80%) of the patients with Merocel alone did not rebleed. [13] In contrast, 29/30 (97%) of patients that received the Merocel/Surgical wrap successfully stopped their bleeding.[13] Within 3 months 22/30 (73%) of the patients in the Merocel group did not experience a rebleed, while 28/30 (93%) in the Merocel/Surgical wrap did not experience a rebleed.[13]

2.2.2 Rapid Rhino

Singer *et al.* conducted a randomized control trial that took place in one urban ER and one suburban ER in the US.[14] This trial compared Rhino Rockets (equivalent pack to Merocel, except with an introducer) to Rapid Rhino.[14] The patients returned for packing removal within 3-days, and any rebleeds during removal were noted.[14] If patients required another nasal pack to replace Rapid Rhino or Rhino Rocket during the initial or pack removal visit, this was considered a rebleed. Rapid Rhino had a 90% (18/20) success rate in initially stopping a bleed. Similarly, Rhino Rocket had a 90% (18/20) success rate initially. This left 18 patients in each group discharged with a nasal pack inserted. Out of 18 patients in each group whose bleed was initially controlled by the nasal packs, 1(6%) patient using Rapid Rhino experienced rebleed while 7(39%) patients using Rhino Rocket had bleeding on pack removal.[14]

Khan *et al.* compared the efficacy of different nasal packing on patients who had presented with epistaxis at the Department of Otolaryngology – Head and Neck Surgery, Freeman Hospital, Newcastle, UK.[15] The study included adult patients who had epistaxis on the year 2012 between November and December. Out of the 101 patients, 49 had anterior epistaxis.[15] Rapid Rhino and Floseal packs were used for secondary care, after conservative measures or other nasal packing had failed. In this study both Rapid Rhino and Floseal were successful in managing bleeding (100%).[15]

2.2.3 Merocel vs. Rapid Rhino

There are multiple studies that compare these two packs directly to each other. Badran *et al.* conducted a randomized control trial in ENT ER comparing Rapid Rhino and Merocel in terms of recurrence of bleeding in patients with anterior epistaxis from February 2002 until June 2002.[16] Patients were included into the study if they were 16 years and over and they had uncontrolled epistaxis after attempting cautery/ pressure for more than an hour.[16] This prospective trial had 52 patients which randomly allocated 26 patients in

each trial group.[16] However, data were lost for 1 person in each group resulting in Merocel and Rapid Rhino having 25 patients each. The study noted how many patients required repacking or were sent to surgery (theatre) during their initial visit after the first nasal pack failed. In this study, 6/25 (24%) of patients in the Rapid Rhino group had to be repacked or taken into the theatre, whereas 7/25 (28%) patients out in the Merocel group were repacked or taken into the theatre during their initial visit.[16] When the pack was in place and removed (24-72 hours later), the degree of bleeding was noted from a scale of 0 to 4. Where 0 indicated no bleeding and 4 indicating that the nasal tampon did not control the bleed.[16] For bleeding during pack insertion in the initial visit, Merocel had a score of 1.6 and Rapid Rhino had a score of 1.3.[16] After the pack was removed, Merocel had a score of 1.4 and Rapid Rhino had a score of 1.3.[16] These results indicate that there was slight bleeding during the initial and follow-up removal for both Rapid Rhino and Merocel.

Another prospective randomized control trial compared Rapid Rhino and Merocel in terms of success at controlling a bleed during the initial visit.[17] In this study, patients over 16 presenting with epistaxis over a two-year period at Otolaryngology Department at Addenbrooke's Hospital, Cambridge, UK were included.[17] In this study, 16/21(76%) patients were successfully treated with Rapid Rhino compared to 17/21 (81%) successfully treated with Merocel during their initial visit to the hospital.[17]

Lau *et al.* conducted a retrospective review where they included 90 patients who had nasal packing at University Hospital Aintree, UK between March 2007 and March 2012. They then checked medical charts to see which patients had recurrent bleeding at 72 hours.[18] From this, 8 patients who had Rapid Rhino returned with recurrent bleeding and 6 patients who had Merocel returned with recurrent bleeding.[18] The number of patients who received Rapid Rhino or Merocel were not clarified.[18] Khan *et al.* utilized Merocel, Rapid Rhino and Floseal in the initial treatment of anterior epistaxis.[15] In this study, one patient received Rapid Rhino and was treated successfully during the initial visit, one

patient received Floseal and required cautery afterwards, and only 3/13 (23%) of patients were successfully treated by Merocel.[15]

Iqbal *et al.* conducted a systematic review of the literature in 2017 on the efficacy of all dissolvable and non-dissolvable packs for both anterior and posterior epistaxis.[5] They found that Rapid Rhino and Merocel had the same rate of rebleeds, but these results included both anterior and posterior epistaxis patients pooled together.[5]

Keane *et al.* looked at the management of epistaxis in a single secondary referral center in Ireland from 2009 to 2012.[19] They had a total of 446 patients of which 434 were included in the study as they had spontaneous epistaxis. In the study about 83.4% of patients were managed by packing or cautery.[19] The study grouped patients that had cautery with patients that had packing. Patients were packed by Rapid Rhino, Merocel, Vaseline gauze, Floseal or BIPP.[19] The study noted that 34 patients came back with recurrent bleeding that had nasal packing, although the follow-up period is not clearly stated, the implied assumption was that the authors meant a recurrence over the 4-year study period.[19]

Lastly, Karia *et al.* conducted a prospective trial comparing patients that received Rapid Rhino or Merocel in the ER between March 2020 and March 2021.[20] They measured rebleeding at scheduled pack removal 1-2 days after initial visit to the ER. Out of the 56 patients that received Rapid Rhino, 6 had a rebleed (11%) during their pack removel.[20] Out of the 24 patients that received Merocel 1 (4%) had a rebleed during their pack removal.[20] The study found no-significant difference between Merocel and Rapid Rhino.

2.2.4 Summary

Overall, many of the studies assessing rebleed rates for Merocel and Rapid Rhino have different follow-up times. Some studies only measure the initial control of a bleed, and others measure a rebleed within 24 hours to 3 months. Due to this inconsistent follow-up

timeframe, it is difficult to assess the rate of rebleeds for a nasal pack. In terms of Merocel rebleed rates, the nasal pack had a lower rate when compared to BIPP and Vaseline gauze[7,10] Merocel had a higher rate of rebleed in contrast to Floseal during the initial visit, had a higher rate of patients admitted to the hospital and higher rate of bleeding at the 30-day mark.[9] This study had a small sample size, and Merocel was combined with Vaseline gauze so it is difficult to assess how many of the rebleeds came from patients packed with Merocel. Various studies had inappropriate or no comparator groups to Merocel, and did not state how many patients received Merocel or how many patients that received Merocel returned with a bleed.[6,8,11-12] Rapid Rhino has even fewer studies relating to anterior epistaxis and these studies have low sample sizes.[14-15] Rapid Rhino appears to have a similar rate of rebleed in contrast to Floseal and lower rates of rebleed compared to Rhino Rocket.[14-15] The study comparing Floseal to Rapid Rhino has a very small sample size.[15] When looking at studies comparing Rapid Rhino to Merocel directly, it appears that Rapid Rhino and Merocel have similar rates of rebleed during the initial visit or during scheduled packing removel.[16-17,20] Only two studies that included Rapid Rhino and Merocel had a follow-up period beyond cessation of initial bleeding (not including bleeding during scheduled follow-up packing removal visit) but these studies did not indicate how many patients received Merocel or Rapid Rhino.[18-19]

2.3 Comfort

2.3.1 Merocel

Corbridge *et al.* measured patients comfort level during insertion and removal of packs.[10] A 10-point visual analog scale was used to measure pain level for patients that had BIPP and Merocel packing. Patients that used BIPP had a decrease in patients' pain level by a score of 1.4 during insertion compared to patients that had Merocel.[10] As well, pain levels for Merocel during removal was on average rated a 3.5 compared to BIPP at 2.8.[10] Pringle *et al.* measured patients comfort level using Merocel along with rebleed rates.[8]

Out of the 83 patients packed with Merocel, 34 completed the 10-point visual analog scale questionnaire.[8] The mean scores for patients' comfort during insertion was 5.3, when the pack was in the patient's nose it was 2.9 and during removal it was 3.4.[8] Murray *et al*. measured patients' pain during insertion, duration of treatment and removal of the nasal tampon using a 10-point visual analog scale.[9] They compared Floseal to a "packing group" that contained Merocel/Vaseline gauze. For insertion, patients that received Floseal scored their pain at 2.4 to Merocel/Vaseline gauze 7.8.[9] During when the pack was in place, patients using Floseal scored their pain a 0.5 to Merocel/Vaseline 4.5. Finally, during removal patient's scored Merocel/Vaseline a 3.9 to Floseal 0.[9] The authors found a significant difference at the 5% level in the pain level for insertion, treatment, and removal felt between the experimental groups.[9]

Abdelkhalek *et al.* measured pain during insertion, for patients that received Merocel or Merocel/Surgical wrap. Patients were classified as experiencing "Mild", "Moderate" or "Severe" pain.[13] Chi-square analysis resulted in there being no difference between Merocel and Merocel/Surgical wrap at the 5% level for the number of patients classified under each category of pain.[13]

2.3.2 Rapid Rhino

Singer *et al*.[14] measured patient's discomfort level when the pack was inserted and removed using a visual analog scale from 1-100. Patients on insertion of Rhino Rocket felt on average a discomfort level of 48 (95% CI: 34 to 61).[14] In contrast patients on Rapid Rhino felt 30 (95% CI: 18 to 41) of pain on insertion.[14] During removal the pain for patients with Rhino Rocket was 23 (95% CI: 13 to 33) to Rapid Rhino's 11 (95% CI: 1 to 21).[14]

Hettige e*t al.* conducted a prospective trial in a clinic in the U.K where they recruited 15 adults to gauge their comfort level when using Rapid Rhino.[21] Out of the 15 adults, 3 dropped out of the trial, leaving 12 individuals in the study. Two Rapid Rhino were

inserted bilaterally, where one pack was attached to a manometer to gauge pressure.[21] The researchers randomly inflated one side, and then inflated the other. Patients' comfort was measured on a visual analog scale from 0 to 10 at different nasal pressure (the detailed results presented in the Appendix B). In summary, patients from 40 mmHg to 60 mmHg ranked their pain less than 2 on the scale for both unilateral and bilateral packing.[21] From 80mmHg to 100mmHg, patients rank their pain from 2.7 to 3.6.[21] While patients ranked their pain for 140mmHg to 160mmHg 4.1 to 5.0.[21] The researchers acknowledged that the measured pain levels from 140 mmHg to 160 mmHg may not be valid as Rapid Rhino is not meant to be used at these high-pressures.[21] Overall, from 40mmHg to 100mmHg patients tend to find Rapid Rhino tolerable.

2.3.3 Merocel vs. Rapid Rhino

Badran *et al*.[16] compared patients' pain level at insertion and removal for Rapid Rhino and Merocel using a 10-point visual analog scale. A significant difference ($p = 0.01$) was observed for insertion where patients rated Merocel a 6.9 and Rapid Rhino a 5.[16] Pain felt at removal was significant ($p = 0.05$) since patients rated Merocel a 4.6 and Rapid Rhino a 3.4.[16] Moumoulidis *et al*.[17] conducted a prospective randomized control trial which compared Merocel and Rapid Rhino in terms of comfort during insertion, course of treatment and removal using a 10-point visual analog scale. For pain during insertion, Rapid Rhino (3.9) outperformed Merocel (6.5) significantly ($p < 0.001$).[17] Pain felt during treatment was not significantly different between the two packs.[17] Finally for pain felt during removal, Merocel had a score of 5.0 and Rapid Rhino has a score of 2.5, a significant difference between the two packs ($p < 0.001$).[17] Iqbal *et al.*[5] in their systematic review found that Rapid Rhino was the most tolerable for patient comfort. However, they included posterior and anterior epistaxis and there are more studies in relation to posterior epistaxis and Rapid Rhino.

Karea *et al.* also measured patients comfort for Rapid Rhino and Merocel during insertion, while the nasal pack was inserted and at removal.[20] They utilized the Wong-Baker FACES pain test, a scale from 0 to 10, with 0 indicating no pain. Patients felt no significant difference in pain at the 5% level during insertion and while the pack was inserted.[20] However, during removal Rapid Rhino had a pain scale of 4.05 to Merocel 6.09 ($p=0.02$).[20]

2.3.4 Summary

Merocel appears to be less comfortable than other nasal packs.[9-10] Meanwhile, Rapid Rhino appears to be more comfortable to other nasal packs, including Merocel.[5,14,16-17,20] However, there were few studies that measured patient comfort and some studies had no comparators.[8,21] Studies measuring patient comfort often used a visual analog scale, which is a subjective indicator of pain level, and it is difficult to measure pain levels without bias. Measuring a patient's overall health related quality of life would be a more suitable outcome to assess. This is because improvement in the pain domain could affect other domains of the health-related quality of life. Moreover, if we wanted to conduct a cost-effectiveness analysis for nasal packs, we need to take into consideration how a patient's overall quality of life would change in response to different interventions for epistaxis management. However, with most studies using the same 10-point scale it allows for comparison between studies.

2.4 Cost Analysis

Limited literature exists on cost-effectiveness, or cost analysis of nasal packs. An economic evaluation compared Floseal to other types of packing for anterior epistaxis patients from the Canadian health care perspective.[22] This study concluded that Floseal was more cost-effective compared to other packings, including Merocel for patients with anterior epistaxis.[22] Patient costs were obtained from the Ottawa Hospital Data Warehouse and physician fees were gathered from the Ontario Schedule of Benefits for

Physician Services.[22] They utilized a Markov Model in this study, using the three transition rates of "well", "recurrent bleeding" and "dead." These transition probabilities were based on the results of Mathiasen and Cruz.[23] Mathiasen and Cruz conducted an RCT where there were 35 patients in the Floseal and 35 patients in the "control group".[23] The control group is composed of patients with any nasal packing depending on the physician's treatment, for example the physician could choose to use Merocel, Rhino Rocket, gauze or any other pack they deem appropriate.[23] Since Mathiasen and Cruz,[23] did not clarify what nasal packs were used in the control group, the efficacy of Floseal is difficult to quantify relative to another specific pack. Furthermore, health utilities for patients experiencing epistaxis were assumed to be the same as the general population in Canada.[22] However, patients experiencing epistaxis would most likely have a lower health utility than the average Canadian, as they are known to have comorbidities like hypertension and conditions requiring anticoagulation.[22]

A recent study by Nithianandan e*t al.* used Newton *et al.* retrospective review on anterior epistaxis patients to conduct a cost analysis. The analysis included direct costs and utilized the Ottawa Hospital Data Warehouse to determine patient costs, while accounting for any recurrence of bleeding into the costs.[24] The case-costing system within the Ottawa Hospital Data Warehouse provides estimated cost information on patients diagnosed with anterior epistaxis. Generalized linear models were utilized to analyze relationships between treatment and cost while adjusting for confounders.[24] Merocel incurred the highest median cost $763.98 (IQR: $632.25, $830.230).[24] The second highest was Vaseline gauze packing $723.12 (IQR:658.94, $810.84).[24] However, there was no significant difference between Merocel and Vaseline gauze ($p=0.90$).[24] The other treatments in this cost-analysis were a nasal clip, no treatment, other treatment (topical TXA or similar interventions) and silver nitrate. These interventions as described before are often used before Merocel, to stop bleeds and because of this they cannot be directly compared to Merocel. Moreover, Merocel was compared to Vaseline gauze in this study, and these two interventions can be compared in terms of the costs but based on other

factors such as ease of use, rebleed and discomfort would not have clinical equipoise for most clinicians. Furthermore, recurrence of a rebleed was defined as 14-days but the total costs in the Nithanandan *et al.* were based on a 30-day period after the patient's initial visit.[24] If after 14 days any bleed is considered a new bleed, then any costs after 14 days incurred by the patient cannot be attributed to the initial intervention.

Murray *et al*. conducted their own economic analysis based on their prospective randomized control trial.[9] They conducted this analysis using the societal perspective, but also included a separate analysis for the Alberta Health Services perspective. The initial costs of emergency rooms visit (included physicians costs) were excluded as they were assumed to be similar in both the Floseal and control group.[9] Costs for surgical fees, physician's fees, medical ward fees, outpatient fees, and nasal packing fees were included. Costs related to patient productivity loss from missed time at work were also calculated.[9] Costs were calculated up to 30-days after admission since in their trial they measured rebleeds up until a month after the initial visit.[9] ICERs were estimated (costs for rebleeds avoided), for both the hospital and societal perspectives.[9] For a single-payer system, Floseal was found to have a mean cost savings of about $1567.61 per patient and from the societal perspective, a mean cost-saving of about $2233.369 per patient.[9] This study had both anterior and posterior epistaxis patients included, so gauging costs for anterior epistaxis patients only is not possible.[9] They also had a mix of gauze and Merocel in their control group with only 13 patients total (10 Merocel, 3 gauze). However, it is not clear how many patients returned to the hospital with a bleed that received Merocel initially and patients requiring admission were the main reason why from the hospital perspective Floseal appeared to be cost-effective.[9] However, when looking at the 6 patients that required admission in the Merocel/Vaseline gauze group it appeared that 1 patient was admitted due to pneumonia and 1 patient required cardiac surgery. While, the study did not consider nasal packs as independent indications to admission, the surgical/medical ward costs associated with these 2 patients would be higher than regular patients.[9] Therefore, these patients could increase costs associated

with using Merocel/Vaseline gauze when in reality it was probably due to other underlying condictions.[9]

Keane *et al.* measured average length of stay for inpatients between 2009 to 2012.[19] They then took the average cost of overnight inpatient stays and calculated the average cost for overnight inpatient stay for each treatment.[19] Then they added the costs of the direct material related to each treatment to the costs for inpatient stay and calculated total cost. In the non-dissolvable nasal packs, Merocel was the cheapest at (€3593.99), then Rapid Rhino (€3613.83) and then BIPP packs (€3617.83).[19]

2.4.1 Summary

There are few cost analysis studies and cost-effectiveness analysis studies for epistaxis in the literature. The main issues with cost-effectiveness analysis studies are the availability of meaningful effectiveness data. The costs in most of the studies were often comprehensive, which include the cost of the initial treatment and any subsequent follow-up treatments, and hospital and overhead costs. On the other hand, the efficacy data were either missing or not meaningful for the purpose of cost-effectiveness analysis. The efficacy data were based on studies with information on recurrence of rebleeds, but it is better to capture this in costs rather than effectiveness. Although rebleeds are a valid way of gauging effectiveness of the initial treatment, patient quality of life is the most important element in a formal cost-effectiveness analysis. A few cost-analysis studies published in the literature focused on inpatient costs or have costs that are not meaningful for comparing nasal packs.[19, 24]

2.5 Gaps in the literature

Studies examining rebleed rates had a small sample size and recurrence of rebleeds seem not to be a common outcome. Usually, data are collected from different studies and

combined to conduct a meta-analysis. This is difficult for rebleed rates as the definition for recurrence of a bleed varies through the studies conducted. As seen in this review, the recurrence of a bleed can be measured at a range from initial management of a bleed to 3 months following discharge. Patients' bleeding might have occurred within hours of leaving the hospital up until the last day of the month depending on the study follow-up. Since rebleed rates are usually measured as dichotomous variables rather than time-to event, this creates more difficulty in assessing exactly where patients rebleeds occurred in between studies. This variability makes combining individual study data for a meta-analysis challenging. Currently there is no good quality study that assess the rebleed rate of Merocel and Rapid Rhino together with a follow-up period beyond the initial treatment of a bleed or during a scheduled pack removal. Only six studies included in this literature review assessed rebleeds for both Merocel and Rapid Rhino together.[15-20] Four of them did not have a follow-up period for assessing recurrence of bleeds excluding any bleeding during scheduled pack removal, and the other two did not calculate the number of patients packed with Rapid Rhino or Merocel when discharged.[15-20] There are few studies that conduct a cost analysis for anterior epistaxis, and there is only one study that compares Rapid Rhino to Merocel directly.[19] This study calculated costs associated with inpatient admissions.[19] Two studies that assessed costs associated with Merocel packs, grouped other nasal packs with Merocel, making it difficult to ascertain what costs are directly associated with Merocel.[9,22] Finally, one study from Ottawa assessed costs of only Merocel packs defined a recurrence of bleed to be within two-weeks but analyzed total costs for 30-days after the initial encounter.[24] Our study aims to fill this gap by assessing and comparing directly the rebleeds for both Merocel and Rapid Rhino using a two-week follow-up timeframe. Indeed, two weeks chosen due to an expert's opinion and two weeks have been previously used as a follow-up timeframe for epistaxis in a previous study based in Ottawa.[7] The costs incurred in the emergency room would be calculated, along with calculating physicians' costs to provide a hospital as well as provincial health system perspective.

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Chapter 3

3 Analysis of healthcare costs associated with Merocel or Rapid Rhino use

3.1 Introduction

Epistaxis can resolve by itself with time. However, some patients with epistaxis require an intervention by clinicians. Some of these interventions include directed therapy. An example of this would be cauterising a nosebleed with silver nitrate. Nasal packs, both dissolvable and non-dissolvable, usually are inserted into the nose to stop a bleed after failure of initial interventions like cautery via silver nitrate. They are then removed 24-48 hours afterwards. Non-dissolvable nasal packs include Rapid Rhino and Merocel. Merocel is a popular choice as it is less expensive relative to Rapid Rhino. Rapid Rhino is more expensive but is proving to be better for patient comfort.[1] Researchers have conducted various studies on the efficacy of Merocel or Rapid Rhino in stopping initial bleeding and in preventing rebleed visits.[2-6] However, these studies have inconsistent definitions for rebleeds, small sample sizes or the studies tend to group various nasal packs together making it difficult to assess the efficacy of Rapid Rhino compared to Merocel. Furthermore, the literature on costs associated with epistaxis interventions are limited to date. According to a 2017 systematic review on epistaxis management, there is no robust economic assessment on dissolvable and non-dissolvable packs.[1] Without data on costs, it is hard for studies to provide recommendations on interventions as both costs and efficacy need to be taken into consideration in evaluating treatment decisions in a healthcare setting. This is especially true in the Canadian context as there is a single-payer publicly funded health care system, and the objective is to maximize population health within constrained resources.

3.2 Methods

3.2.1 Study population

A list of patients presenting with epistaxis in the ER was generated from the administrative departments from both University and Victoria hospitals, containing every patient encounter over the calendar year 2018. This list also contained “ER time in” and “ER time out” for each patient in the emergency room. “ER time in” represented the time a patient had checked into the emergency room, and “ER time out” represented the time a patient had been discharged from the hospital.

Ethics approval was obtained to retrieve medical charts needed for this study. The corresponding HSREB number for this study is 119264. This included submitting an ethics application with a project proposal, data collection tools and details on information needed from these medical charts. A copy of the ethics application can be found in Appendix C. Furthermore, Standard Operating Procedures for Clinical Research and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans training needed to be completed. Hospital mandated trainings, including patient empathy training, safety training, COVID-19 Compliance with Infection Prevention & Control Practices were completed. Further training was required for REDCap (Research Electronic Data Capture) which is an electronic data capturing system hosted on the Lawson network.[7] REDCap is a secure, web-based software platform designed to support data capture for research studies.[7] After REDCap training was completed, a platform to host data from the medicals charts was created on the REDCap software and handed over to the ethics committee to approve.

After ethics approval was obtained, medical charts were pulled for each adult patient visiting the ER with epistaxis as the primary diagnosis between January 1, 2018, and December 31, 2018. To ensure further accuracy, the dates of patient encounters on the medical charts were cross-referenced with the dates on the generated patient lists, and the electronic patient record was reviewed to verify any missing data. Patients were included

into the study if; they were adults, had a primary diagnosis of anterior epistaxis, and received Merocel or Rapid Rhino between January 1,2018 and December 31, 2018.

Information on the type(s) of intervention(s) a patient received was retrieved from the medical charts. The patient's sex and age were also collected from their respective medical charts. Additional information, like patient's use of anticoagulant medication, and their use of an ambulance to arrive to the ER was also retrieved from the charts.

3.2.2 Variable Definitions

The explanatory variables in this study include sex, age, use of anticoagulant medications and the use of an ambulance for the initial ER visit. These variables were chosen from taking into consideration previous literature that indicated that these variables were potential risk factors for epistaxis incidence and rebleed events, and therefore could confound the relationship between the nasal pack and total costs.[8-10] The use of an ambulance was not a previously considered a risk factor in the literature, however, using an ambulance could indicate a more severe bleed which may incur more costs and was therefore included in this study. Sex was a dichotomous variable representing 0 for male and 1 for female. Similarly, data on anticoagulant medication and the use of an ambulance were binary variables representing 1 for presence and 0 for absence. Age and age-squared were continuous variables. Inclusion of age and age squared could help provide potential non-linear relationship between age of the patients and total cost.

The first time a patient was packed in the ER with Merocel or Rapid Rhino, this was included in the data set with 0 representing Merocel and 1 representing Rapid Rhino. This did not necessarily mean that this was the patients' first time coming into the ER for epistaxis treatment. Only 2 patients that received Merocel were repacked with Merocel after our two-week follow-up window. Therefore, to make the dataset cleaner these patients were included once. No patient that received Rapid Rhino had repacking with Rapid Rhino after two weeks.

3.2.3 Treatment Effectiveness

To gauge initial treatment effectiveness in managing epistaxis, rebleed events were calculated. A rebleed event was defined as the first rebleed that occurred within 14 days since a patient had been discharged from the hospital after s/he was packed or if an ENT was required to provide further intervention during the initial visit after the use of a nasal pack to manage the bleed. The follow-up period was chosen to be 2 weeks to be consistent with a previously published study in Ottawa as well as expert opinion.[11] For the expert's opinion we asked a specialist in epistaxis management about the appropriate timeframe they would consider a patient returning to the ER as a rebleed. While, remaining consistent with the literature should not be the only rationale behind the two-week follow-up period, measurement of rebleeds varies considerably in the literature.[1-6,11] Therefore, we reasoned that a combination of an expert's opinion, plus a previously published study in a similar setting would justify our 2-week follow-up in the absence of recommendations and inconsistency in the literature**.** After 2 weeks, any bleed was considered a new bleed and could not be attributed solely to the failure of the nasal pack used in the first ER visit.

As medical charts usually only note if an ENT was consulted, electronic notes were reviewed to understand what the ENT did if the ENT was consulted during the patient's initial visit. This was because at times the ENT is consulted but they provide no further intervention if the patient's bleed had stopped. Here, ENT consult fees would still apply but there is no rebleed, as the nasal pack inserted managed to stop the bleed with a tincture of time alone.

After, conferring with an expert, it was decided that representations for rebleeds should be measured as a dichotomous variable (0 for absence, 1 for presence), and costing information only included the first rebleed after the patient was discharged from the ER even if there were multiple bleeds within the two weeks. Multiple rebleeds are defined as

patients returning to the ER for more than 1 rebleed visit after their initial discharge due to rebleeding within the two-week follow-up period. This was due to the difficulty in allocating costs for subsequent interventions a patient would receive after multiple visits as being related to the initial intervention, rather than the subsequent packing or intervention chosen. From our expert's opinion, there are a small subset of patients that have multiple visits within days of the initial interventions regardless of what packing they received, or these patients come back to the ER for reassurance. In our study only 8 of the 62 patients in Merocel and 2 of the 17 patients in Rapid Rhino had multiple visits. As only a small subset will have multiple visits and including costs after the first rebleeds would result in including costs associated with other interventions, only the first rebleed after discharge was included. A sensitivity analysis excluding patients that had multiple bleeds was conducted to see if this affected the results. Another sensitivity analysis was conducted by excluding patients that were classified as a rebleed that required an ENT consult during their initial visit. Patients that require an ENT consult might have a more severe bleed, therefore it is important to see if excluding them will change the results. We also excluded patients that had missing packing removal visit after the initial visit to the ER to understand if this would affect our conclusions.

3.2.4 Cost Data

Cost analysis was conducted from two distinct perspectives: the hospital, and the provincial health care system. For both perspectives, costs were divided into initial visit and follow-up rebleed visit. The initial visit included the first ER visit for Merocel or Rapid Rhino packing. If the patients came back for packing removal this was also included in the initial visit encounter as these costs are associated with the initial packing intervention. Patients that were classified as a rebleed due to needing an ENT to manage their bleed during the first visit, were included under the initial visit as this happened during their initial visit. The first rebleed after discharge from the initial ER visit is

considered follow-up rebleed. If a patient was repacked when s/he experienced a rebleed and came back for packing removal this was included in the follow-up rebleed costing.

3.2.4.1 Hospital Perspective

For the hospital's perspective, costing data were obtained from the LHSC case-costing centre. The data obtained from the hospitals could be classified into direct and indirect costs from the hospital's perspective based on the Canadian Patient Costing Database.[12] The total cost is the sum of the direct and indirect costs (from the hospital's view). These costs include administrative costs, costs for utilities, cost for supplies, costs for materials used on patients, cost related to the building and costs related to the labour (with the exception for physician billing).[12]

3.2.4.2 Provincial Health Care Perspective

For the provincial health care perspective, all physician costs were added to the costs from the hospital perspective. This was because the province pays for the physician's time and any associated billings. An ER physician fee is difficult to calculate as often they are juggling multiple patients and do not spend the entire time a patient is in the ER with them. However, physician costs are an important aspect in determining costs associated with nasal packing. To include physician costs, we consulted an ER physician. The physician recommended using the "multiple systems assessment billing" found in the Schedule of benefits.[13] The multiple systems assessment billing is when an ER physician has to examine or take a patient's history for more than one part or system in their body.[13] From the ER physician experience, this billing is usually applied to epistaxis cases on a community center setting, and can be used to assess physician fees in the ER. The fee for multiple systems assessments changes depending on weekdays, evenings, nights, and weekends. The fee is applied when patients are checked into the hospital or in other words their "ER time-in". Table 3.1 presents the exact breakdown of the costs.

There was an additional cost component that need to be included in the provincial health care perspective: physician billings. This was because physicians could be eligible to submit billings for preforming any medical procedures that are needed for the patient and these procedures are billable under the Ontario Schedule of Benefits for Physicians.[13] The first instance of billing was if a physician must cauterise a bleed using silver nitrate. The second was if they must pack the nose. When a patient failed silver nitrate, and a pack was put in place, the physician is allowed to bill for both interventions.

Finally, if a consultation by an ENT was needed then additional billings were included. These billings are typically paid out to the physician by the Ministry of Health. After conferring with an ENT specialist, there were certain billings that were typically included for an ENT consult in the ER. ENT have a base-consult fee, and usually bill a "travel premium", and a "first person seen premium" when consulting patients in the ER. When an ENT specialist is consulted, they should be using a flexible endoscope to examine the patients' nasal cavities. This service has a "scoping fee" attached to it.

ENT consult fee = base consultation fee + scoping fee + travel fee + first person seen fee.

If an ENT needs to repack or re-cauterize a patient, they can charge the same billing fee for packing and cauterizing that ER physicians use to the Ministry. If they scope a patient, pack a patient, or cauterize a patient on what is considered "off-hours" provided in Table 3.2, they can apply a percentage increase from the regular billings (also reported in Table 3.2). Since, an ENT is consulted as a last resort, the patient "ER time-out" (discharge time) was used to assess which billing codes to use.

Table 3.1: Physician's fees in 2018

Fees	**Canadian Dollars**	**Billing Code**

Monday to Friday - Daytime (08:00h to 17:00h)	$35.65	H103
Monday to Friday - Evenings (17:00h to 24:00h)	$42.40	H133
Saturdays, Sundays and Holidays - Daytime and Evenings (08:00h to 24:00h)	$56.95	H153
Nights (00:00h to 08:00h)	$65.95	H123
Cauterization	$11.50	Z314
Packing	$15.35	Z315

Table 3.2: ENT Fees for the year 2018

	Fee	**Code**
Travel fee for Weekdays Daytime (07:00- 5pm)	$36.40	K960
First person seen fee for Weekdays Daytime (07:00- 5pm)	$20.00	K990
Travel fees for Evenings (17:00- 24:00) Monday through Friday	$36.40	K962
First person seen fees for Evenings (17:00- 24:00) Monday through Friday	$60.00	K994
Travel fees for Saturdays, Sundays and Holidays (07:00- 24:00)	$36.40	K963
First person seen fees for Saturdays, Sundays and Holidays (07:00- 24:00)	$75.00	K998
Travel fees for Nights (00:00- 07:00)	$36.40	K964
First person seen fees for Nights (00:00- 07:00)	$100.00	K996

ENT base consultation fee	$77.9	A245
Scoping fee for ENT	$19.2	E839
ENT procedural fee for evenings (17:00h – 24:00h) Monday to Friday or daytime and evenings on Saturdays, Sundays, Holidays	Increase by 50%	E409
ENT procedural fee for Nights (00:00h – 07:00h)	Increase by 75%	E410

3.2.5 Statistical Analysis

Descriptive statistics for baseline covariates for patients that received Merocel, or Rapid Rhino were calculated. T-test and bivariate analysis were used to compare baseline characteristics in relation to both treatment status and total costs.

The primary analysis was to compare total costs between Rapid Rhino (treatment) and Merocel (control group), where the total cost was examined from the hospital and provincial health care perspectives. To make the two groups of patients comparable, propensity scores (i.e., the probability that a patient will receive treatment based on their baseline characteristics) were generated for all patients. There needs to be sufficient overlap or "common support" in propensity scores between the Merocel and Rapid Rhino groups, as this indicates that there are individuals with similar covariates that can be compared to each other across treatment groups.[14] We used a common support restriction that tests for balance in-between propensity scores across treatment groups, if individuals fell in the common support region.[15] If individuals were out of the common support region they were dropped from the analysis.

Regression models, along with the margins command in STATA were used to assess how each covariate (sex, medication usage, ambulance usage, age, age-squared, and rebleed occurrence) affected total costs.

Balance in baseline characteristics in relation to treatment status was important as the treatment a patient received was not randomly assigned in this study. Rather, a healthcare practitioner decided which nasal pack to use for a patient visiting the ER with anterior epistaxis. However, since physicians had to chose between Rapid Rhino and Merocel only at University hospital for the first 6 months of the year, the chance of selection bias via physicians would be lower. Inverse probability weighting regression adjustment (IPWRA) and Covariate balancing propensity scores (CBPS) were used to calculate difference in total costs, after accounting for the differences in observed patient characteristics between the two groups.[16-17] Since only cost data for the first rebleed visit was utilized, a sensitivity analysis was undertaken by excluding patients with multiple rebleeds. A sensitivity analysis was also conducted for patients that had a rebleed due to requiring an ENT specialist to manage their bleed during their initial visit. This is because we wanted to see if the difference in total costs between Rapid Rhino and Merocel changed when these patients were excluded. Another sensitivity analysis excluding patients that did not return for packing removal to the hospital was conducted to assess if our results change. As the standard errors at the second stage cannot be independent of the first-stage regression, bootstrapped standard errors were generated using 500 iterations. The results are presented in Table 3.12.

3.2.5.2 IPWRA and CBPS Weighting

To rectify issues with treatment status not being randomized (potential selection bias) inverse probability weighted regression adjustment was used.[18] IPWRA uses propensity scores to balance patient covariates in the treatment and control groups.[18] IPW weighting estimates the chance of receiving treatment by calculating the inverse probability of treatment and then estimating the outcome based on the new weights.[18] Essentially, IPWRA requires two models, one would be the treatment model, and the other would be the outcome model. If one model was not specified correctly and the other model is

correctly specified, the estimator would be consistent, which is known as the doubly robust property.[16] IPWRA was used to estimate the average treatment effect of the treated (ATT). ATT is the estimate for the average treatment effect on people who actually received the treatment.[16] In other words, it calculates the estimate for all of the population who received the treatment instead of the control.[16] For our study, ATT would measure the estimate for average total costs for those patients that received Rapid Rhino instead of Merocel.

Covariate balancing propensity score weighting is another alternative method to calculate and weight propensity scores. CBPS is a type of propensity score weighting that optimizes covariate balancing requirement in both the treatment and control groups.[17] This is done through calculating the treatment assignment and then treating the propensity score as a covariate balancing score using a generalized method of moments framework that combines score conditions and covariate balancing moment conditions.[17] CBPS model estimates propensity scores that achieve the best possible balance between treatment and control groups.[17] STATA user written procedure "psweight" was used to estimate covariate balancing propensity scores. Here, the propensity scores are calculated using the following logit regression model:

$$\mathrm{p} = \mathrm{invlogit}\,(\mathrm{X} * \mathrm{b}')$$

In this model, X stands for the vector of matching variables and b depends on the command given.[19] In our case we want to generate propensity scores that will have the best balance, so STATA psweight uses an internal optimization program to get a "b" that will help us produce propensity score weights to have the best balance between treatment and control groups.[19] This is why before weighting the IPWRA and CBPS propensity scores look different.

3.2.5.3 Treatment and Outcome Model Specifications

In this study, the treatment model was specified using a logit regression. The variables included in this model were patient's sex, age, age-squared, anticoagulant medication use and the use of an ambulance at the initial visit. The chance of selection bias is low in the study, as Victoria hospital never had a Rapid Rhino option for patients. However, both Rapid Rhino and Merocel were available from January to June at the University hospital (Merocel was available year-round). Physicians had some degree of choice between Rapid Rhino and Merocel during this period at the University hospital. Therefore, including these covariates in the propensity score model could address selection bias arising from these variables via treatment selection by the physician.

$$\mathrm{P}(Y_i = \text{Rapid Rhino}|\ \mathrm{x}) = \frac{e^{X\beta_{\text{Rapid Rhino}}}}{1 + e^{X\beta_{\text{Merocel}}} + e^{X\beta_{\text{Rapid Rhino}}}}$$

$$\mathrm{P}(Y_i = \text{Merocel}|\ \mathrm{x}) = \frac{1}{1 + e^{X\beta_{\text{Rapid Rhino}}} + e^{X\beta_{\text{Merocel}}}}$$

In the above equations, P(Y_i) represents the probability of treatment assignment. X refers to the covariates in treatment selection and *βs* are regression coefficients specific to Rapid Rhino or Merocel.

The outcome model was specified as a linear regression. Some of the variables included in the treatment model were also included in the outcome model. These variables include the patient's sex, age (including age-squared), use of anticoagulant medication and use of an ambulance. These variables were included into the outcome model as well because they were previously discussed risk factors associated with epistaxis or in the case for ambulance use could indicate a more severe bleed, resulting in more costs incurred.[8-10] Therefore, these characteristics could result in more severe bleeds and greater rates of rebleeds which could result in confounding the relationship between the nasal pack and

total costs. The outcome model also had a variable for rebleed occurrence, as patients who experienced a rebleed would incur more costs. Also, interaction with treatment status and other variables were included into the regression model as part of the IPWRA estimation procedure.

$$Y=\beta_1\times\text{treat}_1+\beta_2\text{*age}+\beta_3\times\text{age}^2+\beta_4\times\text{sex}+\beta_5\times\text{medication}+\beta_6\times\text{ambulance}+\beta_7\times\text{rebleed}+\beta_8\times\text{treat}\times\text{age}+\beta_9\times\text{treat}\times\text{age}^2+\beta_{10}\times\text{treat}\times\text{sex}+\beta_{11}\times\text{treat}\times\text{medication}+\beta_{12}\times\text{treat}\times\text{ambulance}+\beta_{13}\times\text{treat}\times\text{rebleed}+\varepsilon$$

Healthcare costing data tends to not be normally distributed. That is why generalized linear models (GLMs) are used to provide alternate comparison, as researchers can specify family and links to capture skewness in the data.[20] In our study, five models were utilized (square root link/gamma distribution, log link/Gaussian distribution, log link/gamma distribution, log link/Poisson distribution and identity link/Gaussian distribution) to evaluate which model fits the data better based on model specifications tests. We tested if any of the specification tests were rejected at the 5% significant level. The first specification test would be the Pregibon link test, that checks linearly of response on scale of estimation.[21] The next test is the Modified Hosmer and Lemeshow, and Pearson's correlation test which checks for systematic bias in fit on raw scale.[21] Finally, the Copas test was used for overfitting and cross-validation.[21]

3.3 Results

3.3.1 Cohort Description

Initially, 72 patients were classified under Merocel. Electronic medical charts for patients who had missing packing removal that could not be explained by a rebleed visit to the hospital were reviewed. From these reviews, four patients were excluded because they were wrongly classified with receiving Merocel, as their electronic charts indicated other interventions were utilized such as silver nitrate. Another patient was excluded as this

was considered a complex patient right after surgery, and therefore had different clinical circumstances. Two additional patients were excluded due to the lack of case-costing data. Finally, “pscore” on STATA was used to identify patients that were not within common support region. Patients are assessed on whether they are in the common support region depending on their propensity scores which are based on their covariates. In our case this would be the patient’s sex, anti-coagulation medication usage, age, age-squared and their usage of an ambulance. This led three patients treated with Merocel that were out of common support to be excluded. There were 62 patients treated with Merocel available for analysis. For Rapid Rhino, there was no exclusions. However, Rapid Rhino was available in one hospital for the first 6 months of the year, so the sample size was smaller than Merocel (N=17).

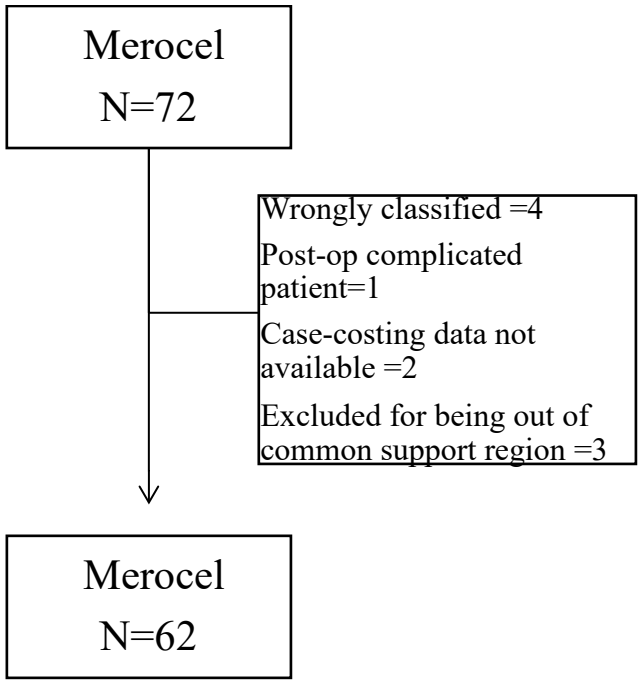

Figure 3.1: Inclusion and Exclusion chart for Merocel

3.3.1.1 Rebleed Rates

Table 3.3 reports the rebleed rates for Merocel and Rapid Rhino. The first row reports the total rebleeds, which include rebleeds requiring ENT intervention in their initial visit after nasal packing had failed and rebleeds within the first-two weeks of discharge. Merocel had a 42% total rebleed rate compared to Rapid Rhino packing at 24%. The second-row reports "follow-up" rebleeds which are rebleeds that occurred due to patients returning to the ER within 14 days of initial discharge after packing. Here, Merocel has a higher rate of rebleed (39%) compared to Rapid Rhino's (18%). The fourth row had rebleeds attributed to requiring ENT consults during the initial visit after failure of nasal packing which encompass patients who required intervention on behalf of an ENT specialist during their initial visit. Merocel and Rapid Rhino have similar rates of uncontrolled bleeding (5% vs 6%) requiring ENT consultation. One patient had an ENT consult, had Merocel removed and had a bleed the next day. It was decided that this patient was both a follow-up bleed and an ENT failure because inserting Merocel can cause trauma which in-turn could cause a bleed. All other patients that were seen by ENT, were repacked with another dissolvable or non-dissolvable pack. Therefore, while overall follow-up bleeds had a 39% rebleed rate, when looking at patients discharged from the hospital with a Merocel inserted (row three) who returned with a bleed it was still 39%. For Rapid Rhino patients discharged with a nasal pack inserted had a rebleed rate of 19%. The fifth row has multiple rebleeds, as in patients who had greater that 1 visit to the ER for a rebleed after their initial discharge. Merocel had a 13% rate of multiple bleeds compared to Rapid Rhino's 12%. When looking at patients discharged with a nasal pack, Merocel had a 14% rate of multiple bleeds and Rapid Rhino had a 13% rate of multiple bleeds.

Table 3.3: Breakdowns of rebleed rates for Merocel and Rapid Rhino nasal packs

	Merocel	**Rapid Rhino**
Total rebleeds	26/62 (42%)	4/17 (24%)
Follow-up rebleeds	24/62 (39%)	3/17 (18%)

Follow-up rebleeds (patients discharged with nasal pack)	23/59 (39%)	3/16 (19%)
ENT consult during the initial visit	3/62 (5%)	1/17 (6%)
Multiple Rebleeds	8/62 (13%)	2/17 (12%)
Multiple Rebleeds (patients discharged with nasal pack)	8/59 (14%)	2/16 (13%)

1

3.3.1.2 Descriptive Statistics on Costs

The total costs per patient for the hospital perspective is $334.10 (95% CI: $292.16 to $376.04), while the initial visit cost for the hospital is $270.02 (95% CI: $232.77 to $307.27). The follow-up rebleed visit cost is the average cost for those individuals who had a follow-up rebleed event. Thus, follow-up rebleed visit cost is $187.51 per patient (95% CI: 135.10 to 239.91). From the provincial health care perspective, the total cost per patient is $470.71 (95% CI: $420.33 to $521.09). For the initial visit the cost per patient is $375.08 (95% CI: $333.97 to $416.19). Finally, the follow-up rebleed visit cost per patient is $279.81 (95% CI: $216.74 to $342.87).

Table 3.4: Descriptive Statistics on Costs from the Hospital and Provincial Health Care Perspectives

	N	Mean	Median	SD	Skew	Kurtosis	Min	Max
Average total costs								
Hospital	79	$334.10	$289.06	$187.26	0.64	3.05	$23.33	$896.44
Province	79	$470.71	$466.32	$224.93	0.66	3.22	$89.65	$1151.92
Average initial visit costs								
Hospital	79	$270.02	$236.01	$166.30	1.32	5.20	$23.33	$896.44
Province	79	$375.08	$332.99	$183.54	0.94	3.92	$89.65	$1004.39
Average follow-up rebleed visit costs								
Hospital	27	$187.51	$159.50	$132.48	0.55	2.27	$21.92	$502.28
Province	27	$279.81	$231.61	$159.42	0.33	1.88	$72.92	$598.57

The total costs related to Merocel, and Rapid Rhino are reported in table 3.5. In terms of total costs per patient, Rapid Rhino had a cost of $353.54 (95% CI: $265.41 to $441.68) while Merocel had $328.77 (95% CI: $279.92 to $377.62) per patient from the hospital's

perspective. When looking at the provincial heath care perspective, similar patterns appear with Merocel having a cost of $466.09 per patient (95% CI: $405.57 to $526.61) in contrast to Rapid Rhino per patients costs of $487.58 (95% CI: $398.92 to $576.24).

Merocel costs $257.26 (95% CI: $310.98 to $402.15) per patient while Rapid Rhino costs $316.52 (95% CI: $228.19 to $404.85) per patient for the initial visit for the hospital perspective. For the provincial health care perspective, Merocel costs $356.56 (95% CI: $317.20 to $405.04) per patient in contrast to Rapid Rhino $442.61 (95% CI: $346.15 to $539.08) per patient during the initial visit. Follow-up rebleed visits costs were averaged between all patients that received a nasal pack, instead of those who just had a rebleed. This was because Merocel and Rapid Rhino have different follow-up rebleed rates (39% vs 18%) which in turn affects costs. Rapid Rhino from the hospital's perspective costs $37.02 (95% Cl: -$12.33 to $86.38) per patient in contrast to Merocel $71.50 (95% Cl: $40.35 to $102.66). From the provincial health care perspective, Rapid Rhino costs $44.96 (95% Cl: -$12.60 to $102.53) per patient in contrast to Merocel costing $109.52 (95% Cl $65.95 to $153.10) per patient.

Table 3.5: Descriptive Statistics on Costs for Merocel and Rapid Rhino

	N	Mean	Median	SD	Skew	Kurtosis	Min	Max
Total costs for the hospital perspectives								
Rapid Rhino	17	$353.54	$367.54	$171.42	0.74	3.02	$88.69	$748.26
Merocel	62	$328.77	$276.80	$192.35	0.64	3.04	$23.33	$896.44
Initial costs for the hospital perspective								
Rapid Rhino	17	$316.52	$283.67	$171.80	1.04	3.81	$88.69	$748.26
Merocel	62	$257.26	$231.62	$163.87	1.44	5.84	$23.33	$896.44
Follow-up rebleed costs for the hospital perspective								
Rapid Rhino	17	$37.02	$0	$96.00	2.31	6.44	$0	$290.95
Merocel	62	$71.50	$0	$122.67	1.78	5.22	$0	$502.28
Total costs for the provincial perspective								
Rapid Rhino	17	$487.58	$491.24	$172.44	0.35	3.12	$168.66	$876.71
Merocel	62	$466.09	$406.02	$238.32	0.71	3.11	$89.65	$1151.92
Initial costs for the provincial perspective								
Rapid Rhino	17	$442.61	$486.85	$187.62	0.52	3.11	$142.17	$876.71
Merocel	62	$356.56	$317.90	$179.50	1.11	4.48	$89.65	$1004.39
Follow-up rebleed costs for the provincial perspectives								

Rapid Rhino	17	$44.96	$0	$111.96	2.23	6.17	$0	$346.22
Merocel	62	$109.52	$0	$171.59	1.41	3.67	$0	$598.57

3.3.2 Outcome Model

Since data relating to the healthcare costs can be skewed due to fewer patients incurring larger costs, it is important to test out different models. As stated in the methods section, the Linktest, Hosmer-Lemeshow, Pearson correlations and Copas tests were run to test if a specific link/family model passed all the specification tests. Below are the results for the GLM test for five different family and link choices.

For the hospital perspective, log-gamma passed all the test except the Copas test. The linear, log-gamma and log-normal regressions passed all the tests except for the Copas test in the provincial health care perspective. Most of the tests were non-significant for total-cost, the regressions for the models that passed all the tests except for the Copas test will be used to provide for alternative perspectives on total costs.

Table 3.6: Tests for the distribution of costs from the hospital perspective

	Linktest	**Hosmer-Lemeshow**	**Pearson correlations**	**Copas test**
Linear	0.71	0.02	0.99	p<0.001
GLM log-gamma	**0.10**	**0.70**	**0.23**	p<0.001
GLM log-normal	0.97	0.001	0.98	p<0.001
Log/Poisson	p<0.001	0.08	0.84	p<0.001
GLM sqrt-gamma	p<0.001	0.59	0.27	p<0.001

Table 3.7: Tests for the distribution of costs from the provincial health care perspective

	Linktest	**Hosmer-Lemeshow**	**Pearson correlations**	**Copas test**
Linear	**0.88**	**0.56**	**0.99**	p<0.001
GLM log-gamma	**0.25**	**0.15**	**0.43**	p<0.001

GLM log-normal	**0.96**	**0.43**	**0.99**	p<0.001
Log/Poisson	p<0.001	0.44	0.90	p<0.001
GLM sqrt-gamma	p<0.001	0.039	0.52	p<0.001

A kernel density and standardized normal probability plot of residuals were created for the provincial health care perspective to assess if linear regression might be the appropriate choice as an outcome model. From the kernel density plots for both the provincial health care perspectives (Figure: 3.2), it seems that aside from a slight deviation, overall, the data seem relatively normal. Furthermore, looking at the normal probability plot (Figure: 3.2), the data points aside from some deviations are relatively normal. Therefore, a linear regression may be a reasonable choice.

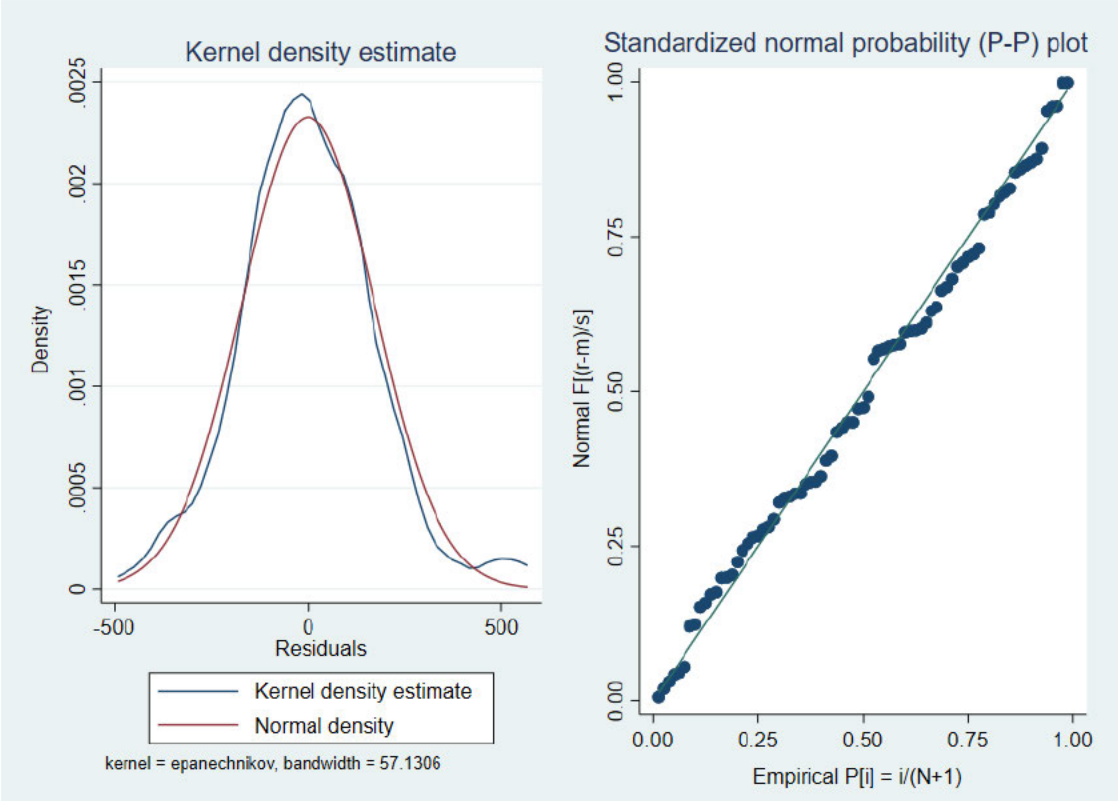

Figure 3.2: Kernel density & Standardized normal probability plot for provincial health care perspective

3.3.3 Effects of Categorical Variables and Total Cost

Below are the coefficients calculated from running the log-gamma regression for both perspectives before weighting, along with "margins" on STATA to understand how various covariates effect total cost. The results are reported in Table 3.8. Results for linear and log-normal glm models for the provincial perspectives can be found in Appendix F.

Table 3.8: Results for the effects of categorical covariates on total costs

	Hospital		Provincial Health Care	
	Gamma	p-value	Gamma	p-value
Sex	30.80 (-42.23 to 103.83)	0.41	29.10 (-50.15 to 108.35)	0.47
Medication	-13.24 (-91.24 to 64.77)	0.74	-9.82 (-94.97 to 75.33)	0.82
Ambulance	78.70 (-9.74 to 167.14)	0.08	99.17 (1.85 to 196.49)	0.05
Rebleed	157.50 (80.86 to 234.15)	p<0.001	233.81 (149.85 to 317.77)	p<0.001

3.3.3.1 Hospital perspectives

When analyzing the hospital perspective, there is no difference in total cost between the sex. The resulting difference of $30.80 per patient (95% CI: -$42.23 to $103.83) between women and men was not statistically significant at the 5% level. Similarly, patients that are taking anticoagulant medication contrasted to those not taking medication have a -$13.24 (95% CI: -$91.24 to $64.77) per patient difference in total costs which is not significant at the 5% level. While patients that did use an ambulance had about a $78.70 (95% CI: -$9.74 to $167.14) per patient difference in total costs in contrast to patients who did not use an ambulance, and this was not significant. Both variables for medication usage and ambulance usage had confidence intervals that had 0 in them. Therefore, our sample failed to provide evidence that costs differ between patient sex, medication usage or ambulance usage. Patients that had a rebleed had a $157.50 (95% CI: $80.86 to $234.15) per patient

increase in total costs than patients who did not have a rebleed. This difference was statistically significant at the 0.1% level ($p<0.001$).

3.3.3.2 Provincial health care perspective

There is a non-significant difference of $29.10 (95% CI: -$50.15 to $108.35) per patient between the sex at the 5% level. There is a -$9.82 (95% CI: -$94.97 to $75.33) per patient statistically non-significant difference between patients who use anticoagulation medications vs. patients who do not. The estimated confidence interval further indicates no difference between the two groups. Thus, our sample did not provide evidence that the costs between men vs. women or anticoagulation usage vs. non-anticoagulation usage were different. Comparatively, taking an ambulance result in an increase of $99.17 (95% CI: $1.85 to $196.49) per patient compared to patients not taking an ambulance. This result was significant at the 5% level ($p=0.05$). Patients that had a rebleed, had an increase of $233.81 (95% CI: $149.85 to $317.77) in total costs per patient in contrast to patients that did not have a rebleed. This was also statistically significant at the 0.1% level, ($p<0.001$).

3.3.4 Effects of Continuous Variables and Total Costs

Figure 3.3 shows the marginal effect of age on total costs for the hospital and provincial healthcare results. From these graphs it was apparent that age has an U-shaped relationship with total costs. The log-gamma regression for the hospital perspective predicted that age is associated with decreasing total costs for patients until patients are 53 years old, and thereafter it is associated with an increase in total costs. The log-gamma model associated age with lower total costs until 56 years old and after it was associated with increasing total costs. The linear and log-gaussian models for the provincial perspectives also produced a U-shaped effect, and can be found in Appendix F.

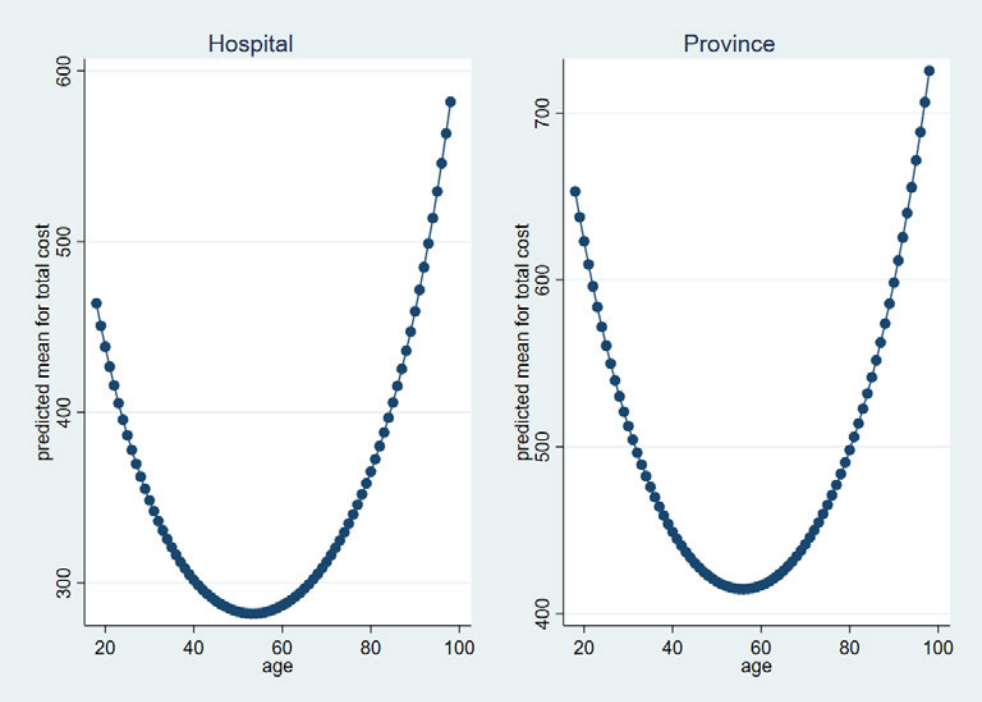

Figure 3.3: Effects of age and total costs for the hospital and provincial health care perspectives

3.3.5 Propensity Score based Weighting Results

3.3.5.1 Before Weighting

On initial analysis, the covariates were relatively balanced for patients in relation to treatment status. The coefficients calculated from chi-square and t-test analysis quantify the difference of the covariates between the treatment groups, and here all had p-values are greater than the 5% significance level. The results are presented in table 3.9. The log-odds ratios of covariates at baseline are presented in table 3.10. The standard mean difference (SMD) and variance ratio before and after IPWRA weighting between Merocel and Rapid Rhino users are presented in Table 3.11. The SMD's after weighting for the covariate's are closer to zero, and the variance ratio's are closer to 1 than before weighting. This is an indicator that IPWRA weighting resulted in greater balance in patient covariates between Rapid Rhino and Merocel.

Table 3.9:Baseline characteristics of patients by treatment status

		Merocel		Rapid Rhino	
Continuous variables					
Age		70.11 [66.58 to 73.64]		65.12 [55.53 to 74.70]	p = 0.11
Age^2		5105.98 [4637.82 to 5574.14]		4567.35 [3478.6 to 5656.11]	p = 0.15
Binary Variables					
Sex	Men	40 (65%)	Men	13 (76%)	p = 0.35
	Women	22(35%)	Women	4 (24%)	
Medication	No	22 (35%)	No	7 (41%)	p = 0.67
	Yes	40 (65%)	Yes	10 (59%)	
Ambulance	No	39 (63%)	No	12 (71%)	p = 0.56
	Yes	23 (37%)	Yes	5 (29%)	

Table 3.10: Log Odds of covariates before weighting in treatment model

	Log Odds	95% Confidence Interval	p-value
Age	-0.07	(-0.25 to 0.10)	0.41
Age^2	0.0005	(-0.0009 to 0.0019)	0.52
Sex	-0.51	(-1.77 to 0.77)	0.44
Ambulance	-0.27	(-1.49 to 0.95)	0.66
Medication	0.096	(-1.17 to 1.36)	0.88

3.3.5.2 Propensity Score Weighting

Figure 3.4 presented below showed the unweighted and weighted propensity scores using IPWRA. Figure 3.5 presented the propensity scores before and after weighting for CBPS weighting. These graphs signified that there was high overlap between Merocel and

Rapid Rhino patients before applying any propensity score weights. This was due to as previously mentioned applying "pscore" from STATA to assess for common support and dropping any patient out of the common support restriction. After weighting using IPWRA and CBPS there is greater overlap between Merocel and Rapid Rhino.

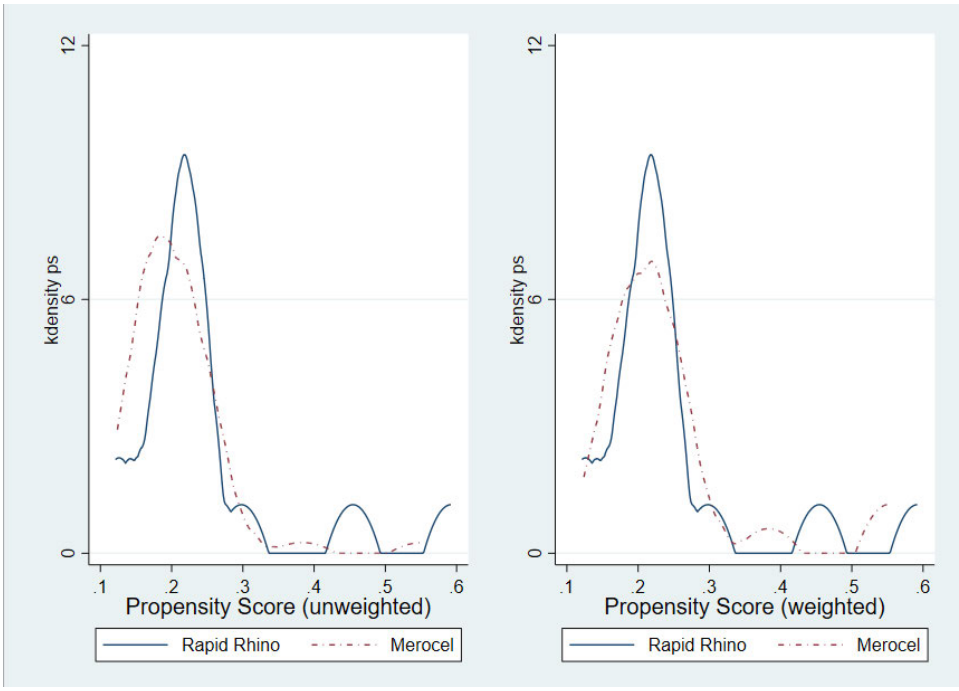

Figure 3.4: Propensity Scores for IPWRA before & after weighting

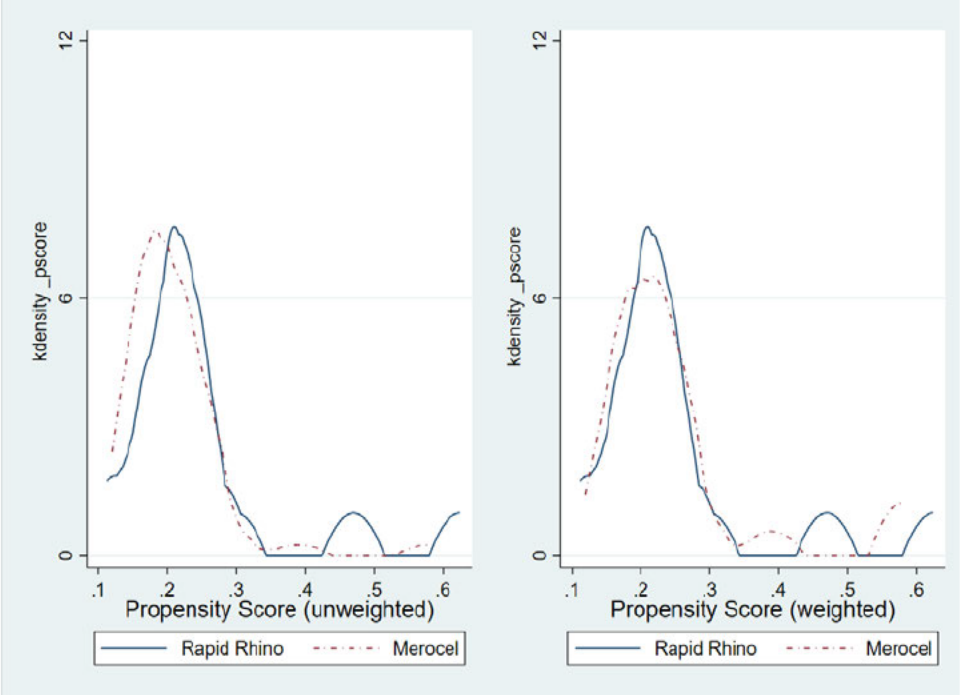

Figure 3.5: Propensity Scores for CBPS before & after weighting

Table 3.11: Weighted coefficients before and after IPWRA weighting

	Standardized Difference in Means		**Variance Ratio**	
	Raw	Weighted	Raw	Weighted
Sex	-0.26	-0.005	0.82	0.99
Age	-0.30	-0.01	1.80	1.06
Age^2	-0.27	-0.002	1.32	0.99
Ambulance	-0.12	0.001	1.11	1.00
Medication	-0.2	-0.02	0.93	0.98

3.3.6 Total Costs

Table 3.12 reported the results for the average treatment effect on the treated estimates of costs from the hospital and provincial health care perspectives. The first-row reports difference in costs per patient using a log-gamma model and CBPS weighting for patients who received Rapid Rhino. From the hospital's perspective, CBPS weighting estimated a non-significant difference at the 5% level in costs per patients of $61.61 (95% CI: -$127.84 to $251.05) for those patients who received Rapid Rhino (p=0.52). Therefore,

our sample did not provide evidence that the costs from Rapid Rhino and Merocel are different. From the provincial healthcare perspective, CBPS weighting resulted in $78.14 (95% CI: -$89.54 to $245.83) difference in costs per patient for those patients treated with Rapid Rhino, which was not statistically significant (p=0.36). Similarly, the linear, log-gamma and log-normal models IWPRA and CBPS results in Appendix F, indicate no significant difference at the 5% level. Thus, our sample failed to provide evidence that costs from two approaches are different.

Table 3.12: ATT estimates using log-gamma and CBPS weighting

	Hospital	p-value	Provincial Healthcare	p-value
Total Cost	61.61 (-127.84 to 251.05)	0.52	78.14 (-89.54 to 245.83)	0.36
Excluding ENT consults for initial visit	72.91 (-5823.82 to 5969.65)	0.98	83.37 (-1371.36 to 1538.10)	0.91
Excluding multiple Bleeds	67.22 (-144.68 to 279.13)	0.53	102.17 (-63.19 to 267.53)	0.23
Excluding patients with missing pack removal	46.11 (-217.88 to 310.09)	0.73	52.44 (-109.73 to 214.61)	0.53

3.3.7 Sensitivity Analysis

3.3.7.1 Excluding Patients with ENT Consultation during Initial Visit

Patients that required an ENT specialist to intervene during their initial visit to the ER, were considered rebleeds. These patients could have simply had a more severe bleed or had different underlying health conditions, which incurred extra costs, and may be nothing to do with the nasal pack. Therefore, we excluded these patients from the analysis on total cost to analyze if our conclusion would change. In this sensitivity analysis, 3 patients from Merocel were excluded and 1 patient from Rapid Rhino was excluded (3 males and 1 female patient; 3 patients were on anti-coagulants; and 2 arrived by ambulance).

The coefficients calculated after excluding ENT consults during the initial visit are available on the second row of Table 3.12. In contrast to the coefficients calculated on the first row of Table 3.12 (with ENT patients included), the coefficients calculated after excluding ENT consult patients were slightly higher. For example, using CBPS weighting for the hospital and excluding ENT consult patients resulted in a $72.91 (95% CI: -$5823.82 to $5969.65) not statistically significant difference in costs per patient (p=0.98) for those patients who received Rapid Rhino. The confidence interval contains 0, indicating there is no difference between Merocel and Rapid Rhino. Including these ENT consults patients had previously resulted in a coefficient of $61.61 (95% CI: -$127.84 to $251.05). Excluding ENT patients for the province healthcare perspective, concluded that there would be a non-significant difference of $83.37 (95% CI: -$1371.36 to $1538.10) per patient for patients who received Rapid Rhino (p=0.91). The confidence interval once again includes 0, which means that there is no difference between the two methods. Including these ENT patients resulted in a coefficient of $78.14 (95% CI: -$89.54 to $245.83) previously. When excluding ENT patients for both the hospital and provincial perspectives, our sample did not provide evidence that costs from using Merocel or Rapid Rhino are different.

3.3.7.2 Excluding Patients with Multiple Rebleed Visits

Multiple rebleeds were defined as visiting the ER more than once for a rebleed event during the 14-day following initial discharge. Patients can have multiple bleeds for various reasons, including needing reassurance, or having different underlying health conditions. Since, costing-data only included the first rebleed, cost for multiple bleeds were not captured. Therefore, we are excluding these patients to understand if this changes the difference in total costs between Merocel and Rapid Rhino. In this sensitivity analysis, 8 patients from Merocel group and 2 patients from Rapid Rhino group were excluded. Out of these patients, 7 were male and 3 were female. There were 6 patients on anti-coagulation medication, and 5 patients arrived via ambulance.

Row 3 on Table 3.12 has the results for difference in total costs after excluding multiple visits. Excluding patients with multiple bleeds for the hospital perspective resulted in the following not statistically significant coefficient: $67.22 (95% CI: -$144.68 to $279.13), p=0.53. If all the patients were included the coefficients was $61.61 (95% CI: -$127.84 to $251.05). While the estimated coefficient increases when excluding multiple visits, our conclusion that our sample did not provide evidence that the costs between using Merocel and Rapid Rhino are different remains the same. Excluding multiple visits for the provincial health care perspective resulted in an estimate of $102.17 (95% CI: -$63.19 to $267.53) which was not statistically significant p=0.23 in comparison to $78.14 (95% CI: -$89.54 to $245.83) if all patients were included. Once again excluding multiple rebleeds causes the estimate coefficient to increase but our conclusion that our sample does not provide evidence that using Rapid Rhino or Merocel results in a difference in costs remains the same.

3.3.7.3 Excluding patients with Missing Packing Removal for their Initial Visit

There are patients that did not return to the ER for packing removal after their initial visit. These patients also did not have a rebleed, so the missing packing removal could not be explained due to a return visit to the ER where the nasal pack would be taken out. In Merocel 16 patients and in Rapid Rhino 2 of patients did not return to get their packing removed. This would lead to lower costs so we excluded these patients to understand if our conclusions would change. There were 11 men and 7 women excluded from the analysis. There were 5 patients not on anti-coagulation medications and 7 patients arrived via ambulance.

The estimated coefficients for average treatment effect on the treated after patients were excluded due to missing packing removal are available in row 4 of table 3.12. The estimated coefficients when excluding all patients with missing packing removal are lower than when all the patients were included (row 1 of Table 3.12). For the hospital perspective, excluding patients with missing packing removal resulted in an non-significant estimate of $46.11 (95% CI: -$217.88 to $310.09), p=0.73. Including all

patients resulted in a coefficient of $61.61 (95% CI: -$127.84 to $251.05). For the provincial healthcare perspective, if all patients are included for the provincial health care perspective, the log-gamma model results in an estimate of $78.14 (95% CI: -$89.54 to $245.83). These estimates are higher then the non-statistically significant $52.44 (95% CI: -$109.73 to $214.61) if all patients with missing packing removal patient's were excluded, p=0.53. However, our sample still failed to provide evidence that there is a difference in costs using Merocel or Rapid Rhino, when excluding patients with missing packing removal.

3.4 Discussion

The mean age of patients reported in our study who received Merocel was 70.11 (95% CI: 66.58 to 73.64) and those who received Rapid Rhino was 65.12 (95% CI: 55.53 to 74.70). The median ages for Merocel were 71 (IQR: 61 to 82) and for Rapid Rhino was 66 (IQR: 62 to 75). The mean age of 76.1 was reported by Van Wky *et al*. for his cohort that included Merocel patients which is slightly higher than our study.[22] Singer *et al.* reported a median age of 78 (IQR: 48 to79) for Rapid Rhino which was higher than the median age in our study.[3] The mean age for our entire cohort was 69.03 (95% CI: 65.67 to 72.41) and the median age was 71 (IQR: 61 to 79). Newton *et al.* reported a similar median age of 70 for their cohort which included patients treated with Merocel.[11]

Goljo *et al.* used a multiple regression equation to evaluate costs on an in-patient basis and found that their age variable was associated with lower costs -$53 (95% CI: $62 to $44).[10] Our age variable shows a quadratic relationship with total costs, which has so far not been explored by previous papers. Overall patients under 60, tend to have a negative association with total costs and patients over 60 have a positive association. Different models have different thresholds of when the negative association becomes positive. For the hospital perspective, using the log-gamma model after 53 years old, the patients age has a positive association with total costs. For the provincial health care perspective, the threshold was 56 years for log-gamma equation. Like our study, Nithianandan *et al.* reported non-significant differences between the sex in terms of totals costs but did report

a significant difference in total costs for patients who received anticoagulants/antiplatelet medications which is a contrast to our results.[23]

Van Wyk *et al.* reported 15% (7/46) rebleed rates with patients discharged with Merocel, in contrast to our 39% (23/59).[22] However, Van Wky *et al.* captured rebleeds within 3 days compared to our 2-week period.[22] This suggests that use of 3-day window to capture rebleed events may grossly underestimate the true rebleed rates. Akkan *et al*. reported a 27% (12/45) rebleed rate for Merocel after 24 hours (this included 3 patients who were initial failures and were not repacked), which is also lower than our follow-up rebleed rates (including patients who were not discharged with a pack) of about 39% (24/62).[6] Newton *et al.* had a follow-up rebleed rate for Merocel about 26% (24/92) using the same two-week time-frame as ours which is slightly lower that our 39% (23/59) rebleed rate for follow-up rebleeds of patients discharged with nasal packs.[11] Singer *et al.* reported rebleeds of Rapid Rhino at the patients pack removal visit. A rebleed was defined as the need to repack after removal of a nasal tampon. The authors of this study reported a 6% (1/18) rebleed rate (excluding patients who were not discharged with a pack), which lower than our 19% (3/16) rebleed rate (excluding patients discharged without a nasal pack).[3] This discrepancy could be because they measured rebleed only at their scheduled follow-up of three days for packing removal and we captured rebleeds until two weeks without a scheduled follow-up.

Akkan *et al.* reported a 7% (3/45) initial rebleed rate; these patients required help from an Otolaryngologist.[6] This is similar to our initial rebleed rate of 5% (3/62) in Merocel patients who required help by an ENT. Other studies calculated "initial failure" of Rapid Rhino or Merocel, and considered them rebleeds, the closest comparator in our study to "initial failures" are rebleeds due to ENT consults. Singer e*t al.* reported a 10% (2/20) rebleed rate initially for Rapid Rhino, which is similar to our 6% (1/17) of patients initially requiring an ENT conult.[3] Their rebleed rate is higher as they define initial rebleed as a need to repack the nose with another nasal tampon, while our definition is a need for an ENT consult. Moumoulidis et *al.* reported an initial failure of management by Rapid Rhino to be 24% (5/21) and Merocel at 19% (4/21).[24] These rates are much higher than our reported 6% (1/17) for Rapid Rhino and 5% (3/62) for Merocel.[24] However, this

was an RCT where patients received one nasal pack ipsilaterally, and if bleeding was not controlled, the nasal pack was considered a failure.[24] While in our study, an ENT consult was the closest measurement to an initial failure.

It is difficult to compare our results of cost analysis with other studies as few comparable cost analyses exists. Nithianandan *et al.* conducted an economic evaluation in Ottawa for anterior epistaxis using 30-day total cost where the reported median cost for Merocel including the first and third quantile.[23] This cost included costs for physicians which would be equivalent to provincial health care perspective costs in our study. They reported a median cost of $763.98 (IQR: $632.25 to $830.23).[23] Our is $406.02 (IQR: $290.14 to $600.22). Since our follow-up time was two weeks, and costing was up until the first bleed, our costing seems plausible.

Murray *et al.* conducted a cost-effectiveness analysis where the median cost for their Merocel/Vaseline gauze group for the healthcare perspective (including physicians) using a 30-day time horizon was $2704.51 (IQR: $354.71 to $3846.71).[4] This estimate was much higher than our estimates even when taking into consideration the different follow-up periods. However, these costs was higher than Nithianandan *et al.* study who used a similar timeframe of 30-days. This difference in cost-estimates is mostly likely because Murray *et al.* included costs for in-patients as well (surgical/medical ward costs).

3.4.1 Strengths and Limitations

Our study is one of the few studies looking at epistaxis management based in Canada.[4,11,23] It is the only study comparing Rapid Rhino to Merocel directly, that clearly measures both initial bleeds and has a follow-up period for measuring recurrence events. Previous studies that directly compared Merocel to Rapid Rhino had either no follow-up period, only measured management of bleeding initially or at scheduled pack removal or did not indicate how may patients were packed by Merocel and Rapid Rhino.[2,24-28] It is also the only study currently that has a cost analysis for anterior epistaxis using Merocel and Rapid Rhino in an outpatient setting. It is one now one of the few studies to take into consideration both the hospital and the provincial health care perspectives.[4]

Our study collected information from medical charts on patients who visited the ERs with epistaxis in a tertiary academic health sciences centre. Although medical charts are a good standard for collecting retrospective data, patients reporting to an ER, that tend to be busy, may not document all relevant information. Therefore, some patients may have their experience in the ER thoroughly explained while others may have few lines written, causing variability in the accuracy of the information gathered. Furthermore, patients can remove their nasal pack at home or visit their family physician for a rebleed, these costs would not be captured in our study. The major limitation in our study was our small sample size in the Rapid Rhino group. The small sample size, led to more variability in the data, making it difficult to conclude on which nasal pack was less costly. Another limitation in our research was the costing analysis from the provincial health care perspective. More specifically, ER physicians billing hours were estimated using fees typically applied in a community setting. Unfortunately gauging hourly fees for an ER physician is difficult using retrospective data as physicians do not spend the entire time a patient is in the ER with them, and they often juggle multiple patients at the same time. Furthermore, to conduct a cost-effectiveness analysis, changes in quality of life for patients need to be captured. We cannot collect quality of life for patients from 2018 and currently there is no literature that measures quality of life for either Merocel or Rapid Rhino. Thus, a formal cost-effectiveness analysis is not possible.

As discussed in the literature review section there are other risk factors and comorbidities such as smoking status, abuse of drugs and bleeding disorders tend to increase the occurrence of epistaxis and can confound the relationship between our treatment and outcome.[29-31] These confounders were not adjusted for in our study so there is potential for model misspecification. We did not stratify between patients who received warfarin vs. newer anticoagulants such as apixaban and rivaroxaban given limited sample size. However, there is evidence indicating that warfarin is associated with a higher rate of bleeds in contrast to apixaban, dabigatran and rivaroxaban which could affect the results of our study.[32] Sowerby *et al.* noted before that fewer than a third of ER physicians and residents knew proper first aid methods for managing epistaxis.[33] It is possible that the lack of knowledge and experience in inserting Merocel or Rapid

Rhino could have lead to more adverse outcomes. Many medical charts gave no indication of which side a patient's bleeding occurred, or how many nasal tampons were utilized. Thus, we did not stratify on these variables but due to this capturing the severity of a patients bleed became difficult. We use ambulance usage as a proxy for severity and by excluding ENT consults. However, capturing lateral vs. bilateral bleeds and counting the number of nasal packs utilized would have been better to capture the severity of a patients' bleed.

3.5 Conclusions

Our study directly compared effectiveness of Merocel to Rapid Rhino by comparing rebleed rates up to two weeks following discharge with a nasal pack. We also assessed how total costs were related to patient covariates such as age, sex, medication usage, ambulance usage and rebleed events. We found an U-shaped relationship between age and the costs of epistaxis treatment. Our results indicate that our sample failed to provide evidence that there is a difference between total costs per patient between Merocel and Rapid Rhino.

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Chapter 4

4 Conclusions and Future Research

4.1 Summary

Management of epistaxis in the emergency room is not an exact science but rather a combination of guidelines involving patient health circumstances and physician expertise. Patients often require different interventions in the ER. Sometimes they require no intervention from physicians, and some other times patients require some help but do not need a nasal pack inserted into them. Merocel is a popular choice of a nasal pack as they are less expensive compared to other nasal packs such as Rapid Rhino. Rapid Rhino is shown to be more comfortable for patients, however. Costs for epistaxis do not only come from the costs of the nasal pack but also potential returns to the ER for rebleed events; rebleeds can increase total costs. In Canada, the costs associated with managing epistaxis burden both the province and the hospital itself. However, there is limited research on the economic impact on nasal pack choice, especially with rebleeds being taken into consideration.

We conducted a retrospective study using patient medical charts in two ERs located in London, Ontario. We measured rebleed rates up until 2 weeks for patients that were packed by Merocel or Rapid Rhino. Then we assessed costs associated with patient encounters using propensity score-based weighting for both the hospital and provincial health care perspectives. Finally, we conducted a sensitivity analysis by excluding (i) patients that had ENT consultations, (ii) multiple rebleeds within the two-week follow-up period and (iii) if patients did not return for packing removal.

4.1.1 Literature Review Findings

We conducted a literature review to understand the relationship between Merocel, Rapid Rhino and other packs in terms of comfort, rebleed rates and economic burden. We found that Rapid Rhino appeared to be more comfortable compared to other nasal packs.[1-4] Data on health-related quality of life was sparse in the literature making it difficult to conduct

a cost-effective analysis. Data on rebleed rates was varied.[3-14] Often, there were a small number of individuals included in the studies. Rebleeds were measured at varying ranges, from the effectiveness of a nasal pack in initially stopping a bleed all the way to 3 months after the initial visit.[3-14] At times, Merocel was compared to interventions such as silver nitrate and TXA.[6,10] These interventions are typically used as a primary management technique, and if a patient continues to bleed, nasal packing is used. Finally, cost analysis studies were rare in the literature and existing published studies fail to account for rebleed costs. For Rapid Rhino and Merocel there is only one study that directly compares costs for both these nasal pack together, however, this study assessed inpatient costs.[14]

4.1.2 Study Findings

Our study focused on the costs of considering a change from Merocel to Rapid Rhino in ERs located in London, Ontario. To provide a thorough analysis, different propensity score weighting techniques were utilized to ensure patients who received Rapid Rhino and Merocel are comparable in terms of the observable patient characteristics. Difference in total costs using Rapid Rhino and Merocel were measured using several different outcome models including a linear, log-gamma and log-normal. Finally, three separate sensitivity analysis was conducted by excluding patients that had multiple rebleeds, excluding patients that required an ENT to manage their bleed and excluding patients who did not return for packing removal.

When looking at total rebleeds, which include initial failure and any follow-up bleeds, Merocel has a 42% (26/62) rate of rebleed contrasted to Rapid Rhino 24% (4/17). Rapid Rhino and Merocel had similar rates of rebleeds requiring help by an ENT during the initial visit, at about a 6% (1/17) and 5% (3/62) respectively. Merocel had about a 39% (24/62) follow-up rebleed rate while Rapid Rhino had an 18% (3/17). A log-gamma regression was the best fit for the hospital perspective. While the provincial health care perspective had multiple regressions including linear, log-gamma and log-normal. For the hospital perspective when using the log-gamma regression with CBPS weighting, patients who received Rapid Rhino, had a non-significant difference in total costs of $61.61 (95% CI: -$127.84 to $251.05) per patient, p=0.52. For the province, log-gamma with CBPS

weighting resulted in Rapid Rhino being associated with a non-significant difference of $78.14 (95% CI: -$89.54 to $245.83) in costs per patients p=0.36. From these models, our sample failed to provide evidence that the costs associated with Merocel, or Rapid Rhino usage is different.

4.2 Future Research

In the future, a prospective trial focused on the hospital's ER would be beneficial. According to our results, Rapid Rhino appears to have a lower rate of rebleeds, which led to lower costs for rebleed visits. However, due to our small Rapid Rhino sample size, we cannot make any definitive conclusions. A large-scale prospective trial would allow for a greater number of patients to receive Rapid Rhino and allow us to assess total costs more precisely. Furthermore, a prospective trial would allow us to measure productivity losses associated with epistaxis management, and patient quality of life. These data would help to undertake a cost-effectiveness analysis from a societal perspective as well as hospital healthcare perspectives.

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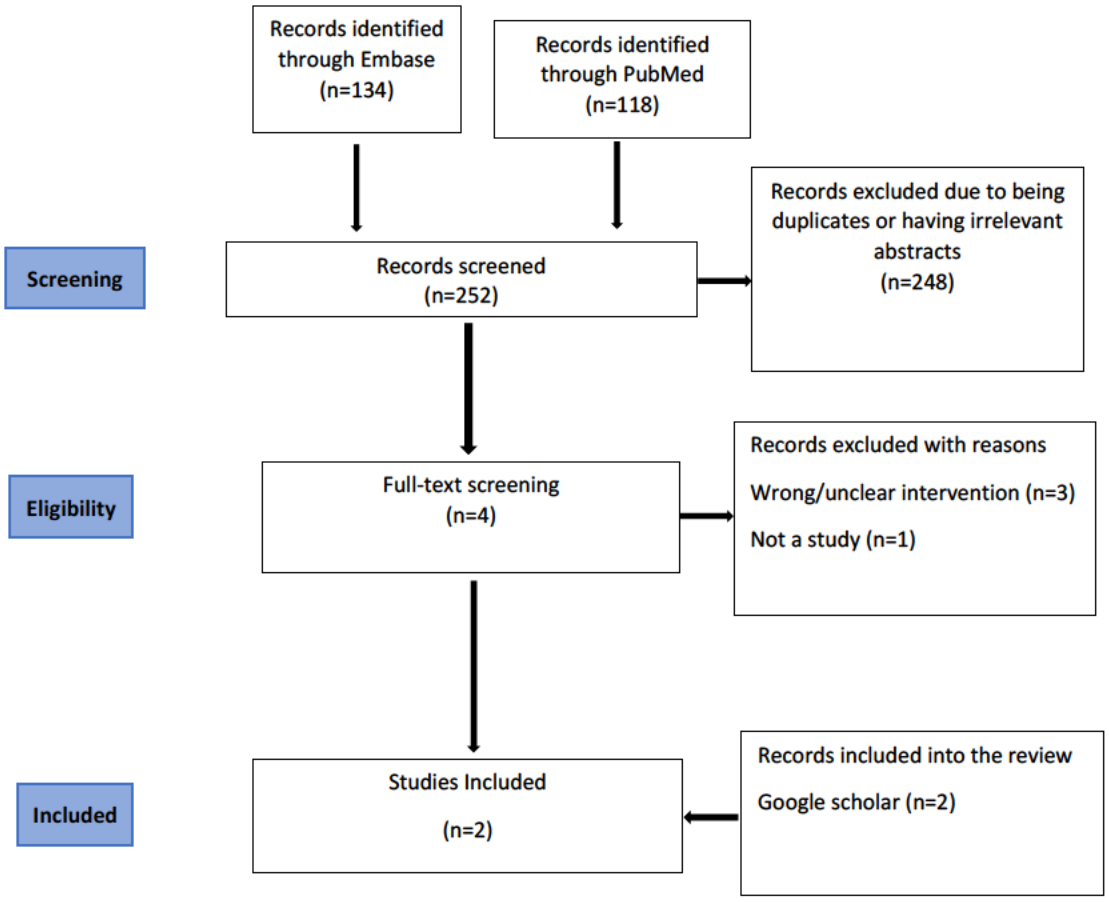
Appendices

Appendix A: Flow chart for updated literature review



Appendix B: Summary of Literature Review

Table B.1. Studies the measure recurrence in bleeds in patients with either Rapid Rhino, Merocel or both

Authors	Year	Study Design	Sample Size	Statistical Methods	Results	Comments
Wyk *et al*	2007	Retrospective study	116	-count data and percentages calculated	Merocel: 62 initial patients packed with Merocel Required admission initially: 16/62 Successfully packed and discharged: 46/62 Rebleed within 3-days: 7/46	-Retrospective review of ER protocol, no statistical analysis - Anterior epistaxis in ER
Newton *et al*	2016	Retrospective review	353	-categorical variables summarized via frequency -chi-square and Fisher's exact for some associations	Rebleed events 1.Silver Nitrate (24/122) 2. Merocel (24/92) 3. No treatment (11/54) 4.Other packing (Vaseline gauze) (19/45) 5.Other (surgical and decongestants) (3/23) 6.Nasal Clip (10/17)	-2 week follow-up - Anterior epistaxis in ER from January 2012- May 2014 -Odds ratio only for Merocel vs silver nitrate (not comparable)
Pringle *et al*	1996	Retrospective review	143	-count data and percentages calculated	Merocel: 7/83 rebleed	- 83 patients packed initially -No follow-up, simply if pack was effective initially - Patients included if referred to the hospital with epistaxis
Murray *et al*	2018	RCT	26	-rebleeds were compared using the Fisher's Exact Test	Post treatment rebleed: Floseal:10/13 Merocel:11/13 Admission required: Floseal: 2/13 Merocel:6/13 48 hours rebleed: Floseal:10/13 Merocel:9/13 30-day rebleed: Floseal: 2/13 Merocel:6/13 *all rebleeds non-significant at the 5% level	-Post-treatment, admission required, 48 hour rebleed rate and 30 day follow up -Patients with persistent epistaxis were included
Corbridge *et al*	1995	RCT	49	-Mann-Whitney		

				U-test for discontinuous variables - Fisher's exact test for proportions	Controlled with primary pack: Merocel: 25/27 BIPP:24/28 Required repacking with second pack: Merocel:1/27 BIPP: 3/28 Uncontrolled with any pack/ epistat balloon : Merocel:1/27 BIPP:1/28 *all rebleeds non-significant at the 5% level	- Patients with epistaxis in the ER -Measured nasal cavities controlled with initial packing, required repacking during the initial visit. -Patients randomized to either Merocel or Bismuth Subnitrate and Iodoform Paste (BIPP)
Akkan *et al*	2019	RCT	135	-Count data and percentages calculated	Rebleeds 15 minutes: Merocel: 3/45 TXA+ compression:4/45 Nasal compression: 13/45 24 hours: Merocel:12/45 TXA+ compression:6/45 Nasal Compression:18/45	- Patients admitted into the ER with anterior epistaxis -Initially rebleed after 15 minutes and 24 hour follow-up - Patients received TXA (with compression), Merocel or compression alone
Mehanna *et al*	2002	Prospective Cohort	50	- count data and frequencies	-10/50 patients rebleed but no specification was given	- Patients requiring packing admitted to the otolaryngology ward -24- hour follow-up after pack removal - Patients were packed with either Merocel, Vaseline gauze or BIPP -no specification on which pack had a rebleed
Abdelkhalek *et al*	2022	Prospective Cohort	60	-chi-square	Initial Failure: Merocel: 6/30 Merocel/Surgical wrap: 1/30 *non-significant at the 5% level 3-months rebleed Merocel: 8/30 Merocel/Surgical wrap: 2/30 *non-significant at the 5% level	- patients are from the emergency room or the ENT room - rebleed initially and within the 3 month mark

Singer et al	2005	RCT	40	-relative risk calculated	Initial failure: Rapid Rhino: 2/20 Rhino Rocket: 2/20 RR: 1.0 (0.8–1.2) 3 day follow up: Rapid Rhino rebleed: 1/18 Rhino rocket rebleed: 7/18 RR: 0.2 (0.03–1.3)	-Anterior epistaxis in ER - Rebleed measured follow-up within 3-days of initial visit during pack removel -Patients at 1 urban and 1 suburban hospital were randomized to Rapid Rhino to Rhino Rocket.
Khan *et al*	2015	Prospective Cohort	101	-Count and frequency data	Primary Intervention Rebleed: Merocel: 10/13 Floseal: 1/1 Rapid Rhino: 0/1 Secondary Intervention Rebleed: Rapid Rhino: 0/3 Floseal: 0/2	- Patients admitted to the otolaryngology department -Measured failure initially -49 patients had anterior epistaxis -Primary interventions are the first interventions a patient receives -Secondary interventions are after primary interventions fail
Badran *et al*	2005	RCT	50	-Count and frequency data plus Wilcoxon rank sum test) for degree of bleeding	Initial failures due to repacking or requiring surgery: Merocel: 7/25 Rapid Rhino: 6/25 Bleeding with pack in place Merocel: 1.6 Rapid Rhino: 1.3 *not significant at the 5% level Bleeding pack removal Merocel: 1.4 Rapid Rhino: 1.3 *not significant at the 5% level	-Anterior epistaxis in ENT ER -Measured number of cases repacked/ need surgery and bleeding when pack is in place and bleeding after pack removal from a range 0 to 4
Moumoulidis *et al*	2006	RCT	42	-Mann–Whitney test	Rebleeds initially Rapid Rhino: 5/21 Merocel: 4/21 *not significant at the 5% level	-Patients with epistaxis -Patients randomized with Merocel or Rapid Rhino -No follow-up, simply if pack was effective initially.

Lau *et al*	2015	Retrospective revie w	90	-count data	Rebleeds in 72 hours: Merocel:6 Rapid Rhino: 8	-72 hour follow-up - Patients that underwent nasal packing at the hospital - Retrospective Review - Patients packed with Rapid Rhino and Merocel
Keane *et al*	2016	Retrospective Review	434	-count data	-34 patients from the nasal pack group came back for recurrence, but number of patients who received nasal pack not apparent	-No clear follow-up , but it is assumed to be might 4 years. - Patients packed with either Merocel, Vaseline gauze, BIPP and Rapid Rhino. Patients also received cautery - Patients admitted to single secondary referral center
Karia *et al*	2021	Prospective Trial	80	-chi-square test	Rebleed at scheduled packing removal: Rapid Rhino: 6/56 Merocel: 1/24 *not significant at the 5% level	-Only measured rebleeds at scheduled follow-up -New article not peer-reviewed yet

Table B.2. Studies the measure comfort in patients with either Rapid Rhino, Merocel or both

Authors	Year	Study Design	Sample Size	Statistic Methods	Results	Comments
Corbridge *et al*	1995	RCT	49	-Mann-Whitney U-test for discontinuous variables - Fisher's exact test for proportions	Insertion: Merocel:6 BIPP:4.6 Removal Merocel: 3.5 BIPP: 2.8 *non-significant at the 5% level	-Pain measured when pack inserted and removed, using a visual analog scale from 1-10 - Patients with epistaxis in ERs
Pringle *et al*	1996	Retrospective review	143	-only visual analog scale	Merocel Insertion:5.3 Treatment: 2.9 Removal: 3.4	- Patients referred to the hospital with epistaxis -143 patients in the study, of which 83 were packed and 34 completed the VAS questionnaire

						- Pain measured when pack inserted, during treatment and removed, visual analog scale from 1-10
Murry *et al*	2018	RCT	26	-Mann-Whitney U Test	Initial: Floseal:2.4 Merocel/gauze:7.8 Insertion: p<0.001 Treatment: Floseal:0.5 Merocel:4.5 Insertion: p<0.001 Removal: Floseal:0.0 Merocel/gauze: 3.9 Insertion: p<0.001	-Pain measured when packing inserted, during the treatment and when removed using a visual analog scale of 10
Abdelkhalek *et al*	2022	Prospective Cohort	60	-Chi-square test	Mild Pain: Merocel: 19/30 Merocel/Surgical wrap: 19/30 *non-significant at the 5% level Moderate Merocel: 8/30 Merocel/Surgical wrap: 9/30 *non-significant at the 5% level Severe: Merocel: 3/30 Merocel/Surgical wrap: 2/30 *non-significant at the 5% level	- patients are from the emergency room or the ENT room - number of patients were classified under "mild", "moderate" and "severe" pain -chi-square utilized to figure out if there is a difference in the number of patients in each group
Singer *et al*	2005	RCT	40	-Mean differences were calculated	Insertion: Rapid Rhino:30, (95% CI 18 to 41) Rhino Rocket: 48 (95% CI 34 to 61) Mean difference: 18, (95% CI 1 to 35) Removal: Rhino Rocket:23, (95% CI 13 to 33) Rapid Rhino: 11, (95% CI 1 to 21) Mean difference: 12 (95% CI −1 to 25)	- Patients at 1 urban and 1 suburban hospital were randomized to either Rapid Rhino or Rhino Rocket -Patient discomfort was measured at insertion and removal using a visual analog scale from 1 to 100 -Only 18 patients in Rapid Rhino and 18 patients in Rhino Rocket were included for assessing pain

						during insertion and removal
Hettige et al	2013	Prospective cohort	12	Wilcoxon rank sum test for unilateral vs bilateral packing	Pain felt by patients on a visual 10 point scale 40mmHg Unilateral: 1.4 Bilateral: 1.2 60mmHg Unilateral: 1.7 Bilateral: 1.5 80 mmHg Unilateral: 2.7 Bilateral: 2.1 100 mmHg Unilateral: 3.6 Bilateral: 2.9 120 mmHg Unilateral: 4 1 Bilateral: 3.7 140 mmHg Unilateral: 5.0 Bilateral: 4.1 160 mmHg Unilateral: 4.8 Bilateral: 4.1	-Patients were packed bilaterally to see their comfort level - Adult participants were recruited into the study
Badran *et al*	2005	RCT	50	-Wilcoxon rank sum test	Insertion: Merocel: 6.9/10 Rapid Rhino: 5/10 p=0.01 Removal Merocel: 4.6/10 Rapid Rhino: 3.4/10 p=0.05	- patients discomfort during insertion and removal measured using a visual analogue scale of 10
Moumoulidis *et al*	2006	RCT	42	-Mann-Whitney U Test	Insertion: Merocel:6.5 Rapid Rhino: 3.9 Insertion: p<0.001 Treatment: Merocel: 2.3 Rapid Rhino: 2.3 *not significant at the 5% level Removal: Merocel: 5.0 Rapid Rhino: 2.5 Removal: p<0.001	- Patients with epistaxis - Patients randomized with Merocel or Rapid Rhino - Pain measured when pack inserted, during treatment and removed, visual analog scale from of 10
Karia *et al*	2021	Prospective Trial	80	-Mann-Whitney U Test	Insertion: Merocel:7.08 Rapid Rhino: 6.74 Not significant at the 5% level	-Pain measured at pack insertion, during treatment and remove using

					Treatment: Merocel: 3.52 Rapid Rhino: 4.98 *not significant at the 5% level Removal: Merocel: 6.09 Rapid Rhino: 4.05 Removal: p=0.02	Wong-Baker FACES pain test -New article not peer-reviewed yet

Appendix C: Ethics Approval

Western Research

HSREB Initial Application

1.1

1.1 *If this is the first time you are submitting this particular application to the REB, select "Initial Submission". If this application form has already been reviewed by the REB and they issued recommendations, select "Response to REB recommendations":

- ○ Initial Submission
- ◉ Response to REB recommendations

1.2

1.2 *Does this study involve the London hospitals (see HELP text if you are unsure):

- ○ No this study does not involve the London hospitals
- ◉ Yes this study involves the London hospitals and this form has been exported from ReDA.
- ○ This study involves the London Hospitals but a ReDA application has not been completed. NOTE: You cannot submit this application until the ReDA application has FIRST been completed and you exported from ReDA to WREM.

*What is the Lawson ReDA number associated with this study?

11625

*As this study IS taking place in the hospital, copy and paste: lawsonapproval@lawsonresearch.com in the below email text box:

Email [redacted]

1.3

Once the PI is added to this form you MUST also add them into the ROLES tile (See ROLES tile in the actions items on the left hand side of your screen).

1.3 Use the Search field to enter the Principal Investigator (PI) details from the WREM user directory:

*Prefix	*First Name	*Last Name
Dr.	Leigh	Sowerby

*Telephone [redacted]

*Email

*Indicate the PI's Western Academic Faculty/Department:

Schulich-Otolarynogology – Head and Neck Surgery

Indicate the PI's Hospital Department/Division:

Otolaryngology - Head & Neck Surgery

1.4

Once study team members are added to this form you MUST also add them into the ROLES tile (See ROLES tile in the action items on the left hand side of your screen).

1.4 *Are there any additional study team members (incl. students, postdocs, coordinators, managers, etc.) from Western and/or its affiliate institutions working on this study?

- (•) Yes there are additional study team members
- ( ) No other study team members involved

1.4 *Complete the following information for additional study team members (from Western and or its affiliate institutions) who are working on this study:

Prefix	*First Name	*Last Name
Miss	Dhatri	Shukla

Telephone

*Email [redacted]

1.4 Specify ROLE, DUTIES, and DEPARTMENT/FACULTY. (E.g. John Doe - Research Assistant - responsible for recruitment, interviews and analysis of data; Psychology/Social Sciences.):

chart review, data analysis

1.4a *Are there any additional study team members (incl. students, postdocs, coordinators, managers, etc.) from Western and/or its affiliate institutions working on this study?

(•) Yes there are other study team members
( ) No other study team members

1.4a *Use the Search field to enter the following information for additional study team members (from Western and or its affiliate institutions) who are working on this study:

Prefix	*First Name	*Last Name
Dr.	Sisira	Sarma

Telephone

*Email [redacted]

1.4a *Specify ROLE, DUTIES, and DEPARTMENT/FACULTY. (E.g. John Doe - Research Assistant - responsible for recruitment, interviews and analysis of data; Psychology/Social Sciences.):

Dr. Sarma- helping to guide analysis, project conception/design, manuscript drafting; Department of Epidemiology and Biostatistics

1.4b *Are there any additional study team members (incl. students, postdocs, coordinators, managers, etc.) from Western and/or its affiliate institutions working on this study?

( ) Yes there are other study team mbmers
(•) No other study team members

1.4 *Complete the following information for additional study team members (from Western and or its affiliate institutions) who are working on this study:

Prefix	*First Name	*Last Name
Miss	Dhatri	Shukla

Telephone [redacted]

*Email [redacted]

1.4 Specify ROLE, DUTIES, and DEPARTMENT/FACULTY. (E.g. John Doe - Research Assistant - responsible for recruitment, interviews and analysis of data; Psychology/Social Sciences.):

chart review, data analysis

1.4a *Are there any additional study team members (incl. students, postdocs, coordinators, managers, etc.) from Western and/or its affiliate institutions working on this study?

- (•) Yes there are other study team members
- ( ) No other study team members

1.4a *Use the Search field to enter the following information for additional study team members (from Western and or its affiliate institutions) who are working on this study:

Prefix	*First Name	*Last Name
Dr.	Sisira	Sarma

Telephone [redacted]

*Email [redacted]

1.4a *Specify ROLE, DUTIES, and DEPARTMENT/FACULTY. (E.g. John Doe - Research Assistant - responsible for recruitment, interviews and analysis of data; Psychology/Social Sciences.):

Dr. Sarma- helping to guide analysis, project conception/design, manuscript drafting; Department of Epidemiology and Biostatistics

1.4b *Are there any additional study team members (incl. students, postdocs, coordinators, managers, etc.) from Western and/or its affiliate institutions working on this study?

- ( ) Yes there are other study team mbmers
- (•) No other study team members

1.5

1.5 *Enter the Complete Study Title:

Retrospective epistaxis review: An economic evaluation for epistaxis management in emergency department in London Ontario

1.6

1.6 *What is the acronym or nickname/short title for the study? (NOTE: The acronym or nickname/short title will be used to identify the study and will be included in all notifications and REB applications associated with this project.):

Retrospective epistaxis review

1.7

1.7 *What type of REB submission is this?

- ○ Full Board
- ○ Delegated Level 2 - Prospective data collection
- ◉ Delegated Level 1 - Retrospective study data and/or biological sample collection

1.8

1.8 *Are any of the investigator(s) based at any of the sites below or will the study utilize any patient data/biological specimens, staff resources or facilities within any of these sites? (Please indicate all applicable sites):

- ☐ No

LHSC Sites

- ☐ Adult Eating Disorder Service (Riverview)
- ☐ Byron Family Medical Centre
- ☐ Children's Hospital
- ☐ Fowler Kennedy Sports Medicine
- ☐ Kidney Care Centre (Westmount)
- ☐ London Regional Cancer Program (LRCP)
- ☐ Southwestern Ontario Regional Base Hospital Program
- ☐ Stroke Prevention & Atherosclerosis Research Centre
- ☑ University Hospital (UH)
- ☐ Victoria Family Medical Centre
- ☑ Victoria Hospital (VH)

St Joseph's Sites

- ☐ Mount Hope Centre for Long Term Care
- ☐ Parkwood Institute – Main Building
- ☐ Parkwood Institute Mental Health Care
- ☐ Southwest Centre for Forensic Mental Health Care
- ☐ St. Joseph's Family Medical and Dental Centre
- ☑ St. Joseph's Hospital

1.9

1.9 *Is this study directly related to a study at this institution (e.g., is this study a sub-study, extension, rollover, subsequent to a pilot study)?

Please note that not only does this provide context for the reviewers at large but also impacts Ethics Officer assignment for continuity with a particular program of research.

- ◉ Yes – This study relates to a previously approved study at this institution
- ○ Yes –This study relates to a study currently under Western's REB review, but has not yet been approved
- ○ No - This study does not relate to a previous study at this institution

*Who was the PI for the study?

Sowerby

*What is the HSREB number?

119264

*Indicate the study title of the previous study. Provide a brief summary of the previous study and indicate how it relates to this current study:

Rapid Rhino vs. merocel epistaxis review. This was a QA project - it has bloomed into potentially more, looking at all possible options for treating epistaxis, and as such we would like to approach it as a formal research protocol now.

1.10

1.10 *Upload the protocol/research plan for this study. NOTE: ALL HSREB submissions require a protocol/research plan:

Documents

Type	Document Name	File Name	Version Date	Version	Size
Protocol	Research Proposal clean copy	Research Proposal clean copy.docx	02/Nov/2021	3	25.5 KB

Note that your document name will appear on the approval notices. Ensure you name your document something that reflects what the document is (e.g., debriefing script, date). Avoid using slang, student names, etc. Upload only the clean version here (i.e., not the tracked copy). Do not include "clean" in the document name.

1.11

1.11 *Is this an Investigator-initiated study?

- (•) Yes
- ( ) No

1.12

1.12 *Who is the Study Sponsor?

- [ ] Industry Sponsored
- [ ] External Non-Profit
- [ ] External PI (outside of Western)
- [ ] Local PI (Western-affiliated team member other than PI on this REB application)
- [x] Self (PI on this REB application)

1.13

1.13 *Is this primarily a student project?

- ☐ No
- ☐ Yes - Resident/Fellow
- ☐ Yes - MD
- ☐ Yes - Post-doctoral Fellow
- ☐ Yes - PhD
- ☑ Yes - Masters
- ☐ Yes - Undergraduate
- ☐ Yes - Other

1.14

1.14 *Has the study undergone a formal scientific or peer review (i.e., internal peer review or external review (e.g., CIHR, NSERC, NIH, etc.))?

- ○ Yes
- ◉ No

1.15

1.15 *Has the study been reviewed and approved by another REB in Canada?

- ○ Yes
- ◉ No
- ○ pending

1.16

1.16 *Has the study been rejected by any other REB?

- ○ Yes
- ◉ No

1.17

1.17 *Is this research study supported/funded by the United States federal government or regulated by the FDA (Food and Drug Administration)?

- ○ Yes
- ◉ No

1.18

1.18 *Is this a multi-centre study?

- ○ Yes
- ◉ No

1.21

1.21 *Is there an external third party (Coordinating or Contract Research Organization) overseeing the study?

- ○ Yes
- ◉ No

1.22

1.22 *Are there any associated sub-studies or companion studies?

- ○ Yes
- ◉ No

1.23

1.23 *Indicate how the results will be communicated to participants and other stakeholders (e.g.; advocacy groups, scientific community).

***To Participants:**

- ☐ Debriefing Script
- ☐ Group debriefing
- ☐ End of study letter
- ☑ Publication(s)
- ☐ Other
- ☐ No Plan

***To Other Stakeholders:**

- ☑ Presentation(s)
- ☑ Publication
- ☐ Other
- ☐ No plan

1.24

1.24 *Provide a brief lay/non-scientific summary of the study (max 250 words)

Nosebleeds are a common problem, and sometimes require management at emergency rooms. There is no singular pathway to managing a bleed. Different interventions to stop bleeds have different efficacies and costs associated with them. To compare and contrast which intervention is best for patients while also being cost-effective for the hospital, information on costs and efficacy is to be collected retrospectively.
A retrospective review using medical charts of patients presenting with epistaxis in the emergency department for Victoria and University hospital from January 2018-December 2020 will be conducted. The study will collect data on the types of interventions used to stop the bleeding. Using this, the average cost associated with each patient and intervention will be calculated. Then we will collect data on the rebleed rate. Time spent in the emergency department will also be collected to assess hospital costs. Using this data a cost-benefit analysis will be conducted using a decision tree model. A decision tree model will be used because epistaxis is usually a short term problem not a life-long one. Sensitivity and probability analysis will be conducted to assess how changes in base variables affect the outcome.

Patient's baseline characteristics will also be collected. This is to assess for confounding as these variables can confound the relation between the intervention and the outcome (rebleed rate). Furthermore, using propensity score matching this data can provide more detailed information on intervention efficacy. We are assuming a sample size of 300 based on previously collected non-research data at Lawson for epistaxis.

2.1

2.1 *Does this retrospective study include the collection of (select all that apply):

- [x] Chart/Record collection
- [ ] Biological Specimens
- [ ] Registry data
- [ ] Existing research dataset
- [ ] Bioarchaeological Human Remains
- [ ] Other

*How many participants charts/records will be accessed?

unknown - based on previous reviews we suspect that Jan 2018- Dec 2020 will include around 300 participants

2.2

2.2 *Provide the Retrospective start date for study data and/or biological sample collection. NOTE: To qualify as retrospective, study data and/or biological sample(s) must have been collected prior to your initial submission.

January 2018

2.3

2.3 *Provide the Retrospective end date for study data and/or biological sample collection. NOTE: To qualify as retrospective, study data and/or biological sample(s) must have been collected prior to your initial submission.

December 2020

2.5

2.5 *What are the study hypotheses or research question(s) or purpose of this study?

As there is limited literature on the economics' of epistaxis management, we are conducting an economic evaluation in London Ontario to expand the literature as well as provide more information to design-makers on cost-effective management methods.

2.6

2.6 *What is the rationale for this study (why is it being done)? In your response ensure to include relevant background information from previous studies that have been done. Cite references where appropriate and add LIST as a separate attachment (do not include within your response).

Epistaxis, more commonly known as a nosebleed, is a regular problem. In a hospital emergency room there is no universal procedure to stop a bleed. A nosebleed can go away by itself with time. However, some patients require an intervention or a combination of interventions from clinicians. Some of these interventions include directed therapy like cauterizing the nose-bleed with silver nitrate. Nasal packs, both dissolvable and non-dissolvable, can be inserted into the nose to stop the bleed. They are then removed within 24 hours by the clinicians. Popular nasal packs include Rapid Rhino, Merocel and Floseal. The efficacy of dissolvable, non-dissolvable packs and other hemostatic agents in preventing re-bleeds is a well researched area of literature (1-5). In the Canadian context, one such study indicates that cautery via silver nitrate is the most effective (6). A systematic review on nasal packs and hemostatic agents, after reviewing twenty-seven articles for non-dissolvable and nine articles for dissolvable packs found that Rapid Rhino is the most tolerable for patients and has at least the same efficacy of nasal tampons in bleeding cessation (7). A 2012 meta-analysis found that compared to Merocel, Rapid Rhino causes less pain for patients (8). However, the literature on costs associated with these interventions are limited. According to a systematic review on epistaxis management there is no robust assessment on dissolvable packs and non-dissolvable packs (7). Without data on costs it is hard for studies to provide recommendations on interventions as both costs and efficacy need to be taken into consideration when in a healthcare setting. This is especially true in the Canadian context as Canada has a public healthcare system.

Upload a list of references used in your rationale above (if applicable):

Documents

Type	Document Name	File Name	Version Date	Version	Size
References	Work cited	Work cited.docx			286.2 KB

2.7

2.7 *Provide a brief summary of the study design type and methodology being employed in this study.

DO NOT include Information about objectives, inclusion/exclusion criteria, study procedures, sample size calculations and data analysis here.

The design for this study is a retrospective cohort. The project will use data from patients' medical chart's who had epistaxis from January 1, 2018 to December 31,2020 in emergency rooms from Victoria and University hospital. Charts are seen as the gold standard when reviewing information retrospectively. They would provide accurate and detailed information on a patient's experience in the emergency room. A cohort design is being used as we have started with a defined cohort and followed them through time to figure out re-bleed rates. Cohort was chosen over a retrospective case-control as the study is not comparing epistaxis patients to non-epistaxis patients, and we are not directly comparing one specific intervention to another specific intervention. A cohort design would allow for relative risk ratios to be calculated for interventions.

The variables in this study being measured are cost's and efficacy. In this study effectiveness is defined as the cessation of bleeding and the rate of recurrence of re-bleeds/readmission to the emergency department in a two week timeframe. The two-week timeframe was chosen due to previous studies based in Canada, which assessed epistaxis using a two-week timeframe. Costs will be based on the number of interventions and time spent in the ER by a patient.

Upload a flow diagram (if applicable):

2.15

2.15 *Does this study include a non-patient group (e.g., caregiver, student, employee, etc.)-SEE HELP TEXT?

- ○ Yes
- ◉ No

2.21

2.21 *Is this a collaborative community-based project?

- ○ Yes
- ◉ No

2.22

2.22 *Indicate your data collection tools/forms by selecting the relevant option(s) below:

- ☐ Paper Survey(s)/Questionnaire(s)
- ☐ Online Survey(s)/Questionnaire(s)
- ☐ Interview Guide(s)
- ☐ Focus Group Guide(s)
- ☐ Non-Participant Observation Guide(s)
- ☐ Participant Observation Guide(s)
- ☐ Case Report Form(s)
- ☑ Other (e.g., visual stimuli, participant diary, data collection forms, etc.)

*Upload "Other" instrument(s) that will be used during this study:

Note that your document name will appear on the approval notices. Ensure you name your document something that reflects what the document is (e.g., debriefing script, date). Avoid using slang, student names, etc. Upload only the clean version here (i.e., not the tracked copy). Do not include "clean" in the document name. Avoid using slang, student names, etc.

*Upload "Other" instrument(s) that will be used during this study:

Documents

Type	Document Name	File Name	Version Date	Version	Size
Other Data Collection Instruments	data collection form	data collection form.xlsx	17/Nov/2021	4	17.0 KB

*Upload "Other" instrument(s) that will be used during this study:

Note that your document name will appear on the approval notices. Ensure you name your document something that reflects what the document is (e.g., debriefing script, date). Avoid using slang, student names, etc. Upload only the clean version here (i.e., not the tracked copy). Do not include "clean" in the document name. Avoid using slang, student names, etc.

*Upload "Other" instrument(s) that will be used during this study:

Documents

Type	Document Name	File Name	Version Date	Version	Size
Other Data Collection Instruments	Master list	Master list.xlsx	17/Nov/2021	4	21.2 KB

*Describe "Other" instrument(s) and how they will be used in this study:

This is the master list.

2.23

2.23 *Will any technological tool(s)/platform(s)/software/device(s) be used (beyond an institutional network or hard drive) throughout the project (e.g., data collection, analysis, transfer, storage, etc.)?

- (•) Yes
- ( ) No

*Specify the tool(s)/platform(s)/software(s)/device(s):

REDCap for storage, Western office 365 (excel) for analysis, Stata for analysis, TreeagePro for anaylsis

*Has the tool(s)/platform(s)/software(s)/device(s) received any of the following:

- Technology Risk Assessment by Western's Technology Risk Assessment Committee (TRAC)?
- Authorized Technology Review at LHSC or SJHC?
- Review by a local institutional privacy office (e.g., Western's privacy office, hospital privacy, or other collaborating institution privacy office)?

○ Yes
○ No
◉ unsure

*Specify what information will be collected through and/or entered into the tool(s)/platform(s)/software(s)/device(s) and for what purpose:

If personal identifiers will be shared using the technology, please list them and ensure consistency with Q13.11

Age, Sex and medical pin will be stored on Redcap plus any other intervention/time spent in the ER as listed on the data collection excel sheet. For excel, Stata and tree age pro sex, age plus other interventions/time spent in the ER as listed on the data collection sheet but not medical pin will be used for analysis.

*Specify who will have access to this information and for what purpose (incl. third party vendors and any future use, if applicable):

The access to information will be limited to Dhatri Shukla, Professor Sirsa Sarma and Dr. Leigh Sowerby

*Specify how long will the information be accessible in the tool(s)/platform(s)/software/device(s):

All the information should be deleted off excel, stata and redcap as soon as analysis of the data is finished around june to july 2022. The information stored on RedCap will be removed according to Lawson retention policy.

*Specify how the information will be removed from the tool(s)/platform(s)/software/device(s):

The saved file will be deleted.

2.26

2.26 *Is the sample size justified in the study protocol/research plan or sponsor protocol?

◉ Yes
○ No

*Describe the sample size justification. If there is a description of the justification in a study protocol/research plan, indicate the page number.

The page number is 2.

2.27

2.27 Describe the method(s) for data analysis.

The hours in the emergency room and the dates the patients visited the room will be used to calculate hospital operational costs. For University and Victoria hospital there is an hourly fixed cost for weekends. On weekdays costs change depending on the time the patient visits the ER. For nasal packing, the hospital provides the cost of all the packs in a package. The study will divide this cost by the number of packs in a package, and then multiply them by the number of consumed packs by the patient. If a medical chart reads that nasal clips, topical txa, cocaine/epinephrine, otrivin, surgiform, surgicel and gauze have been used, this study will assume a patient will consume one unless stated otherwise. Usually 3-4 sticks are needed for cauterizing bleeds with silver nitrate. This study will assume an average of 2.5 unless explicitly stated otherwise.

Using the efficacy data, probabilities associated with rebleeds for each intervention will be calculated. Each probability will be assigned a continuous probability distribution (gamma, beta etc) depending on the data. To ensure accuracy, re-bleed-rates for current literature will be reviewed to see if this model's probabilities align with them. If a large number of patients use Merocel then a relative risk ratio would be calculated for different interventions using Merocel as the control group. The comparison groups will be based on the number of patients in each intervention to ensure large groups. Based on the previously collected data, Merocel is likely to be the control group, with Rapid Rhino as one comparison group. If there is a small number of patients in other interventions, they may be grouped together based on similar characteristics (directed therapy, non-dissolvable packs).

The economic evaluation would take a perspective based on the payer. Since epistaxis tends to be a short-term problem a decision tree model would be better suited than a Markov model which is used for more life-long problems. The modelling approach will follow the guidelines outlined by the Canadian Agency for Drugs and Technologies in Health (CADTH). An incremental cost-effective ratio will be calculated using the re-bleed rate and costs. Furthermore, given if there is a large sample size, the study will use propensity score matching based on patients baseline clinical characteristics. This will adjust for baseline characteristics allowing for more direct comparisons between interventions while also adjusting for confounding. A thorough sensitivity analysis (both deterministic and probabilistic) will be conducted to account for uncertainty in parameters of the model. The deterministic sensitivity analysis will be used to test what happens if changes are made to any underlying parameter value. While the probabilistic analysis will be conducted to assess the parameter uncertainty in the calculations.

2.28

2.28 *Provide the inclusion criteria:

The inclusion criteria for this study is any patient whose primary diagnosis is epistaxis.

2.29

2.29 *Provide the exclusion criteria.

The exclusion criteria is anyone whose secondary diagnosis is epistaxis or those who have died before the two week follow-up.

2.30

2.30 *What is/are the primary objective(s) of the study and briefly describe how it/they will be measured. NOTE: For qualitative research studies-If this is not applicable indicate "NA"

The primary objectives are to calculate the efficacy and costs related to different methods of epistaxis management in emergency rooms for both Victoria and University Hospital.

In this study effectiveness is defined as the cessation of bleeding and the rate of recurrence of re-bleeds/readmission to the emergency department in a two week timeframe. The two-week timeframe was chosen due to previous studies based in Canada, which assessed epistaxis using a two-week timeframe.

Costs will be measured using information gathered from the medical charts. From the medical charts information on types of interventions (listed on excel sheet), repeat visits, date/time in the ER, any add information on consumable costs, and any referrals to Otolaryngology will also be collected for the purposes of analyzing costs. The costs associated will be estimated using the London Health Science Center case-costing information, submitted to the Ontario case costing initiative. The direct costs of any intervention will be obtained from the hospitals' finance departments.

2.31

2.31 What is/are the secondary objective(s) (if applicable) of the study and briefly describe how it/they will be measured.

11.1

11.1 *Describe any direct benefits to the study participants. If there are no direct benefits to the participants themselves, please state as such:

There is no direct benefits to the study participants

11.2

11.2 *What is the overall anticipated public and scientific benefits of the study?

The findings from this thesis will be communicated to London Health Sciences decision-makers and clinicians through seminar through presentations and grand round presentations to both the Departments of Emergency Medicine and Otolaryngology – Head and Neck Surgery. This project will also be presented at Lawson Health Research Day. It will provide them with valuable information to determine if switching to certain interventions/packs will be a cost-effective strategy, and its implications for adoption in hospitals in Canada and beyond. This study will also provide important insights into the cost-effectiveness of nasal pack choices and help to decide which packs should be chosen for efficient resource allocation. This study would contribute to the developing literature on selection of nasal packing.

12.1

12.1 *Will Personal Information (PI) and/or Personal Health Information (PHI) be used to identify potential participants (pre-screening)?

- ○ Yes
- ◉ No

12.2

12.2 * Is a waiver of the requirement to obtain informed consent being requested for any aspect of this study (If you are obtaining consent for part of the study and requesting a waiver for another aspect of the study select both Yes AND No)?

- ☑ Yes I am requesting a waiver of consent
- ☐ No I am not requesting a waiver of consent

*Specify for what type of data the waiver is being requested?

- ☐ Prospective data collection
- ☑ Secondary use of identifiable information
- ☐ Secondary use of non-identifiable information

*In accordance with Tri-Council Policy Statement 2, Article 5.5A, please confirm that ALL of the following conditions apply:

- Identifiable information is essential to the research
- The use of identifiable information without the participants' consent is unlikely to adversely affect the welfare of individuals to whom the information relates
- The researchers will take appropriate measures to protect the privacy of individuals, and to safeguard the identifiable information
- The researchers will comply with any known preferences previously expressed by individuals about any use of their information
- It is impossible or impracticable to seek consent from individuals to whom the information relates

The researchers have obtained any other necessary permission for secondary use of information for research purposes

- ◉ I confirm

*Explain why identifiable information is essential to the research:

Identifiable information is essential to the research as an important part of this project is to capture rebleed rates. Rebleed rates might be missed if patients were to go to for example Victoria hospital seeking treatment, for there bleed after primarily going to University Hospital. This is why we need the study pins to identify if there has been any crossover and to capture all the data.

*Explain why not obtaining consent is unlikely to adversely affect the welfare of individuals to whom the information relates:

The study pin are simply to check for crossover, the pin will not be used during the analysis data, a study id will be used instead. The patients pin will not be made public and a study id will ensure privacy.

*Explain what measures will be taken to protect the privacy of individuals, and to safeguard the identifiable information:

The master list (containing study id and pin) is being stored separately from the other study data on an encrypted laptop.

*Explain why it is impossible or impracticable to obtain consent:

There are 300 charts to go over, which would mean contacting about 300 people. Furthermore, the average age of this individuals is 65 and up, which means many could have passed away by now.

13.1

13.1 *(For patient orientated research studies.) Do you plan now or in the future to link your study data to the large healthcare databases held at the Institute for Clinical Evaluative Sciences (ICES)? For example, this would allow you to follow patients passively life-long, determine their healthcare costs, assess how similar your patients are compared to Ontario citizens, and help identify control groups.

- ○ Yes
- ◉ No
- ○ N/A

13.2

13.2 *Are you collecting personal identifiers for this study?

- ◉ Yes
- ○ No

13.3

13.3 *Identify any personal identifiers collected for this study. Select all that apply.

- ☐ Full Name
- ☐ Initials
- ☐ Ontario Health Card Number
- ☐ Address
- ☐ Full Postal Code
- ☐ Partial Postal Code
- ☐ Telephone Number
- ☐ Email Address
- ☐ Family Physican or other care provider names
- ☐ Full Date of Birth
- ☐ Partial Date of Birth
- ☐ Full Date of Death
- ☐ Partial Date of Death
- ☑ Sex
- ☐ Gender
- ☑ Age
- ☐ Medical Device Identifer
- ☑ Hospital Patient Identification Number (PIN)
- ☐ Full Face Photograph
- ☐ Voice/Audio Recording
- ☐ Race
- ☐ Ethnicity
- ☐ Other

*Explain and justify sex and if it will be stored on paper or electronically

This variable will be stored electronically. Sex can affect how patients react to certain interventions. For example Men might benefit positively from an intervention but this intervention may have little to no effect on women. Furthermore, sex can effect the rate of re-bleeds. Men may have higher re-bleeds rate then women. This could have nothing to do with the efficacy of an invention but simply a biological difference. In-order to adjust and assess for this sex needs to be taken into consideration when analysis. This would also allow for more tailored recommendation of epistaxis management based on patients baseline characteristics.

*Explain and justify age and if it will be stored on paper or electronically

This variable will be stored electronically. Older patients may have more occurrence of re-bleeds due to their age and not due to the efficacy of an intervention. Furthermore, certain interventions like nasal tampons may be less effective on old patients. Nasal tampons can be uncomfortable /painful which can lead to removal of the tampon at home or earlier than prescribed. This in turn could increase re-bleed rates.

*Explain and justify hospital PIN and if it will be stored on paper or electronically

This variable will be stored electronically. Medical pins are needed to cross-reference the online chart with paper charts to make sure we have not missed any patient visits to one of the hospitals. However, they will not be used in the analysis portion.

13.4

13.4 *Will there be a master list linking identifiers/identifiable information (e.g., name, contact information) to the unique participant code (e.g., study number, pseudonym)?

- (•) Yes
- ( ) No

*Who will have access to the master list?

Dhatri Shukla, Dr. Leigh Sowerby, Professor Sirsa Sarma

13.5

13.5 *Where will information collected as part of this study be stored (applies to both paper copy and electronic copy)? (select all that apply)

- [x] University or Hospital network drive
- [ ] University or Hospital local hard-drive
- [ ] Office/Lab of PI or Research team member on Institutional Property
- [ ] Laptop
- [ ] Memory Stick
- [ ] Cloud Storage
- [ ] Off-site
- [ ] Other

*Specify the University or Hospital network drive:

Redcap is a software server, which is on the local web server at university and Victoria hospital.

13.6

13.6 *Indicate the measures in place to protect the confidentiality and security of any study data including Personal Information (PI) or Personal Health Information (PHI) that is accessed, collected and used (select all that apply):

- [x] Access to study data and/or medical recordswill be limited to authorized personnel
- [x] Access to electronic data will, at least, be password protected (if not password protected AND encrypted)
- [x] Electronic data will be stored on a Western, hospital or other institutional server with firewalls and other security and back-up measures in place
- [ ] Study data stored on external hard drive, laptop(s) and/or portable device(s) will be encrypted
- [ ] Paper copies of study data will be stored in locked filing cabinets in a secure location
- [x] A master log with identifiers will be stored separately from the study data
- [ ] Other

13.7

13.7 Describe where study data/database, source data (including completed surveys), and Letters of Information and Consent, whether electronic or paper, will be kept:

Data will be stored on REDCap

13.10

13.10 *Are you transporting materials (paper, devices and/or media) that include Personal Information (PI) and/or Personal Health Information (PHI) between sites? (See Confidentiality and Data Security guidelines)

- ○ Yes
- ◉ No

13.11

13.11 *Will you be sending/sharing data off-site for this study?

- ◉ Yes
- ○ No

13.11a *Describe where and to whom the data will go:

This information will go to Dr. Sowerby and Dr. Sarma but they will access online from REDCap.

13.11b *Specify what data is going off-site?

De-identified data will be sent off-site for analysis via Stata

13.11c *Does the data to be transferred include any of the following identifiers? Select all that apply.

- ☐ Full Name
- ☐ Initials
- ☐ Ontario Health Card Number
- ☐ Address
- ☐ Full Postal Code
- ☐ Partial Postal Code
- ☐ Telephone Number
- ☐ Email Address
- ☐ Family Physican or other care provider names
- ☐ Full Date of Birth
- ☐ Partial Date of Birth
- ☐ Full Date of Death
- ☐ Partial Date of Death
- ☑ Sex
- ☐ Gender
- ☑ Age
- ☐ Hospital Personal Identification Number (PIN)
- ☐ Medical Device Identifer
- ☐ Full Face Photograph
- ☐ Voice/Audio Recording
- ☐ Other
- ☐ N/A

13.11d *How will the data be transmitted?

- ☐ Secured Fax
- ☐ Electronic (online) data collection
- ☑ Secure file transfer
- ☐ Encrypted email
- ☐ Private courier delivery
- ☐ Canada Post registered mail (NB: Regular mail may not be used)
- ☐ Other

*Describe the details of the secure file transfer:

Filesafe

13.11e If applicable, specify any additional details on data transmission (otherwise leave answer blank):

13.12

13.12 *Who will have access to the identifiable data?

Dhatri Shukla, Leigh Sowerby, Sisira Sarma, Western HSREB and Lawson QAEP

13.13

13.13 *How long will you retain identifiable data?

- ○ 7 years as per UWO policy
- ◉ 15 years as per Lawson policy
- ○ 25 years as per Health Canada policy
- ○ Other

13.14

13.14 *How will you destroy the identifiable data after this period (if applicable)?

All the information will be deleted from REDCap.

13.15

13.15 *Will you link the locally collected data with any other datasets, databases or registries (e.g., health registries, Statistics Canada)?

- ○ Yes
- ◉ No

13.16

13.16 *Is the purpose of this study to establish a registry/database?

- ○ Yes
- ◉ No

13.17

13.17 *Indicate the extent the study participant is able to withdraw their study data from the research study and any limitations on the withdrawal

Since it is a retrospective study and we are waving the consent wavier it would be difficult for a participant to withdraw.

14.1

14.1 *Is this study funded?

- (•) Yes
- ( ) No

14.2

14.2 *How is the study funded?

- [ ] Industry
- [ ] Internal Grant (departmental/faculty, VP, IRF/SRF, etc.)
- [ ] External Grant (Tri-Council (e.g., CIHR, SSHRC, NSERC, NCE), government, charitable foundation, etc.)
- [x] Other

*Specify Other:

Self-funded from clinical trial residual funds

14.3

14.3 *Are there any (or will there be) research funds held in an account at Western or Lawson?

- [ ] Lawson
- [ ] Western University
- [x] No

14.4

14.4 *What is the status of funding from this source?

- ( ) Obtained
- (•) Awarded but not received

*Will you be able to proceed with the study?

Yes. Clinical trial residual funds are covering the cost of pulling charts. Dept of Otolaryngology funding is covering a stipend for Ms. Shukla

14.5

14.5 Indicate what compensation, if any, will be provided to participants and include a justification for compensation. If this question does not apply, indicate "not applicable" or "N/A".

N/A

14.10

14.10 Attach an itemized study budget. The budget should reflect all costs to complete the study (e.g., REB fees for industry sponsored studies, database extraction, student payments, participant reimbursements, etc.).

Documents

Type	Document Name	File Name	Version Date	Version	Size
Study budget	costs	costs.xlsx			8.9 KB

16.1

16.1 *Will the PI or Co-Investigator(s) or anyone connected to them through their interpersonal relationship (including their partners, family members, or their former or current professional associates) receive any personal financial benefit in connection with this study?

- ○ Yes
- ◉ No

16.2

16.2 *Will the PI or Co-Investigator(s) or anyone connected to them through their interpersonal relationships (including their family members, friends, or their former or current professional associates) receive any personal (financial or otherwise) benefits including patent or intellectual property rights, royalty income, employment, share ownership, stock options, etc?

- ○ Yes
- ◉ No

16.3

16.3 *Is the PI or Co-Investigator(s) aware of any other community relationships, academic interests, financial partnerships, or economic interests (e.g., spin-off companies in which researchers have stakes or private contract research outside of the academic realm) or any other incentives that may compromise their integrity, independence or ethical duties in the conduct of the research?

- ○ Yes
- ◉ No

16.4

16.4 * Is the PI to Co-Investigator(s) aware of any institutional conflicts of interest (financial or non-financial) that may have an impact on the research?

- ○ Yes
- ◉ No

16.5

16.5 * Does the PI or Co-Investigator(s) or anyone connected to them through their interpersonal relationships (including their family members, friends, or their former or current professional associates) have any proprietary interest in the product under study or in any entity that is sponsoring or otherwise supporting the conduct of the study?

- ○ Yes
- ◉ No

16.6

16.6 *Will or does the PI or Co-Investigator(s) or anyone connected to them through their interpersonal relationships (including their family members, friends, or their former or current professional associates) have any association or connection with an entity that is sponsoring or otherwise interested in the outcome of the study? (e.g., consultant, advisor, board member, employee, director, etc.)

- ○ Yes
- ◉ No

16.7

16.7 *Are you or your institution the sponsor of this investigator-initiated/sponsored study?

- ○ Yes
- ◉ No

16.8

16.8 * Are there any other real, potential or perceived conflict of interest to declare to the REB?

- ○ Yes
- ◉ No

18.1

Although the REB requests that you delete previous version documents and replace them with updated, revised documents please DO NOT delete any of the response letters. They can all stay attached. Ensure you have different version date and/or number for each response letter.

18.1 *Upload the Response Letter, listing all REB recommendations/questions/comments and an explicit response to each:

Documents

Type	Document Name	File Name	Version Date	Version	Size
REB Response Letter	Comment 1	Comment 1.docx	24/Oct/2021	1	21.0 KB
REB Response Letter	Comment 2	Comment 2.docx	02/Nov/2021	2	22.4 KB
REB Response Letter	Comment 3	Comment 3.docx	09/Nov/2021	3	22.7 KB
REB Response Letter	Comment 4	Comment 4.docx	17/Nov/2021	4	23.2 KB

18.2

18.2 If changes have been made to a previously submitted consent/assent form(s) at the request of the REB, upload track-changes versions of all proposed consent and/or assent form (e.g. screening, main, optional), if applicable:

18.3

18.3 If changes have been made to a previously submitted study instruments/stimuli (e.g., survey, questionnaire, interview guide, focus group guide, observation guide, etc.) at the request of the REB, upload the track-changes version(s):

Documents

Type	Document Name	File Name	Version Date	Version	Size
Tracked Changes Document	master list part 2	master list part 2.xlsx	17/Nov/2021	4	20.7 KB
Tracked Changes Document	data collection form part 2	data collection form part 2.xlsx	17/Nov/2021	4	15.6 KB

18.4

18.4 If changes have been made to a previously submitted protocol, research plan, research outline please upload the track-changes version(s):

Documents

Type	Document Name	File Name	Version Date	Version	Size
Tracked Changes Document	Research Proposal	Research Proposal.docx	02/Nov/2021	3	29.2 KB

18.5

18.5 Please provide any additional comments for the REB to consider (if applicable):

19.1

19.1 *Confirm that all study team members have received a certificate for completion of human research ethics training through one of the following (select ALL that apply):

- ☑ Tri-Council Policy Statement (TCPS2) Core Tutorial
- ☑ Collaborative Institutional Training Initiative (CITI Program)
- ☐ Other

19.3

19.3 *Principal Investigator OR Delegate Signature:

The Principal Investigator may choose to sign off electronically on all **re-submissions** (i.e., response to REB recommendations) or he/she may delegate this task to another qualified individual. **NOTE:** The PI is still fully responsibility for the scientific and ethical conduct of the study at this institution.

- I attest that this application as submitted is in compliance with the TCPS2 (2nd edition of Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans); AND, if applicable, with the provisions of the Ontario Personal Health Information Protection Act and its applicable Regulations; AND, with all other applicable laws, regulations or guidelines (e.g., if applicable, Food and Drugs Act and applicable Regulations; International Conference on Harmonization Guidance E6: Good Clinical Practice);
- I attest that, to the best of my knowledge, the information in this application is complete, current and accurate;
- I attest that this application contains the current and complete protocol, including, if applicable, any sub-studies;
- I acknowledge that I am responsible for promptly reporting any of the following to the REB:
  - modifications or amendments, such as changes in PI, changes in Co-investigator (if applicable), specific required changes to the Letter of Information/consent form, etc.;
  - all local reportable events that meet the REB reporting criteria, including but not limited to local unexpected, serious adverse events (SAEs), privacy breaches, protocol deviations and any new information that may adversely affect the safety of the participants or significantly affect the conduct of the study;
  - progress report (renewal/ continuing review form), annually or as often as requested by the REB;
  - study completion or termination;
- I certify that REB approval and all external and local institutional approvals will be obtained before the study will commence;
- I certify that the research team will adhere to the protocol and consent form as approved by the REB unless to eliminate an immediate safety hazard to participants and in accordance with any conditions placed on the REB approval;
- I certify that all information provided in this application represents an accurate description of the conduct of the study.
- I have made efforts to ensure that the research intent, purpose, and impact of this study will be free from bias or discrimination in accordance with the Canadian Charter of Rights and Freedoms.

Privacy and Security Acknowledgement:

- On behalf of all members of my research team, I recognize the importance of maintaining the confidentiality of personal health information (PHI)/Personal Information (PI) and the privacy of individuals with respect to that information;
- I will ensure that the PHI/PI is used only as necessary, to fulfill the specific study objectives and related study questions described in the application approved by the REB. This includes all conditions and restrictions imposed by the REB and the institution in which the study is being conducted, governing the use, security, disclosure, return or disposal of the study participants' personal information;
- I agree to take any further steps required by the REB or the institution to ensure that the confidentiality and security of the PHI/PI is maintained in accordance with the Personal Health Information Protection Act (PHIPA) and/or Freedom of Information Protection of Privacy Act (FIPPA), its accompanying regulations, and the Tri-Council Policy Statement

Signed: This form was signed by Dr. Leigh Sowerby [redacted] on 17/Nov/2021 2:40 PM

Appendix D: Propensity Score results using “pscore” and “teffects” on STATA

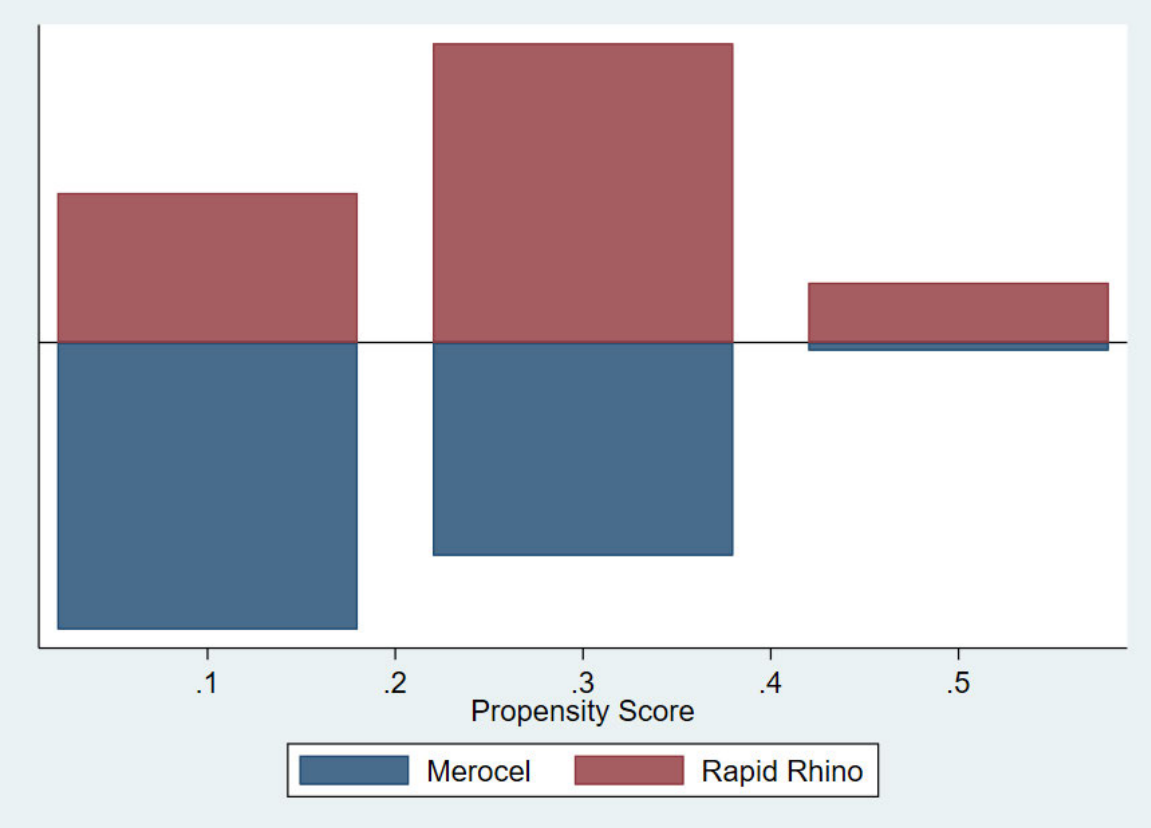


Figure D.1: Matching propensity scores after common support restrictions

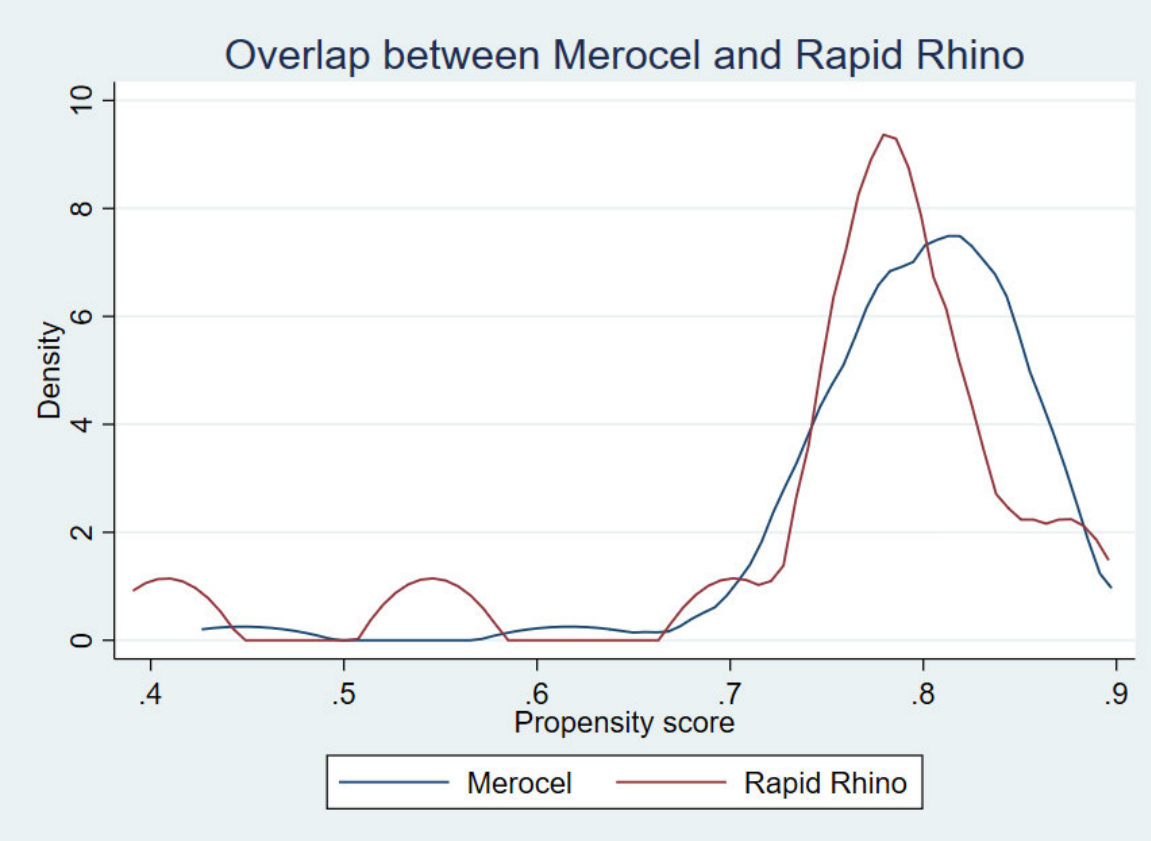


Figure D.2. Overlap of propensity scores between Merocel and Rapid Rhino for ATT

Appendix E: Additional results from the analysis

E.1. Median ages for patients included into the study

	Median	1st and 3rd Interquartile
Whole Cohort	71	61 to 79
Rapid Rhino	66	62 to 75
Merocel	71	61 to 82

Table E.2. Median costs for the hospital's perspectives

	Median	1st and 3rd Interquartile
Whole Cohort	$289.06	$209.61 to $467.24
Rapid Rhino	$ 367.54	$224.86 to $407.59
Merocel	$276.80	$209.61 to $467.82

Table E.3. Median costs for the provincial health care perspective

	Median	1st and 3rd Interquartile
Whole Cohort	$466.32	$307.73 to $598.24
Rapid Rhino	$491.24	$322.56 to $550.80
Merocel	$406.02	$290.14 to $600.22

Appendix F: Additional cost-analysis

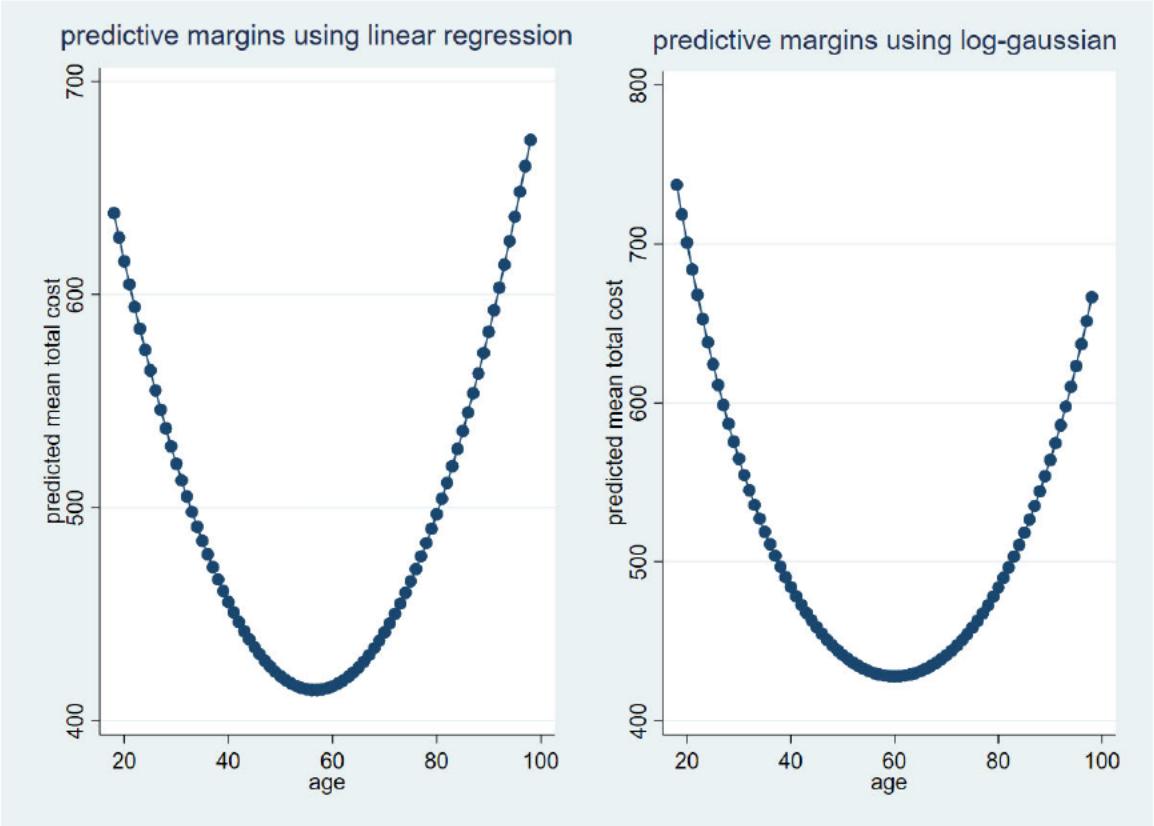


Figure F.1. Age and total costs using glm models for the provincial perspectives

Table F.1. Results for covariates for the provincial perspective using glm models

	Linear	Gaussian
Sex	35.81 (-56.31 to 127.93)	74.45 (-26.08 to 174.98)
Medication	-9.88 (-103.21 to 83.44)	1.58 (-90.81 to 93.97)
Ambulance	106.36* (-1.17 to 213.89)	118.94* (15.99 to 221.89)
Rebleed	214.53* (125.87 to 303.20)	206.67* (116.82 to 296.52)

* Significant at the 5% level

Table F.2. Results for ATT and total costs

	Hospital	Provincial Health Care
Unweighted (linear)	N/A	73.99 (-65.75 to 213.74)
Unweighted (log-gamma)	56.70 (-533.46 to 646.86)	71.20 (-292.52 to 434.91)

Unweighted (log-normal)	N/A	69.07 (-414.57 to 552.71)
IPWRA (linear)	N/A	78.25 (-55.23 to 211.74)
CBPS (linear)	N/A	78.06 (-43.49 to 199.61)
IPWRA (log-normal)	N/A	75.17 (-725.38 to 875.72)
CBPS (log-normal)	N/A	74.98 (-161.78 to 311.73)
IPWRA (log-gamma)	61.55 (-696.80 to 819.90)	78.15 (-370.66 to 526.97)

Table F.3. Results for ATT on total costs excluding ENT visits

	Hospital	**Provincial Health Care**
Unweighted (linear)	N/A	84.13 (-43.15 to 211.42)
Unweighted (log-gamma)	70.60 (-203.48 to 344.68)	79.97 (-244.25 to 404.18)
Unweighted (log-normal)	N/A	79.51 (-175.21 to 334.23)
IPWRA (linear)	N/A	84.93 (-44.66 to 214.51)
CBPS (linear)	N/A	84.69 (-37.07 to 206.46)
IPWRA (log-normal)	N/A	79.91 (-182.04 to 341.86)
CBPS (log-normal)	N/A	79.41 (-99.69 to 258.52)
IPWRA (log-gamma)	72.94 (-411.61 to 557.49)	83.51 (-308.61 to 475.62)

Table F.4. Results for ATT on total costs excluding multiple visits

	Hospital	**Provincial Health Care**
Unweighted (linear)	N/A	94.09 (-59.30 to 247.47)

Unweighted (log-gamma)	60.56 (-501.00 to 622.13)	94.91 (-306.36 to 496.17)
Unweighted (log-normal)	N/A	87.30 (-463.63 to 638.23)
IPWRA (linear)	N/A	100.23 (-33.78 to 234.23)
CBPS (linear)	N/A	99.93 (-20.20 to 220.05)
IPWRA (log-normal)	N/A	98.44 (-237.65 to 434.53)
CBPS (log-normal)	N/A	97.73 (-165.25 to 360.71)
IPWRA (log-gamma)	67.27 (-287.37 to 421.92)	102.30 (-149.78 to 354.38)

Table F.5. Results for ATT on total costs excluding patients with missing pack removal

	Hospital	**Provincial Health Care**
Unweighted (linear)	N/A	34.51 (-147.38 to 216.41)
Unweighted (log-gamma)	42.92 (-691.93 to 777.77)	41.51 (-373.54 to 456.57)
Unweighted (log-normal)	N/A	10.77 (-662.20 to 683.74)
IPWRA (linear)	N/A	50.46 (-109.05 to 209.97)
CBPS (linear)	N/A	54.55 (-98.04 to 207.13)
IPWRA (log-normal)	N/A	42.14 (-440.14 to 524.42)
CBPS (log-normal)	N/A	48.36 (-208.63 to 305.34)
IPWRA (log-gamma)	47.37 (-471.72 to 566.46)	52.21 (-200.99 to 305.42)

Curriculum Vitae

Name:	Dhatri Shukla
Post-secondary Education and Degrees:	The University of Western Ontario London, Ontario, Canada 2020-2022 M.Sc. (Epidemiology and Biostatistics) York University Toronto, Ontario, Canada 2016-2020 B.Sc. (Kinesiology and Health Sciences)
Honours and Awards	Western Graduate Research Scholarship 2020-2022 Schulich- Otolaryngology Graduate Research Stipend 2020-2021
Related Work Experience	Teaching Assistant (Introduction to Health Economics) The University of Western Ontario 2021