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A Systematic Review and Meta-Analysis of Intravenous Sedation in Modern Cataract Surgery

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Abstract

Phacoemulsification is a surgical technique in which a cataract is extracted and replaced with an intraocular lens implant. This can be done under intravenous sedation, oral sedation, or no sedation, in addition to local anesthetic techniques. The purpose of this systematic review and meta-analysis is to assess the effectiveness of intravenous sedation versus non-intravenous sedation methods. Results found that intravenous sedation was significantly associated with a decrease in pain when compared to non-intravenous methods (SMD = -0.86, 95% CI 1.49 to -0.23, p=0.0008) (WMD = -1.01, 95% CI -1.66 to -0.36, p=0.002). The subgroup analysis found patients did not have a statistically significant reduction in pain when using intravenous sedation over oral sedation. The meta-analysis of perioperative complications found that intravenous sedation did not have a statistically significant increase in adverse events when compared to non-intravenous anesthesia techniques. These findings could inform policy and help develop definitive guidelines for sedation and anesthesia strategies during phacoemulsification.

Keywords

Cataract, cataract surgery, phacoemulsification, intravenous sedation, sublingual sedation, pain, complications, ophthalmology, systematic review, meta-analysis

Co-Authorship Statement

The work presented in this document was performed entirely by the author. The only exceptions were the literature search, level 1 and 2 screening, data extraction, the risk of bias assessment, and quality assessment. The search strategy was created with the help of Dr. John Costella, who was the librarian on my project. For level 1 and 2 screening, James Jacob Armstrong (JJA) was the second reviewer alongside myself (EK). For data extraction, risk of bias assessment, and quality assessment, Stephen Tsioros (ST) was the second reviewer and I (EK) was the first reviewer. Discrepancies between any of the processes were solved by Dr. William Hodge (WGH).

Dedication

This thesis is dedicated to the loving memory of my grandfather, Efstathios Patsas, who I still miss every day.

Thank you to my family for their unconditional love and constant support.

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First, I would like to thank the Department of Epidemiology and Biostatistics at Western University for providing me with an excellent education that fosters academic achievement. The course work, although demanding, gave me a thorough understanding of epidemiology and biostatistics, and allowed me to complete this document. Thank you to the faculty and staff for their continuous understanding and support through my graduate school experience.

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Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

COS	Canadian Ophthalmology Society
CNIB	Canadian National Institute for the Blind
IV	Intravenous
IOL	Intra-ocular Lens
USA	United States of America
MKO	Midazolam-Ketamine-Ondansetron
ASCRS	American Society of Cataract and Refractive Surgery
STB	Sub-Tenon's Block
SCH	Suprachoroidal Hemorrhage
PCO	Posterior Capsule Opacification
CME	Cystoid Macular Edema
TASS	Toxic Anterior Segment Syndrome
PONV	Post-Operative Nausea and Vomiting
PICOS	Population, Intervention, Comparator, Outcome, Study Design
I^2	Heterogeneity
x^2	Chi-squared test
RR	Risk Ratio
OR	Odds Ratio
RD	Risk Difference
NNT	Number Needed to Treat
RCT	Randomized Controlled Trial
ARVO	Association for Research in Vision and Ophthalmology
AAO	American Academy of Ophthalmology
SOE	European Society of Ophthalmology
ECCE	Extracapsular Cataract Extraction
ICCE	Intracapsular Cataract Extraction
VAS	Visual Analogue Scale
VPS	Visual Pain Scale
NRS	Numeric Rating Scale
REB	Research Ethics Board

PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
MD	Mean Difference
SMD	Standardized Mean Difference

CHAPTER 1 Introduction & Thesis Objectives

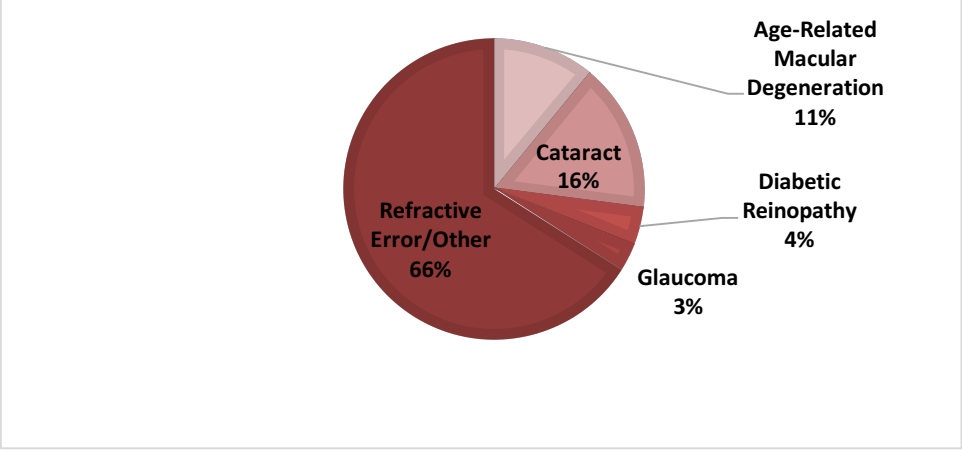
1.1. Financial Cost of Cataracts

The focus of this thesis will be to analyze sedation techniques during cataract extraction surgery. I will first give an overview of cataracts, and their financial burden in Canada.

According to the World Health Organization's latest assessment in 2010, cataracts account for 51% of global blindness, representing more than 20 million people worldwide.[1] Cataracts are a significant problem not only globally, but in Canada as well.

In Canada, cataracts are responsible for 16% of vision loss (Figure 1.1); the direct and indirect financial cost of cataracts to the health care system is 1781.4 million dollars.[2] Further, the number of Canadians with vision loss is expected to double in the next 25 years due to the aging population.[2] Unless policy changes are implemented to battle the rising costs of vision loss, the health care system will become even more overburdened affecting the lives of many Canadians.

Figure 1.1: Prevalence of Vision Loss by Cause



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In general, vision loss places a large economic burden on the Canadian health care system. The financial cost of vision loss in Canada was estimated to be $15.8 billion[2] in 2007, which is consists of indirect health-related costs ($7.2 billion) and direct costs ($8.6 billion) (Figure 1.2).[2,3] The largest burden is placed on the federal and provincial government at 55%.[2] Additionally, vision loss is responsible for the highest direct cost to the health care system compared to any other condition in Canada, including all cancers, cardiovascular disease, mental disorders, respiratory disease, and endocrine disorders such as diabetes (Figure 1.3).[2] This is a result of Canada's aging population, specifically, the large group of baby boomers which have deteriorating vision that require publicly funded care from optometrists, ophthalmologists, and opticians, requiring specialized devices and equipment.[2]

Figure 1.2: Total Financial Costs of Vision Loss in 2007

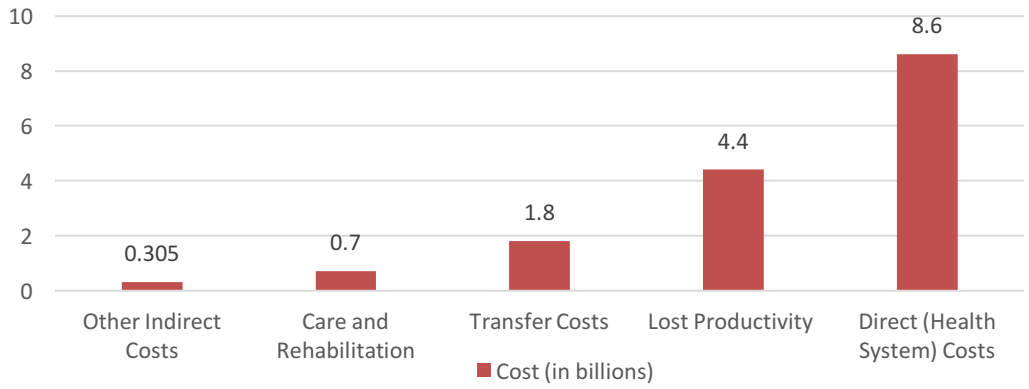

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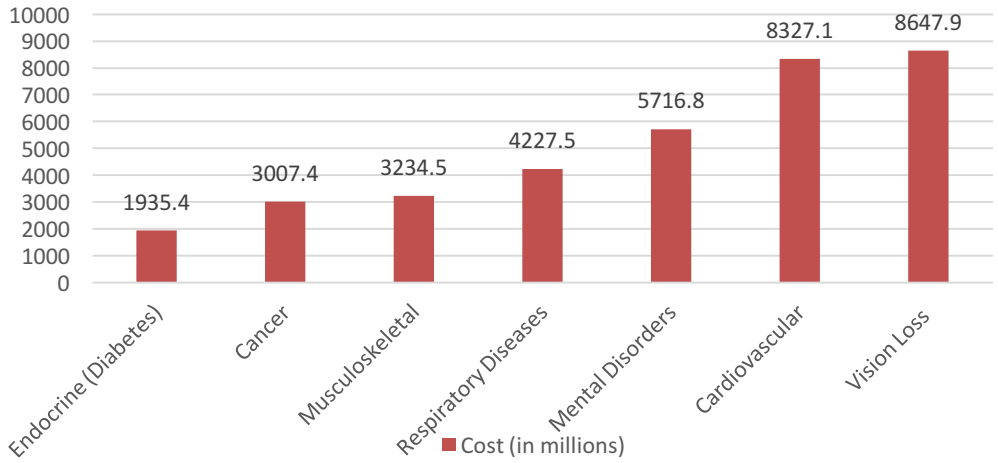
Figure 1.3: Direct Costs of Vision Loss Compared to Other Diseases



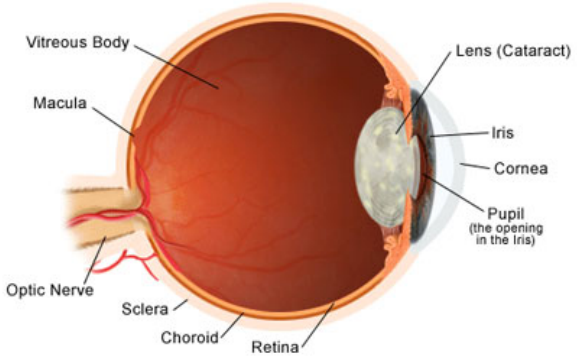
Recreated from: CNIB, Canadian Ophthalmology Society, Access Economics Pty Limited. The Cost of Vision Loss in Canada: Summary Report; 2008.

1.2. Cataracts & Treatment

A cataract is a clouding of the normally clear lens of the eye (Figure 1.4). It is so highly prevalent because it is an inevitable consequence of aging. The lens is mainly comprised of water and protein, arranged in a way that keeps the lens clear. However, as we age the protein may begin to clump together forming the cataract. A cataract may develop due to a number of reasons, which are further explained in Chapter 2. With time, a cataract progresses, making it more difficult to see.[4] An untreated cataract can cause legal blindness in an individual. The Canadian Ophthalmology Society (COS) and Canadian National Institute for the Blind (CNIB) claim that "every Canadian will develop cataracts if they live long enough".[2] Surgical intervention is required for treatment as there are no known conservative or medical options to alleviate cataract development. During modern day cataract extraction surgery (known as phacoemulsification), the clouded lens is removed, and replaced with a clear, artificial lens. This procedure can be performed in approximately 15 minutes, is very safe, highly successful, and restores vision to 95% of patients after surgery.[5] However, there are over 2.5 million[5] Canadians with cataracts. This means a great deal of cataract surgery is required now, with a projected increasing need in the coming years due to Canada's aging population. In 2004, the government signed the *10-Year Plan to Strengthen Health Care*, with the aim

of reducing wait times in five priority areas.[6] It speaks volumes that one of selected areas is cataract surgery; it is a very common and important procedure that consumes a substantial part of the health care budget. Maximization of visual potential is an essential element in keeping Canadians independent, and contributes to a favorable health related quality of life. A safe, effective, accessible, and cost conscious approach would ensure optimal management of the current, and anticipated, need. It is for this reason that the sedation and anesthesia techniques surrounding cataract extraction will be discussed next.

Figure 1.4: Anatomy of the eye and location of Cataract[7]



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1.3. Perioperative Anesthesia Techniques Associated with Cataract Surgery

Cataract surgery is performed under a wide range of anesthetic techniques, sedation, and monitoring options. Anesthesia can occur as a combination of the following: perioperative injections, intraocular injections, topical anesthesia, and lidocaine gel. Additionally, conscious sedation may or may not be used in addition to topical anesthesia and/or ocular injections. When conscious sedation is used, it can be administered intravenously or sublingually.

There is little concrete knowledge regarding the trade-offs in complications among commonly used techniques, or patient perceptions of pain and preference. The majority of cataract surgeries in North America are performed using neuroleptic anesthesia with the presence of an anesthesiologist or anesthetist to monitor vital signs

and administer sedation intravenously, but at an international level there is significant variation in the management of anesthesia strategies[8].

A substantial cost in cataract surgery can result from the anesthesia and sedation strategy. When intravenous neuroleptic sedation is included as part of the anesthesia management strategy, it calls for the added personnel cost of anesthesia nurses and anesthesiologists, as well as preoperative, intraoperative and postoperative medications, and several disposable materials associated with the intravenous therapy. Anesthesia assistants may also be used depending on the model employed. Cataract surgery can also be performed without any sedation, or with sublingual sedation, both methods eliminating the additional personal and materials needed for intravenous sedation. An article by Schuster, Standl, Wagner et al.[9] details the cost of anesthesia in different subspecialties. It was found that anesthesiologists spend the least amount of time with a single patient in ophthalmology, but that the cost of anesthesiologists are highest in ophthalmology.[9] A cost analysis study[10] published in 2001 found that the most cost effective anesthesia management in cataract extraction was oral sedation, with an ocular block, and without an anesthesiologist available ($16.47). The most expensive method involved intravenous sedation, topical anesthesia, and the presence of an anesthesiologist present throughout the operation ($324.72). The question becomes whether having intravenous (IV) sedation (and the extra cost that comes along with it) is an advantage or disadvantage to the patient and their health outcomes? A systematic review comparing the effects of intravenous sedation versus non-intravenous sedation methods has never been done before to answer this question. This is the topic of my thesis.

1.4. Thesis Rationale

Currently, there are no systematic reviews and meta-analyses on the utilization of intravenous sedation compared to non-intravenous methods (whether that is no sedation, or oral/sublingual sedation) on our primary outcomes – patient pain and complications during cataract extraction. The effects of pain perception and adverse complications have not been quantitatively summarized to present a common effect. Presently there are no standards or guidelines for the choice of sedation during

phacoemulsification, and the decision relies entirely on the preference of the ophthalmologist, the anesthesiologist, or the administrators in the location where the surgery is performed. It is very apparent that intravenous sedation is associated with an amplified operating cost – costly personnel (such as anesthesiologists, anesthesia assistants), medications, and equipment is mandatory in most clinics in North America as soon as intravenous therapy is involved. In an article by Reeves et al[10], intravenous therapy costs 11 times as more, on average, when compared to oral sedation. That is a tremendous difference.

As mentioned in the literature review, there is a split in the literature on which method produces better sedation. There are studies[11–13] that conclude sedation is not needed for adequate pain control during cataract surgery, with topical/local anesthesia being sufficient. On the contrary, other studies[14–16] show that intravenous sedation increases patient comfort and surgeon satisfaction, and decreases anxiety. Although there are a small number of randomized controlled trials measuring pain during cataract extraction, the results have not been summarized to produce an overall effect size. In this study, we propose to address both of these gaps in the literature (IV sedation vs. non-IV methods on perioperative pain and adverse complications), to be able to meaningfully contribute to the body of knowledge surrounding anesthesia and sedation during cataract surgery.

1.5. Thesis Objectives

The objective of this study is to synthesize the literature on non-intravenous sedation methods versus intravenous sedation use via a systematic review and to conduct a meta-analysis to generate effect measures when comparing the primary outcomes of this study which are patient pain and perioperative complications. This thesis has the potential to impact resource allocations in both publicly and privately funded environments.

1.6. Structure of Thesis Document

This thesis is presented in monograph format in compliance with the standards outlined by Western University School of Graduate and Postdoctoral studies. I

conducted a systematic review and meta-analysis that met eligibility criteria. The following list briefly describes the content found in each chapter:

- Chapter 1 (introduction) describes a brief introduction to the topic, alongside the objectives and rationale.
- Chapter 2 (literature review) describes the terminology needed to understand what cataracts are, the epidemiology of the disease, and the history of surgical treatment.
- Chapter 3 (literature review) describes the concepts and terminology that is important for describing and interpreting the meta-analysis.
- Chapter 4 (methods) describes the methods used to reach our objectives
- Chapter 5 (results) summarizes the results for the systematic review, quality assessment, meta-analysis, and publication bias analysis.
- Chapter 6 (discussion) interprets and discusses the results, lists strengths and weaknesses of the thesis, and possibilities for future research.

CHAPTER 2 Literature Review

2.1. Introduction

The purpose of this thesis is to summarize the effects of intravenous sedation use versus non-intravenous sedation methods in modern cataract surgery, when comparing pain perception and the adverse complication rate. This chapter provides the terminology needed to describe what constitutes a cataract and its associated symptoms, etiology, and epidemiology. This chapter also goes into detail about the surgical treatment (phacoemulsification), the anesthetic techniques, and possible complications of cataract extraction. This is the first systematic review performed to compare the effect of an IV method and a non-IV method of conscious sedation on patient pain perception and complications during cataract extraction.

2.2. Classification of Cataracts

There are three main types of age-related cataracts: nuclear, cortical, and posterior subcapsular (Figure 2.1).

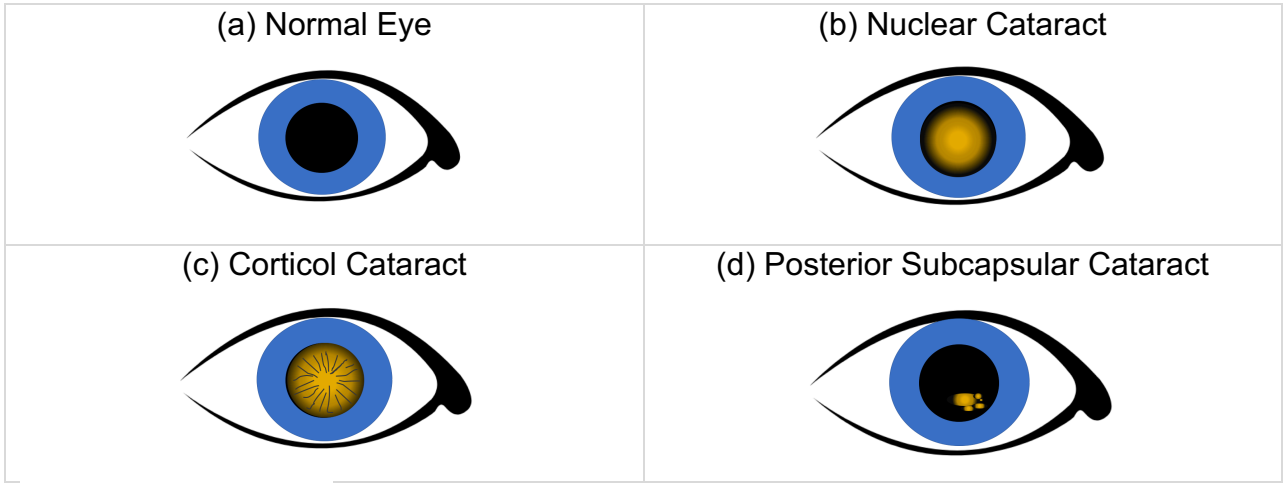
Nuclear Cataracts - Nuclear cataracts are caused by the lens hardening and yellowing over time. Also called “nuclear sclerosis”, these cataracts progress slowly over time, and can eventually become a brown or black colour in advanced stages.[17] They are the most common type of cataract and the most common reason for cataract surgery to be needed (Figure 2.1b).

Cortical Cataracts - In cortical cataracts, the cataract begins in the periphery of the lens, moving towards the center, shaped like a spoke (Figure 2.1c). This occurs in the lens cortex. Since this type of cataract starts in the outer edge of the lens, the best-corrected vision may be unaffected for many years until the central portion of the lens is affected. However, degradation of visual perception caused by glare and loss of contract sensitivity may result.[17]

Posterior Subcapsular Cataract - This cataract type begins on the back surface of the lens as a small opaque cluster. It forms adjacent to the lens capsule, hence the name

"subcapsular". The cataract will appear as small dust-like particles at first (Figure 2.1d), eventually becoming thicker and more dense. Since light focuses through the back of the lens, posterior subcapsular cataracts can cause excessive symptoms for their small size including debilitating glare.[17]

Figure 2.1: Cataract Classification



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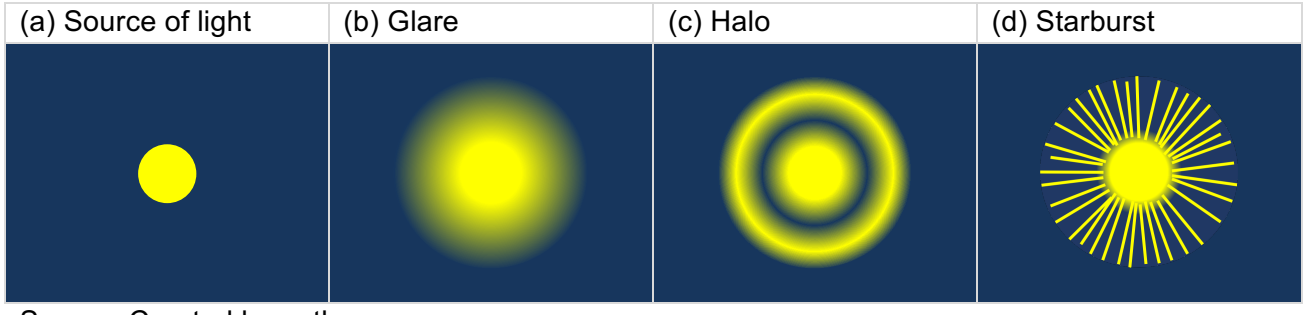
2.3. Symptoms of Cataracts

Symptoms of cataract include: blurred, clouded vision, a visual decline (distance, near, or both) that can occur over weeks, months, or years, decreased color discrimination, increased or extreme glare, halos or starbursts (Figure 2.2). Eventually, corrective glasses are no longer being able to improve eyesight, or there may be double vision in only one eye.[18] Untreated cataracts can lead to an individual becoming legally blind.

Figure 2.2: Glare, Halos, and Starbursts



Source: Created by author

2.4. Etiology

There are a multitude of causes and risk factors that may contribute to an individual developing a cataract. Cataracts may develop due to genetics, metabolism, environmental factors, nutritional diet, local accidental or surgical trauma, local or systemic medications, or from other systemic disorders such as diabetes.[17]

Age - Increasing age is the leading cause of cataract development. Oxidative damage to the lens' nucleic acids, lipids, and proteins is considered to be the dominant factor in age-related cataract.[17] As a result, the lens becomes cloudy and opaque.

Diabetes - Individuals with diabetes have a higher risk of developing cataracts. High glucose levels in the lens are converted into sorbitol. When sorbitol collects in the lens, it will cause it to become more opaque, eventually leading to cataract formation.[19]

Obesity - Obesity is yet another risk factor for cataract development. In fact, one study found that a 2 unit increase in body mass index predicted a 12% increase in risk of cataract in a proportional hazards model that adjusted for potential confounding variables.[20]

Trauma - Blunt trauma to the eye can result in swelling and thickening of the fibers in the lens, causing localized opacity.[17] Additionally, previous eye surgery may cause trauma to the lens, increasing the risk for cataracts.

Radiation / Excess Exposure to Sunlight - Ultraviolet light (particularly UVB) has been shown to cause cortical and posterior subcapsular cataracts.[21] The scientific literature suggests that by wearing sunglasses, starting at a young age, it can provide protection against developing cataracts.[22]

Genetics - A risk factor of cataracts that cannot be avoided is one's genetics. The cellular biology of the lens determines how prone an individual will be to developing cataracts. This may be inherited, or secondary to another systemic disease.[23] The

current set of genes that are known to be associated with cataracts is extensive but far from complete.

Smoking - Smoking is a known risk factor for numerous diseases. Tobacco smoke contains hundreds of toxins and chemicals that play a role in development of cataracts. A meta-analysis of the literature found that smoking was directly associated with an increased risk of age-related cataract.[24]

Alcohol - Although there has been conflicting evidence over the relationship between alcohol and cataracts, a well-designed population based prospective cohort study found that daily consumption of 2 or more standard drinks was associated with an increased likelihood of developing cataracts, thus requiring cataract surgery.[25]

Inadequate Vitamin C - A lack of vitamin C has been associated with an increased risk of cataracts. It was found that increased vitamin C intake is associated with a reduced risk of cataract.[26]

Corticosteroid Medication – Cataract development has been associated with the use of inhaled corticosteroids. A systematic review conducted in 2009 found that the risk of cataracts increased by approximately 25% per 1000μg daily dose of an inhaled corticosteroid.[27] This is a substantial risk for developing the most common cause of blindness, due to cataract, internationally. Specifically, corticosteroid medication has shown to be a significant factor for the development of posterior subcapsular cataracts.[28]

Hypertension - A recent meta-analysis brought clarification to the indication that hypertension may play a role in the development of cataracts. Yu et al (2014)[29] found that high blood pressure increases the risk of cataract anywhere between 8%-28%.

2.5. Epidemiology

Globally

According to the World Health Organization, cataracts are the leading cause of blindness, accounting for 51% of global blindness, representing more than 20 million people worldwide.[1] It also accounts for 33% of vision impairment worldwide.[30] Although cataract extraction is a highly successful and safe procedure (vision is restored to 95%[5] of patients after surgery) there are immense barriers in many developing countries that prevent individuals from having access to this crucial surgery, resulting in moderate to severe disability.[1] As a result, 90% of visually impaired people live in developing nations without access to cataract extraction.[31] With a large aging population globally, even more people will be at risk for visual impairment due to cataracts in the coming decades. It is tragic that 20 million[1] people are blind due to cataracts when it is such a treatable disease. Increased access to cataract surgery is vital to prevent disability and increase quality of life for many individuals.

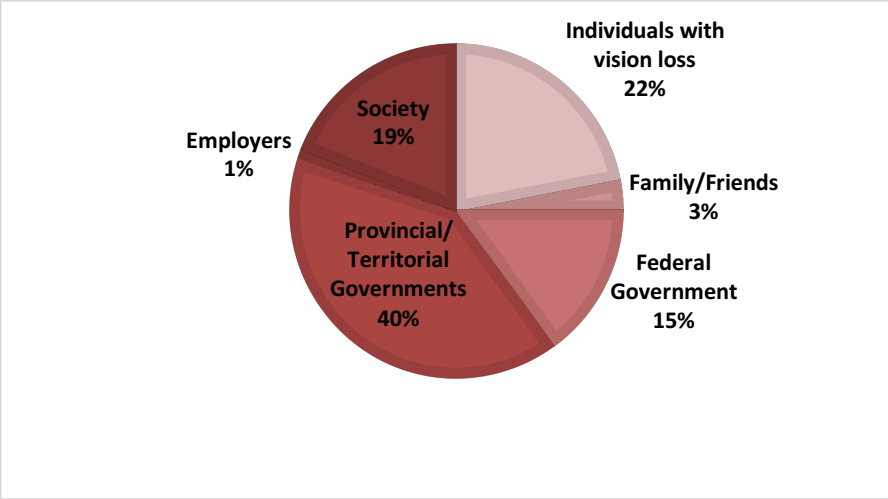
United States

In 2010, there were 24.41 million[32] cases of cataracts, with 1.82 million[33] cataract extraction procedures performed in the United States. The following age specific prevalence rates for cataracts in the United States display how common this condition is; 24.75% of citizens aged 65-69, 36.49% of those aged 60-74, 49.49% of those aged 75-79, and a very significant 68.30% of those that are over 80 years old have cataracts.[32] Consequently, phacoemulsification (modern cataract surgery) is one of the most commonly performed surgical procedures in any field. It has been estimated that 3.3 million[33] surgeries will be performed in 2020, and that there will be 50.2 million[32] individuals with cataracts in the United States by the year 2050. The increasing number of cataract extraction procedures expected will place a growing strain on medical resources and expenditures. Ensuring this procedure is cost effective is crucial to the health care system.

Canada

More than 2.5 million[5] Canadians are currently battling cataracts in their everyday life. In 2007, the direct health-related cost of vision loss in Canada was estimated to be $8.6 billion, with indirect costs totaling $7.2 billion.[2] 55.3% of this burden comes directly from Canada's taxpayers via the federal and provincial governments, 22% from the individuals with vision loss, 19% from society, and 4% from family, friends, and employers (Figure 2.3).[2] Cataracts are solely responsible for 16% of Canada's vision loss with a financial cost of 1781.4 million dollars.[2]

Figure 2.3: Financial Costs by Bearer, 2007



Recreated from: CNIB, Canadian Ophthalmology Society, Access Economics Pty Limited. The Cost of Vision Loss in Canada: Summary Report; 2008.

Like many other countries around the globe, the proportion those who are 65 years of age or older in Canada is rapidly growing. This is due to the "baby boomers", which were born after World War II, now reaching retirement age. In 1990, 11.3% of Canada's population was over the age of 65, this creeped up to 12.5% in the year 2000, and 16.5% in 2016.[34] The proportion of seniors will continue to increase in the coming years; it is estimated that by the year 2036, seniors will represent between 23%-25% of the population, and by 2061 they will represent between 24%-28%.[35] Naturally, this means that the need for, and number of, cataract surgeries in Canada will also increase. In fact, the greatest demand for services in coming years among all surgical specialties will be in ophthalmology.[36] In 2012, Hatch et al.[37] used Ontario's population

data to predict the volume of cataract surgery for the next 25 years. From the 143,000 cataract operations in Ontario in 2006, a 128% growth was projected, estimating 326,000 operations annually by 2036.[37] It is feasible that this estimation can be applied to a nation-wide level. Cataract surgery is, and will continue to be, one of the most common surgeries in North America.

2.6. Treatment

When cataracts are diagnosed early, vision can be improved with new prescription eye glasses, anti-glare sunglasses, magnifying lenses, or brighter lighting. When cataracts begin to interfere with activities of daily living such as reading and driving, and vision deteriorates, the only effective treatment is to remove the cataract via surgical intervention.

2.7. A Brief History of Cataract Surgery

Couching

The oldest case of a cataract is documented in the form of a statue with a white left eye from approximately 2460 B.C., located in Egypt. A wall painting from 1200 B.C. depicts an oculist treating the eye of a workman. The tomb of a physician from 2630 B.C. filled with 30 bronze tools and writing on the walls suggests that ocular surgery, specifically couching, was occurring.[38] Couching is an ancient technique in which a sharp tool is used to push the cloudy lens into the vitreous to settle at the bottom of the eye. Once the patient begins to see movement or shapes, the procedure ends. Since the patient no longer has a lens, a strong prescription eyeglass lens is required. In fact, couching is still performed in remote, developing areas of the world.[39] This technique is extremely unsuccessful by today's standards; a population-based survey located in rural area of Mali in 1996 found that of those who had couching performed on their cataracts, 70.9% were left blind, and the remaining 29.1% had poor vision.[40] Although this method is often futile, it paved the way for the invention of new techniques.

Intracapsular Cataract Extraction

In the 2nd century (year 100-200), a new technique was invented by the Greek physician Antyllus, where the cloudy lens was removed with a hollow instrument by suctioning. The entire lens including the capsule around it was removed. This method ensured that the lens could not migrate back into the field of vision, unlike couching which simply pushed the lens aside.[41] This too, was an ineffective procedure by today's standards due to the amount of tissue disruption and complication rates. Nevertheless, the intracapsular method was still the main method used until the early 1970's. As the 20th century progressed, a cold icicle (a cryo probe) was used to extract the lens relatively efficiently, and an artificial lens was placed in front of the iris which is not the natural position of the lens. This was the only option as the procedure destroyed the natural support structure, which is now retained in newer procedures that support the lens implant.

Extracapsular Cataract Extraction

In 1747, a French ophthalmologist named Jaques Daviel was the first physician to extract cataracts from the eye successfully. His method involved slicing a large opening in the cornea and passing a small spatula through the pupil to extract the lens.[42] In this method, the capsule around the lens was kept intact and so the potential to put a new plastic lens back in its proper position was born. Although an improvement, this method had many potential complications at the time. Another surgeon named John Taylor offered contributions around the same time to the procedure. He was known for removing cataracts by breaking them into small pieces.[38] As this technique was refined, it became the main cataract procedure in the 1980's and 1990's. A large 6mm incision was created in the eye and the front of the capsule peeled off. The lens was extracted leaving the back of the capsule intact, and the new plastic lens put in this place, its natural position.

The Intraocular Lens

On February 8th, 1950, Sir Nicholas Harold Lloyd Ridley invented the first synthetic intraocular lens in London, England.[38] Ophthalmologists worked to

continuously improve this surgery, and in 1966 the first international conference on intraocular lenses was held.

Modern Phacoemulsification

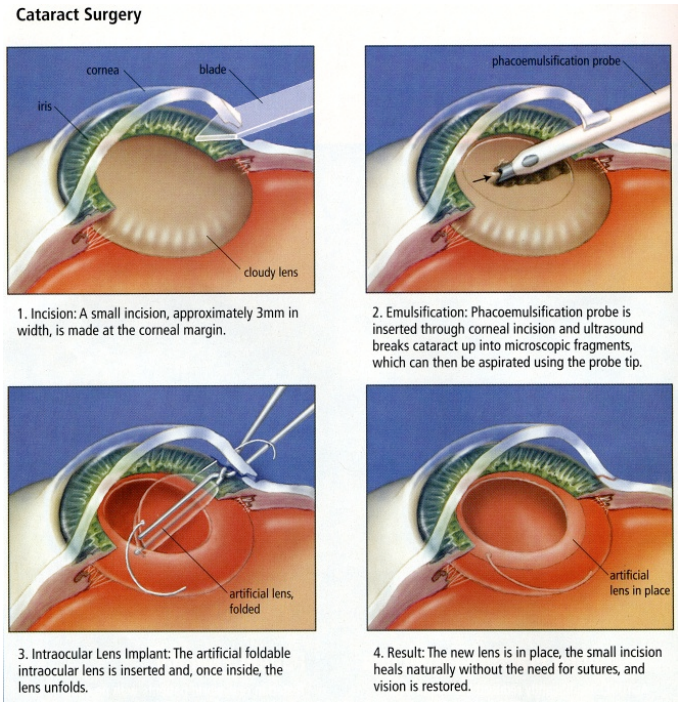
In 1967, Charles D. Kelman invented the start of modern phacoemulsification in New York. Inspired by the ultrasonic probe his dentist used, Kelman recreated and modified this concept so that ultrasonic waves can be used to liquefy the center of the lens, allowing the cataract to be easily removed without a large incision.[38] In principal this surgery is the same as extracapsular cataract surgery except that the ultrasound energy allows the lens to be vacuumed through a 2.5 mm incision. A foldable lens is inserted through the same incision into the space in front of the retained capsular support system. Kelman's new technique resulted in a shorter hospital stay, quicker healing and recovery, and decreased pain for the patient. Since its invention, phacoemulsification has been improved and refined, becoming the gold standard technique globally since the mid 1990's.

2.8. Fundamentals of Modern Phacoemulsification

Phacoemulsification is the most common methodology employed for cataract surgery today. During phacoemulsification, the surgeon first anesthetizes the eye with topical drops, and possibly an ocular block for additional anesthesia. Additionally, the patient may or may not be sedated via intravenous or sublingual methods. A small incision that is approximately 3mm[43] is then made on the cornea. An opening is surgically constructed in the capsule that surrounds the cataract (a basement membrane) and peeled anteriorly only. Next, an ultrasonic device with a very small needle-like tip is used; this is called a phaco-probe. This device is inserted into the incision, and its tip vibrates using ultrasonic frequency to emulsify the cataract, breaking it into small pieces, which are then removed from the eye with suction.[44] Once the cataract has been completely removed, an intraocular lens (IOL) is implanted into the space through the tiny incision into the remaining capsule. If the case is uncomplicated, the IOL can be inserted into, and remain in, the normal anatomical position of the human lens. The IOL is an artificial lens with various focusing powers, similar to

prescription eyewear. The majority of patients will choose to have the focusing power of their artificial lens prescribed so that they can see clearly in the distance, with reading glasses for objects that are close. Technology in this area is rapidly advancing as implants are now available that can potentially correct for corneal astigmatism and presbyopia, causing patients to move even closer to complete spectacle independence after surgery. After the IOL is implanted, the incision is usually able to heal on its own, not requiring any stitches.[45] Figure 2.4 summarizes the process. This procedure can be performed, on average, in approximately 15 minutes, is done on an outpatient basis, and recovery is nearly immediate. Since 1967 when this procedure was first introduced, a multitude of improvements developed not only in the surgical technique, but in the equipment as well. There were "better microscopes, phacoemulsification machines, irrigation systems, sutureless incisions, and intraocular lenses all contributing to increasing patient safety and [improved] visual acuity".[46] Consequently, the acceptance of phacoemulsification rose from 16% in 1985[47] to 97% in 1996[48]; the practice of phacoemulsification became the universal technique in developed countries nearly 29 years after its invention.

Figure 2.4: Phacoemulsification



Source: http://concordeyecenternh.com/services-procedures/cataracts/#1447797946062-f9438d9d-dc828088-6c82

2.9. Introduction to Anesthesia and Sedation Strategies

Since the focus of this thesis is sedation and anesthesia techniques surrounding cataract extraction, the focus will now turn to the available sedation and anesthesia strategies. An extensive variety of anesthetic techniques are available for phacoemulsification. These may include any of the following on their own or in combination with each other: topical anesthesia with lidocaine gel, topical anesthesia with anesthetic drops (i.e. proparacaine, tetracaine), periocular blocks, paraocular blocks, intravenous sedation, and sublingual sedation. There is also a wide variety of personnel and monitoring options available for the patient. Personnel required for phacoemulsification to occur may include: surgical nurses, anesthesia nurses, respiratory therapists, and anesthesiologists with or without assistants. Every model exists in Canada, ranging from no monitoring, no pre-assessment and/or no anesthesiologist present, to monitoring, pre-assessment, and/or an anesthesiologist present. There is a wide range of anesthesia and sedation management available, reinforcing the need for guidelines on the topic. This section will describe various anesthesia techniques, sedation options, and the personnel involved.

In addition to local and/or topical anesthetic techniques, conscious sedation is used to further complement anesthesia. The goal of conscious sedation is to allow the patient to remain calm and cooperative, allowing the surgeon to perform the operation without distractions. Sedatives, anxiolytics, hypnotics, and opiate analgesics are given via oral, sublingual, or intravenous sedation. However, not using any conscious sedation is also an option. Sedation is not mandatory or required, but may be a distinct preference of many surgeons.

2.9.1. Conscious Sedation

The ability to be able to communicate with the sedated patient intraoperatively with respect to eye placement has been shown to help the surgeon have greater success.[49] At the same time, patient movement caused by pain or anxiety can negatively affect the surgery and potentially increase the complication rate. Thus, there is a fine art to ensuring the patient is sedated enough so that they don't feel pain, are able to communicate, and at the same time are not overly sedated causing unintentional

movement. It has been shown in various studies[11–13] that sedation is not needed for adequate pain control during cataract surgery, and that topical/local anesthesia is sufficient. On the other hand, there are studies[14–16] that show intravenous sedation increases patient comfort and surgeon satisfaction, and decreases anxiety. There is a split in the literature, showing the need for further research into the topic.

When the patient is sedated intravenously, the following is required: blood pressure monitors, pulse oximetry, electrocardiogram monitors, supplementary oxygen must be available, and trained resuscitation personnel and equipment must be standing by.[18] Presently, there are no national guidelines or standards for conscious sedation during cataract surgery. The decision on which method to use is dependent on the preference of the ophthalmologist, anesthesiologist, or the administrators in the center where the surgery is performed. A range of practice patterns currently exist in which patients can undergo cataract surgery with no conscious sedation at all, oral sedation, sublingual sedation, or intravenous sedation. Intravenous sedation is associated with a significantly higher cost, when compared to the other methods, and is one of the most widely used techniques in North America. What is not known is whether intravenous sedation is truly associated with better patient outcomes, less complications, and significantly less pain? This is a particularly important question in view of the fact that the cataract procedure itself has evolved significantly over the last few years, and continues to evolve. Advancements have been made which require greater technical skill, delivered in a shorter period of time. Moreover, there has been a trend for cataract surgery to move out of hospitals and into privately-funded clinics. Historical methods of perioperative anesthesia may not be the most optimal for the patients, the surgeons, and the ambulatory settings in which the surgery is now being performed. The thesis aims to address this question.

Intravenous Conscious Sedation

Intravenous conscious sedation may involve a combination of medications that will help the patient relax (sedative) or block pain (anesthetic) without the loss of verbal communication. The medicine is received through an intravenous line, is fast acting, and allows for quick recovery. Common agents include: propofol, remifentanil,

dexmedetomidine, midazolam, fentanyl, alfentanil, sufentanil or clonidine.[50] Although this method is common, like all anesthetic techniques, conscious intravenous sedation is not without its risks. Respiratory depression, cardiac arrest (more pronounced in the elderly and alcoholics), post-operative vomiting, increased intraocular pressure, reduced blood pressure, pain during the injection of the intravenous line, patient movement, increased intracranial pressure, hyper-salivation, muscle hyperactivity, constipation, urinary retention, muscle rigidity, or airway obstruction are all potential risks and side effects that may occur from intravenous sedation.[51] In a prospective cohort study[52] of 19,250 cataract surgery at nine centers in Canada and the United States of America (USA), it was shown that the use of intravenous sedation was associated with a significant increase in adverse effects and complications associated with topical and injection anesthesia, compared to topical anesthesia without intravenous sedation. This may have been a confounding situation where only the most anxious patients, or those with more complicated procedures, were given intravenous sedatives. This may have resulted in those with intravenous sedation having more complications.

Pharmacological knowledge is crucial when using sedative agents. For this reason, the presence of anesthesia nurses or anesthesia assistants, as well as the supervision of anesthesiologists are required in the United States[53] and Canada[54]. If there is a significant increase in complications, is intravenous sedation worth the extra cost? It is difficult to answer this question using only one cohort study since there is less power; for this reason we conducted a systematic review to compare the complication rate when using intravenous sedation, compared to non-IV sedation methods.

Oral/Sublingual Sedation

Oral or sublingual sedation for cataract surgery is available as midazolam, diazepam, or MKO (midazolam-ketamine-ondansetron) melt[55] tablet. There are many benefits to sublingual sedation; it is a more cost-effective sedation method, there is no pain from the insertion of the IV line, and it eliminates many risks involved with intravenous sedation. Additionally, an anesthesiologist is not required to be in direct supervision during the surgery, but rather to be present in the center's premises or on call, which can result in great cost savings for the center and government. Chen et al.[56]

found that when comparing oral diazepam to IV midazolam, the sublingual medication performed better and was more cost effective. However, when choosing sublingual conscious sedation, examining the patient is crucial; it may benefit those with extreme anxiety to be given intravenous sedation.

No Sedation

Cataract surgery can also be performed with no conscious sedation. Local anesthetics provide adequate anesthesia for the patient and surgeon to be satisfied with the procedure. It is routine in many clinics to not sedate patients prior to cataract extraction, but if anxiety occurs pre-operatively, a sublingual sedative can be given to relax the patient.

2.9.2. Central Nervous System Medications via Intravenous Therapy

There are multiple functions of drugs that depress the central nervous system. They can control seizures (anticonvulsants), relieve pain (narcotic analgesics), control agitation (anxiolytic agents), and provide a calming effect (sedation).[57]

Benzodiazepines, barbiturates, and opiate analgesics are all classes of drugs that may be used in phacoemulsification via intravenous therapy. Benzodiazepines are a family of drugs that result in sedation, anxiolysis, relief of muscle tension, and amnesia. Midazolam, diazepam, and lorazepam are all examples of drugs in the benzodiazepine family.[58] Barbiturates are central nervous system depressants that can provide sedation and anesthesia (common barbiturates include thiopentone and methohexitone). Opiate analgesics prevent the transmission of electrical nerve impulses caused by painful stimuli. Examples of opiates include morphine and fentanyl.[58]

Anesthesia injection has been documented as one of the most painful aspects of minor surgeries and procedures.[59,60] There are many studies on the most effective way to inject anesthesia in with the least amount of pain for the patient.[61] For this reason, it is important that those inserting intravenous lines are experienced and have excellent technique. Another option is to avoid the use of intravenous injections when possible.

2.9.3. Cost of Various Anesthesia Management Strategies

Chen et al.[56] found that sublingual sedation was much more cost effective than intravenous sedation; in their study, IV midazolam cost $2.50 per unit price, while oral diazepam cost $0.03 per unit price. Similarly, in 2001 Reeves et al.[10] conducted a decision analysis to compare the trade-offs in costs, preferences, and benefits of various anesthesia management strategies in cataract surgery. They found that the most cost effective management was oral sedation with an ocular block, and without an anesthesiologist available ($16.47), and that the most expensive method involved intravenous sedation, topical anesthesia, with an anesthesiologist present throughout the operation ($324.72). The study concluded that there are substantial cost savings available for a small change in preference between sublingual and intravenous sedation (Table 2.1). It is apparent that avoiding the use of intravenous sedation will result in immense cost savings; in equipment, medication, and personnel. As previously mentioned, one study[52] found that the use of intravenous sedation was associated with a significant increase in adverse effects and complications in comparison to surgeries in which no sedation or oral sedation was used.

If intravenous sedation is more costly and causes more adverse events, should we really be putting our limited healthcare dollars towards sedating patients intravenously? Comparing complications during cataract extraction is one of the primary objectives of this thesis. The other, is intraoperative pain perception. The result of these two outcomes will determine the practicality of using intravenous sedation.

Table 2.1: Cost to Providers for Various Sedation Methods in Cataract Surgery

Sedation	Local Anesthesia	Anesthesiologist	Cost
Intravenous	Block	Present	$324.42
Oral	Block	On call	$41.47
Oral	Block	Not present	$16.47
Intravenous	Topical	Present	$324.72
Oral	Topical	On call	$41.77
Oral	Topical	Not present	$16.77

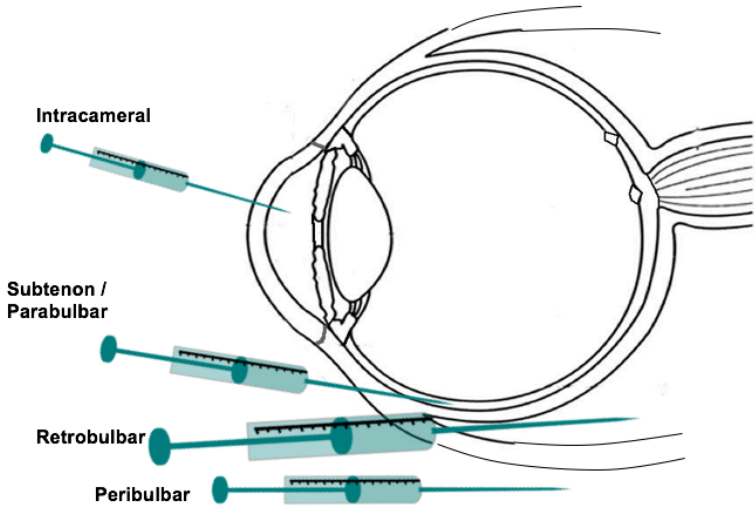
Recreated from: Reeves SW, Friedman DS, Fleisher LA, Lubomski LH, Schein OD, Bass EB. A decision analysis of anesthesia management for cataract surgery. Am J Ophthalmol. 2001;132(4):528-536.

2.9.4. Topical and Regional Anesthetic Techniques

Retrobulbar Block

The first report of a retrobulbar block reported in 1884 by Herman Knapp in his book “Cocaine and Its Use in Ophthalmic and General Surgery”, where he injected 4% cocaine before ophthalmic surgery.[62] With this method, a local anesthetic is injected into the area behind the eye with a sharp needle (Figure 2.5), causing akinesia (loss of movement) in the muscles surrounding the eye. The injection goes through the extraocular muscle cone. Although this produces good anesthesia, some potential complications include: retrobulbar hemorrhage, damage to the extra-ocular muscles, ocular penetration, and diplopia.[63] In 2003, a survey of the members of the American Society of Cataract and Refractive Surgery (ASCRS)[48] was conducted. It was found that in 2003, retrobulbar blocks were used by 10% of the members, a large decrease from 1985 where 76% of members were using employing this technique.

Figure 2.5: Ocular Injections



Source: Created by author

Peribulbar Block

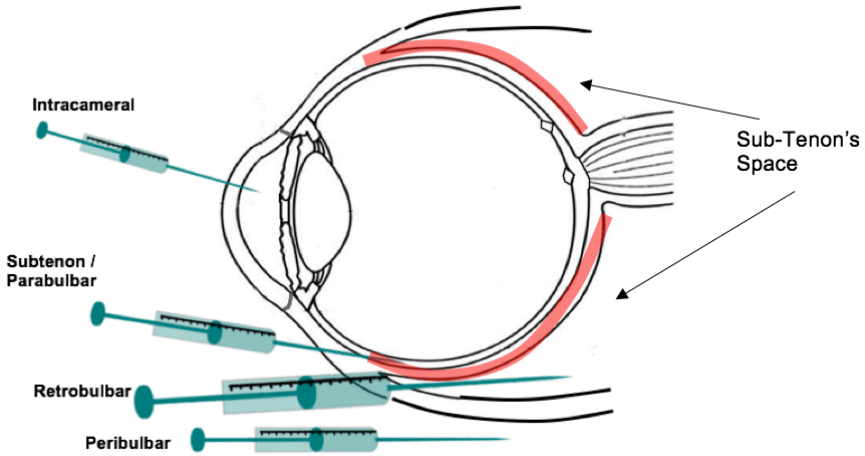
The peribulbar block was first introduced in 1986 by David Davis and Mark Mandel as a safer alternative to retrobulbar block.[64] With this method, a local anesthetic is injected above and below where the eye of situated in the eye socket with a sharp

needle (Figure 2.6). This injection lies outside the extraocular muscle cone. Peribulbar blocks produce excellent akinesia and anesthesia. Although safer than retrobulbar blocks, complications are similar to those occurring with retrobulbar blocks, including globe perforation.[63] This use of this method has also decreased over the years with the introduction of topical and Intracameral anesthesia. In 2003, 17% of ASCRS members reporting using periocular blocks, down from 38% in 1995.[48]

Sub-Tenon's Block

Sub-Tenon's block (STB) is also known as parabulbar block, episcleral block, and pinpoint anesthesia. This method was first described in 1884 by Turnball, in 1956 by Swan, and then re-introduced and popularized again in the early 1990s.[65] Sub-Tenon's block involves inserting a local anesthetic with a flexible, blunt, cannula into the sub-Tenon's space (Figure 2.6). This newer method provides excellent anesthesia, and reduces the risks typically associated with peribulbar and retrobulbar injections, mainly penetrating globe injuries.[17] A UK study found that the retrobulbar and peribulbar block techniques had a 2.5-fold increased risk of complications compared with sub-Tenon's block.[66] However, sub-Tenon's is not without potential complications; globe penetration, orbital hemorrhage, retinal ischemia, optic nerve damage, and orbital swelling are all potential complications.[67]

Figure 2.6: Sub-Tenon's Space



Source: Created by author

Intracameral Injection

Intracameral lidocaine injections were first introduced in 1997 by Dr. James Gills.[68] A local anesthetic is injected directly into the anterior chamber at the time of surgery (Figure 2.7). Topical anesthesia is often complemented by Intracameral injection of non-preserved lidocaine to ensure patient akinesia and anesthesia. Intracameral injections are often complemented with topical anesthetic drops, as well as a form of conscious sedation; this combination has largely replaced the use of retrobulbar, peribulbar, and sub-Tenon blocks in North America.

Topical Anesthetic Drops

The use of topical anesthesia was re-introduced in 1992[49], later becoming the standard of care for phacoemulsification. Topical drops are safe and efficient; they block the conduction of nerve impulses, eliminating sensation. The following anesthetic agents are used in ophthalmology: benoxinate, proparacaine, tetracaine, didocaine, centbucridine, cocaine, phenacaine, dimethocaine, piperocaine, dibucaine, naepaine, butacaine, xylocaine, oxybuprocaine, and proxymetacaine. Potential side effects to these drops include: lens epithelial toxicity, stinging, decreased blinking, vasodilation, corneal edema (swelling of the cornea), increased healing time, and allergic reactions in a small percentage of patients. Additionally, they may cause incomplete anesthesia, requiring multiple drops throughout the surgery. Agents used in phacoemulsification today are tetracaine, proparacaine, and benoxinate, which last for 15 to 20 minutes.[69] The most commonly used agent is lidocaine in gel form. The gel allows for a longer lasting effect than liquid lidocaine preparations, and will be discussed in more detail to follow.

Gel Anesthetics

Topical anesthetics are also available in the form of gel for ophthalmology. Gels are advantageous in areas such as the eye, where it is surrounded by tear film which may dilute topical anesthetic drops to reduce the effectiveness. A recent review[70] on lidocaine gel in ophthalmic surgery found that lidocaine gel is often more effective than anesthetic drops for preventing pain related to cataract extraction, with few adverse side

effects. Patient and surgeon satisfaction is generally high with this method, and is often used in combination with topical anesthetic drops. Anesthetic gels also became very popular as a cost-saving strategy by reducing the amount of nursing time involved in preparing the patient for surgery. It is for all of these reasons that this is the most commonly used anesthesia technique used today in modern phacoemulsification.

Mydriatic Drops (Pupil Dilation)

Mydriatics are a type of pharmaceutical drug that cause the pupil to dilate. In phacoemulsification, this is achieved by the topical administration of mydriatic drops, or intracameral injection. Mydriasis in cataract surgery is necessary for a successful outcome.[71]

2.9.5. General Anesthesia

Although general anesthesia was used for the first time in surgery in 1846 by dentist William Morton,[72] it wasn't until 1954 that general anesthesia was used for cataract extraction.[73] Today, general anesthesia is rarely used in cataract surgery due to the associated higher risks[74], and costs. Furthermore, non-general anesthesia techniques are very effective. Nevertheless, general anesthesia today is used for children, and uncooperative or disabled patients.[63]

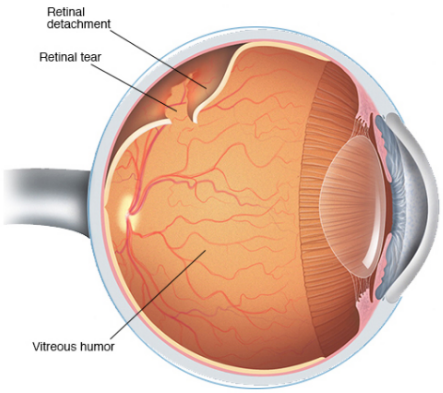
2.10. Ocular Complications from Cataract Surgery

Although cataract surgery is a safe and successful procedure (vision is restored to 95%[5] of patients after surgery) there are always risks with any surgery, and complications may result during or after the procedure. The complications may range from minor inflammation to severe infection resulting in complete enucleation of the eye. Surgeons, anesthetists, and nurses have many protocols and procedures put in place to avoid and prevent complications throughout cataract surgery, from pre-op to post-op. As previously mentioned, intravenous sedation has been associated with a higher rate of complications in a large cohort study.[52] If this is truly the case, sedation management should be switched in order to reduce the following perioperative complications.[75]

Posterior Capsule Rupture: A posterior capsule rupture is a tear in the posterior capsule. This can result in vitreous from the posterior chamber flowing into the anterior chamber of the eye.[76] This is a complication that can happen at the time of surgery, and is one of the most detrimental complications that can occur. A posterior capsule rupture can lead to severe visual disability, and result in blindness from retinal detachment. Furthermore, since the intraocular lens implant is ideally placed in the remaining capsule, when the capsule is ruptured, proper placement of the IOL becomes very challenging and sometimes impossible.

Retinal detachment: Retinal detachment is one of the most severe complications post cataract surgery.[77] The incidence of retinal detachment after phacoemulsification has been reported to be 0.27% within one year of the surgery, and 0.71% within five years of the surgery date.[78] This condition occurs when the retina (thin layer of tissue at the back of the eye) pulls away from the underlying retina pigment epithelium and choroid which has blood vessels that provide it with oxygen (Figure 2.7).[79] This can result in permanent vision loss if not treated right away.

Figure 2.7: Retinal Detachment

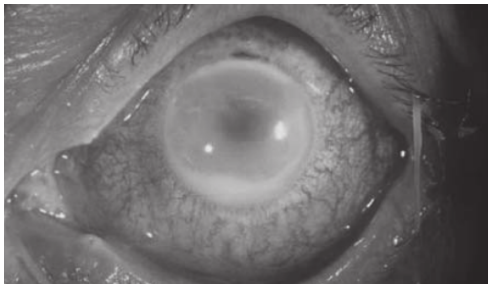


Source: Mayo Clinic Staff. Retinal Detachment. Mayo Clinic. http://www.mayoclinic.org/diseases-conditions/retinal-detachment/home/ovc-20197289. Published 2016.[79]

Endophthalmitis: Endophthalmitis is rare (incidence: 0.023%[80]) but has potential to be a highly destructive post-operative complication (Figure 2.8). Endophthalmitis is a fungal or bacterial infection that may result in complete enucleation of the eye, and can occur

up to 6 weeks after cataract extraction, but usually occurs in the first 10 days. It can also be a chronic condition that reoccurs months and years after surgery.[18] Infection usually originates from the bacterial flora in the conjunctiva or lids. Less commonly involved mechanisms can be: immunocompromised host, improper draping during the procedure, contaminated instruments, rubbing the eye, and leakage from the site of operation. [81] It is most often treated with intraocular injections of antibiotics or antifungals, with subsequent surgery for more serious cases.[75]

Figure 2.8: Endophthalmitis



Source: Henderson BA, Pineda R, Chen SH. Essentials of Cataract Surgery. Second. Slack Incorporated; 2014.[18]

Suprachoroidal hemorrhage (SCH): This can occur during phacoemulsification or in the immediate postoperative period. A SCH is, in most cases, an explosive accumulation of blood in the suprachoroidal space due to low intraocular pressure in the eye during surgery.[82] This is a devastating complication as it can result in severe vision disability, total loss of vision, or even phthisis, which is a shrunken, non-functioning eye. Fortunately, the small incisions of modern phacoemulsification make this complication very rare.

Corneal edema: Corneal edema is swelling of the cornea, and one of the most common complications post-cataract extraction. This can result from increased intraocular pressure, inflammation, trauma from the operation, or chemical injury.[75] Although the procedures and instruments used for cataract extraction have improved a great deal over the past decade, there is still the possibility that the cornea may be

injured which may result in the patient developing a corneal edema. Persistent corneal edema can result in the need for corneal transplantation.

Descemet membrane tear and detachment: This is an iatrogenic injury to the cornea that results in corneal edema, and can be a very serious complication after cataract extraction. This occurs when Descemet's membrane is torn out during routine phacoemulsification. Descemet's membrane is the membrane that lies between the stroma and the endothelial layer of the cornea. This can affect visual acuity, however with medical treatment and time, reattachment is possible.[75]

Intraocular lens dislocation: This complication can occur immediately after or many years after phacoemulsification. As mentioned in the posterior capsule opacification description, the IOL is placed inside the capsular bag of the original lens. However, this capsular bag is fragile and thin – approximately as thick as a single red blood cell! It can rupture, break, dislocate, or dislodge and move positions. This can result in decreased visual acuity or double vision. If treated in a timely manner, the IOL can be repositioned successfully in a second procedure. In more severe cases, an entirely new IOL may need to be implanted into the eye.[83]

Posterior capsule opacification (PCO): This is the most common post-phacoemulsification complication. It is sometimes referred to as a "secondary cataract" even though it is not a cataract at all. During cataract surgery, although the lens is removed and replaced with an intraocular lens, the outer clear membrane (lens capsule) that surrounds the lens is left intact. However, between 11.8%-28.4%[84] of patients develop haziness due to epithelial cells growing on the lens capsule. This can cause decreased visual acuity, and in some cases, be worse than before the cataract extraction.[84] Fortunately, there is a laser surgery (Nd:YAG laser capsulotomy) able to correct this problem efficiently and painlessly.

Cystoid macular edema (CME): CME is a condition that affects the central retina or macular, in which multiple cystic spaces appear in the macular and cause retinal

swelling or an edema (excess of fluid collecting).[85] This typically takes 6-8 weeks to appear after the procedure, and is the most common cause of decreased vision clarity. The incidence of CME after cataract surgery was found to be between 1%-2%.[18,75,86] Although most cases of CME can resolve on their own, topical non-steroidal anti-inflammatory drugs are often applied.[87] The next step in treatment is topical steroids.

Surgically induced astigmatism: Astigmatism can result from poorly constructed surgical wounds, overly tight sutures, or thermal injury during phacoemulsification.[75] Astigmatism is a refractive error which causes images to be blurred or distorted. Although this can be corrected with eyeglasses, contacts, or refractive surgery such as laser eye surgery, avoiding this complication is always better for the patient.

Dysphotopsias: This is a common side effect after uncomplicated cataract surgery. Dysphotopsias are unwanted visual manifestations occurring from light that is reflected off the IOL and onto the retina. Positive dysphotopsias results in glare, streaks of light, haloes etc. Negative dysphotopsias occurs as a dark crescent in the visual field.[75]

Toxic anterior segment syndrome (TASS): TASS is a noninfectious inflammation of the anterior segment of the eye that materializes within 24 hours of cataract extraction. Symptoms typically include corneal edema and clumps of white cells in the anterior segment of the eye.[88] If not treated immediately, vision loss can occur.

Post-operative inflammation: All intraocular procedures will result in some degree of inflammation, which is a risk factor for more serious complications. If inflammation worsens, decreased vision can result. Steroids drops and anti-inflammatory drops are generally prescribed to the patient to prevent such scenarios.[75]

2.11. Systemic Complications during Cataract Surgery

Pain: Pain is a common complication of surgery – especially when the patient is awake and conscious for the procedure. Although surgeons and nurses go to great lengths to ensure cataract extraction be as pain free as possible, pain still occurs in patients.

Additionally, inserting an intravenous line can cause a patient great pain, especially if they are an older adult with frail veins who gets "poked" several times by a nurse trying to locate the vein.

Hypertension: High blood pressure is one of the most common medical conditions globally.[89] Cataract extraction surgery is one of the most common surgeries today, and generally affects adults over 60, the exact group plagued the most from hypertension. Anxiety about undergoing a surgical procedure may exacerbate a patient's hypertension, requiring the surgery to be postponed or rescheduled.

Unwanted movement: Unwanted eye and head movement is a potential complication resulting from the anesthesia management strategy used intra-operatively. The ocular or systemic anesthesia may cause the patient's eye to move, making the procedure more challenging for the surgeon. Systemic sedation may cause the patient's head to move as well, which is why most clinics reinforce the patient's head to a stationary position. Movement may cause the surgical instrumentation to unintentionally move, which can cause immense complications with such a microscopic procedure.

Post-Operative Nausea and Vomiting (PONV): PONV occurs in 20-30% of patients in the first 24 hours after surgery.[90] This can occur from intravenous therapy, sublingual sedation, or inhalation anesthesia.

Bradycardia: Bradycardia is an abnormally slow heart beat; less than 60 beats per minute in adult to be exact.[91]

Tachycardia: Tachycardia is an abnormally fast heart beat; more than 100 beats per minutes in adults.[92]

CHAPTER 3 Literature Review for Methodology

3.1. Introduction to Meta-Analysis

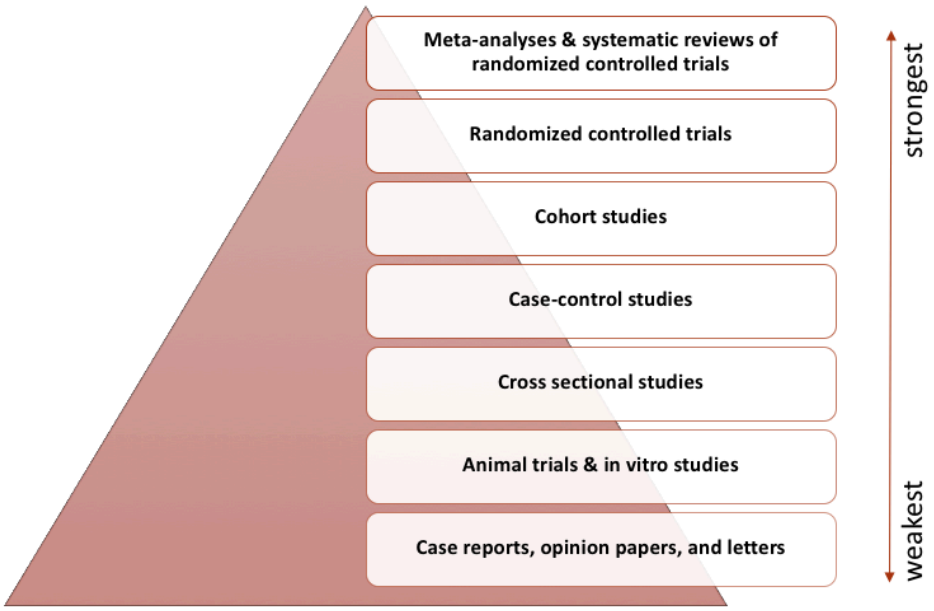
The Cochrane Collaboration has been a meticulous leader in the development of the methods surrounding systematic review and meta-analyses. For this reason, much of this chapter will be referring to their guidelines and tools. According to the Cochrane Handbook, a meta-analysis is the "statistical combination of results from two or more separate studies". This is often the next step after a systematic review, synthesizing the results of the included studies.

Meta-analyses most commonly concentrate on pair-wise comparisons of interventions. In a meta-analysis of randomized control trials, this comparison is between the experimental intervention versus the control, or a comparison between two experimental interventions. In terms of this thesis document, we will conduct a meta-analysis to statistically analyze the studies included in the systematic review, which compare intravenous sedation versus non-intravenous methods in phacoemulsification.

3.2. History of Meta-Analysis

The first documentation of a meta-analytic concept can be traced to the 17th century, where astronomers combined an independent set of observations.[93] Then, in 1904, statistician Karl Pearson published an article combining the results of multiple clinical studies on typhoid vaccination; this was another meta-analytic approach.[94] In 1940, the first genuine meta-analysis was published by psychologists from Duke University.[95] However, meta-analyses of medical interventions were not regularly done until the 1970's.[96] Up until 1976, this form of statistical analysis was known as an advanced form of secondary analysis. Then, in 1976, modern statistician Gene Glass invented the term "meta-analysis" in a published article.[97] Today, meta-analyses are common, and are considered the strongest type of study in the hierarchy of evidence (Figure 3.1).

Figure 3.1: Hierarchy of Evidence



Source: Created by author

3.3. Reasons to Conduct a Meta-Analysis

According to the Cochrane Handbook[98] there are four major reasons to conduct a meta-analysis when conducting a systematic review. These are: to increase power, improve precision, compare studies, and settle controversies. These will be further explained below.

Power

Power is "the chance of detecting a real effect as statistically significant if it exists" (The Cochrane Collaboration, 2008). In other words, the likelihood that an effect will be detected, when there truly is an effect to be detected. Statistical power is affected by two main study characteristics: The size of the effect (a larger effect is easier to detect than a smaller effect), and the sample size (larger samples will have a greater proportion of positive results). Power calculations are done to determine what the minimum required sample size is to detect a specific effect size. Generally, researchers and scientists aim for a statistical power of at least 0.8; in other words, there will be an

80% chance of detecting a real effect if the calculated sample size is enrolled with complete data (including variables, participants, results, follow-up etc).

A meta-analysis should be included in reviews because the power of the combined studies increases. Many studies have too small of a sample size to detect an effect, but when multiple studies are combined, there is a greater chance of detecting an effect. For example, a small study may have a 50% chance of detecting an effect, whereas a large study, or combined studies from a systematic review and meta-analysis, may have a 90% chance of detecting an effect.

Precision

Accuracy and precision are often used interchangeably, however, the distinction between the two is crucial in scientific research and literature. Accuracy involves how close you get to the correct result i.e. If you obtain a weight of 2kg for an item, but the item truly weighs 10kg, it is not accurate. Precision is how consistently you get a result using the same methods. If you weigh the item 10 times, and each time it weighs 2kg, then the measurement is very precise, but inaccurate. If the items weigh 10kg each time, then the measurement is precise and accurate. If the items have a different weight each time, then the measurement is neither precise nor accurate. Precision and accuracy are independent of each other.

Precision is a key reason to conduct meta-analyses in systematic reviews. Testing for precision will allow us to determine how consistent the effect size is over multiple studies. The estimation of an intervention effect will be improved when it is based on multiple studies testing the same outcome.

Consistency

Randomized controlled trials typically involve a specific type of patient, with pre-specified, definite interventions. A group of studies with slight variations in the population and intervention will allow researchers to study how consistent the effect is.

Settle Controversies

There are many instances where multiple studies studying the same exact intervention have opposite, conflicting, results. Analyzing all the results together to produce a summary effect allows researchers to determine where the true effect lies, producing a more accurate result.

3.4. True Effect Size, Observed Effect Size, and Summary Effect Size

The *true effect size* is what the correct answer to a research question would be for the underlying population of a study, if the entire population was used as the study sample, and not a small, random, percentage of the population. The *observed effect size* is the effect size that is measured from the small, random sample of the population in a research study. The *summary effect size* is the result when a meta-analysis is performed. This measure is the weighted mean of the observed effect sizes of all the included studies. There are two models for calculating the summary effect size, which is described in the next section. One is the fixed effects model, and the other is the random effects model.

3.5. Random Effects versus Fixed Effects

When conducting a meta-analysis, there are two models for calculating the summary effect size using a software package; fixed effects models and random effects models.

Fixed-Effects

When a meta-analysis is conducted with fixed effects modeling, it is assumed that the true effect is the same in each study, and that the different effect sizes between studies is solely due to chance.[99] In this scenario, if all the studies are conducted in the same exact way, then the true effect size would theoretically be the same in every study. The difference between the true effect size and the observed effect size is the error, thus, if there are variations in the observed effect size, it is due to intrinsic random error in each study, such as sampling error or measurement error. To use fixed effects models, two conditions must be met. First, the researchers must conclude that all the

studies in the analysis are identical in terms of the underlying population, intervention, comparator, outcome, study design, and the methods. Second, the goal is to determine the effect size for the identified population, and not to generalize to other populations.[100] An example of a meta-analysis using fixed effects models would be if a pharmaceutical company wanted to run a trial using 500 patients, but only had enough resources to test 100 patients at a time. They would then run 5 trials, using 100 patients each time, and use fixed-effect models.[100] Since there is less heterogeneity in fixed effects models, the treatment effect will be more precise, producing smaller confidence intervals.

Random-Effects

When a meta-analysis is conducted with random effects modeling, it is assumed that the true effect in each study will vary around an overall average treatment effect.[99] In this scenario, if all the studies are conducted in the exact same way, the true effect size in each study would be close, but not identical. There is random error within each study, and between the studies. In random-effects modeling, the aim is to estimate the mean of the distribution of effects.[100] To use a random-effects model, two conditions must be met. First, the included studies have been performed by researchers working independently and/or at different institutions. Second, the goal of the analysis is to generalize to multiple populations. An example of a random-effects model would be a meta-analysis of 10 randomized controlled trials that were independently conducted in different countries, with non-identical populations. Since there is more heterogeneity in random-effect models, the treatment effect will be more conservative, resulting in wider confidence intervals.

3.6. Heterogeneity

Heterogeneity can be described as any kind of variability between individual study results in a systematic review.[98] Heterogeneity is difference between studies that are not due to chance. There are three main types of heterogeneity.

Clinical heterogeneity: This occurs when there is variability in the characteristics of participants, interventions, and outcomes (how they are defined and measured). Clinical heterogeneity is always present, as the patients in each study will always be

different. Even if two studies are giving patients the exact same drug, it can be given in different quantities, introducing heterogeneity from the intervention. It is important to be rigorous in the inclusion and exclusion criteria when screening articles to reduce variability as much as possible in the PICOS.

Methodological heterogeneity: This occurs when there is variability in study design and degrees of bias (blinding, concealment allocation). Another manner to introduce methodological heterogeneity is each study having a different scale to measure the outcome. For example, one of the primary outcomes this thesis is investigating is the pain levels during phacoemulsification. Each study will certainly be using different pain scales to measure this, which will introduce heterogeneity into the analysis.

Statistical heterogeneity: This occurs when there is variability in intervention effect sizes, and is due to clinical and/or methodological heterogeneity. In other words, studies that have different results from each other. For example, one study may show that a pharmaceutical intervention is harmful, while the other shows it is beneficial. When there is statistical heterogeneity, the true effect is different in each study.

It is crucial that meta-analyses are generated only when the PICOS (population, intervention, comparator, outcome, and study design) across studies is reasonably homogenous.

3.7. How to Measure Heterogeneity (I^2)

Heterogeneity is a descriptive statistic (also known as I^2) that can only be evaluated when a forest plot is created during a meta-analysis. Heterogeneity is always present to some degree in a systematic review. A way to measure if heterogeneity is present is to examine the p-value of a chi-squared (χ^2, or Chi^2) test, which tells us if it is fair to combine the studies in the meta-analysis, or if they are too different. A chi-squared test assesses how likely it is that the observed distribution of results is due to chance; it measures how well the observed distribution fits with the expected distribution.[98] Expressed differently, the chi-square test tests the null hypothesis that all studies are evaluating the same effect, and that they are homogenous. A high p-value

(over 0.5) suggests that homogeneity is present. A low p-value suggests there is heterogeneity present, and that the variation of effect estimates is beyond chance.[98]

The I^2 is the perception of variation across studies that is due to heterogeneity, and not due to chance. According to the Cochrane Handbook, 0%-40% represents low heterogeneity, 30%-60% represents moderate heterogeneity, 50%-90% represents substantial heterogeneity, and 75%-100% represents considerable heterogeneity.[98] An issue with the chi-squared test is that it has low power (the likelihood that an effect will be detected, when there truly is an effect to be detected, is low). This is because there are usually very few studies included in a meta-analysis. Once heterogeneity is identified, there are two ways to investigate where it may be coming from: subgroup analysis, and meta-regression.

3.8. Investigation of Heterogeneity

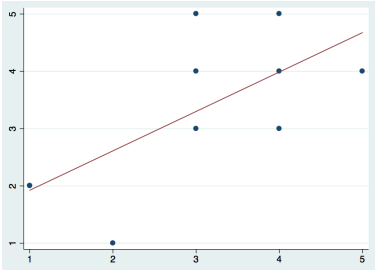
Subgroup Analysis

A subgroup analysis involves separating all the data into subgroups to make comparisons between them. This may be impactful to conduct, as some patients may have more benefit, more harm, or neither benefit nor harm. Clinically, it is important for a physician to know if there is a certain patient group that would benefit from an intervention, while another patient subgroup may be harmed by the same therapy. These analyses can be done either by comparing subsets of participant characteristics (i.e. opposite sex, age, ethnic groups, presence of disease), treatment characteristics (i.e. high dose vs. low dose, intravenous vs. non-intravenous, intravenous vs. oral, etc.), or study characteristics (i.e. by location).

Meta-Regression

A regression analysis is a statistical method to estimate relationships among one or more explanatory variables. The relationship between a dependent and independent variable is quantified with a line of best fit, allowing researchers to predict the outcome variable (Figure 3.2).

Figure 3.2: Regression Analysis Example



Source: Created by author on STATA13

A meta-regression uses the same concept of a simple regression but in the context of a meta-analysis, with the aim being to predict the outcome variable of a meta-analysis. In a meta-regression, the outcome variable is the effect estimate (i.e. standardized mean difference, mean difference, risk ratio, odds ratio, risk difference, etc), with the explanatory variables being characteristics of studies (i.e. study location, year of study, type of study, male/female, mean age of participants, etc.) with potential to influence the intervention effect size. The regression coefficient from a meta-regression describes how the outcome variable changes with a unit increase in the explanatory variable.

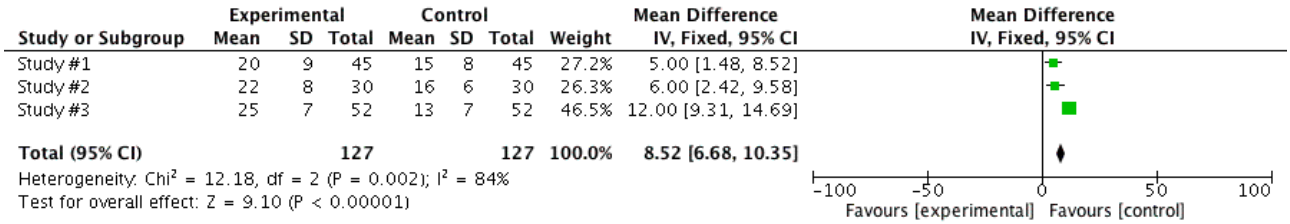
3.9. Statistical Principles of Meta-Analysis

A meta-analysis is done in two stages. First, a summary statistic is calculated for each individual study. If the data are continuous (quantitative traits measured on interval scales such as height, weight, blood pressure etc.) the summary statistics will be a difference between the means. If the data are dichotomous (can only take on the value 0 or 1 i.e. if the individual has clinical improvement it is 1, if the individual does not it is 0), the summary statistic may be a risk ratio or an odds ratio.[101]

The second stage of a meta-analysis is the calculation of a summary intervention effect. A weighted average of all the intervention effects (which are calculated in the first stage) are pooled. If a random effects meta-analysis is performed, it is assumed that not all included studies are evaluating the same intervention effect, but that a distribution across studies is followed. If a fixed-effect meta-analysis is performed, it is assumed all included studies are evaluating the same exact intervention effect.

These two stages are visually displayed on a forest plot (Figure 3.3); the effect estimates and confidence intervals for both the individual studies and overall summary effect are presented. The individual studies are represented by a square at the effect estimate, with the size of the block depicting the weight of the study. The horizontal line passing through the block is the confidence interval.

Figure 3.3: Forest Plot Example



Source: Created by author in RevMan.

3.10. Effect Measures for Dichotomous Outcomes

In clinical trials with dichotomous data, the most common effect measures are the risk ratio (RR), odds ratio (OR), risk difference (RD), and number needed to treat (NNT). The meta-analysis summary effect will describe the outcome in one group relative to the other group. The risk ratio describes the probability of an event occurring in the intervention group, to the probability of the event occurring in the comparison group. The odds ratio describes the odds that an outcome will occur compared to the odds of the outcome not occurring, in the presence or absence of an exposure, respectively. A risk ratio or odds ratio of 1 indicates that the effects are the same in both the intervention and comparator group. There are four well-established methods of conducting a meta-analysis for dichotomous outcomes.

Inverse Variance Method (fixed effects)

This approach is used in both dichotomous and continuous data. The weight of each study is analyzed as the inverse of the variance of the effect estimate $(1 / \sqrt{(Standard\ Error)})$. As a result, larger studies (with smaller standard errors) are given more weight than smaller studies (which have larger standard errors). The smaller the

standard error, the more precise the study, therefore this method attempts to minimize imprecision.[98]

DerSimonian and Laird Method (random effects)

This approach produces a random-effects, inverse-variance meta-analysis. It is conducted on the assumption that the studies are estimating different intervention effects that are related. In this analysis, the calculations are adjusted to account for heterogeneity among the intervention effects.[98]

Mantel-Haenszel Method (fixed effects)

This approach is more appropriate than the inverse variance method when there are rare events or very small trials. Instead of using the inverse variance of the effect estimate to assign weighting to the studies, a distinct weighting scheme is used depending on the effect measure (OR, RR, RD).[98]

Peto Odds Ratio Method (fixed effects)

This approach is an alternative method to the Mantel-Haenszel method for pooling odds ratios when the events are rare. Corrections for zero cell counts do not need to be done when using this method, as the focus of the Peto analysis is on rare events.[98]

3.11. Effect Measures for Continuous Outcomes

In clinical trials with continuous data, the most common summary statistics are mean differences, and standardized mean differences. The mean difference summary statistic measures the absolute difference between the mean values in the intervention and comparator groups in a clinical trial. This is used when each RCT in the analysis uses the same outcome scale. The standardized mean difference summary statistics is used when every RCT in the analysis measures the outcome in different ways i.e. each study measures pain using a slightly different visual pain scale. This method standardizes the results; the size of the each intervention effect is relative to the standard deviation in that study.[98] The scales may be different sizes, however they must

all point in the same direction. Corrections can be made for scales in opposite directions.

$$Standardized\ Mean\ Difference = \frac{Difference\ in\ mean\ outcome\ between\ groups}{Standard\ deviation\ of\ outcome\ among\ participants}$$

To perform a meta-analysis of continuous data using mean differences or standardized mean differences, authors must extract the following from each study: the mean value of the outcome measure in each group, the standard deviation of the outcome value in each group, and the number of participants in each group

Inverse Variance Method (fixed effects and random effects)

There are two common methods of analysis for continuous outcomes: inverse variance fixed effect method, and inverse variance random-effects method. When heterogeneity is not present, both methods will give an identical answer. When heterogeneity is present, confidence intervals for the effect sizes and summary effect will be wider with utilization of the random effects method, and the P-values will be less significant.

3.12. Effect Measures for Count Data

Count data in statistics is when the observations in an analysis only include non-negative integer values. An example of using count data is to analyze the number of complications occur in each treatment group in a study, or number of myocardial infractions, hospital visits, etc. Count data may be analyze using dichotomous or continuous methods. The most common summary statistic in a meta-analysis for count data is the risk ratio.[98] The mean difference of events will be used compare the intervention group to the comparison group. In the case of zero event cells, a correction of 0.5 may be added to the cell.

Count Data as Dichotomous Outcome

For count data to be treated as a dichotomous outcome, the number of participants in each intervention group, and the number of participants in each group

who experience at least one event must be extracted from each study. For this thesis, we will be extracting complication outcomes as dichotomous count data.

3.13. Publication Bias – Funnel Plots

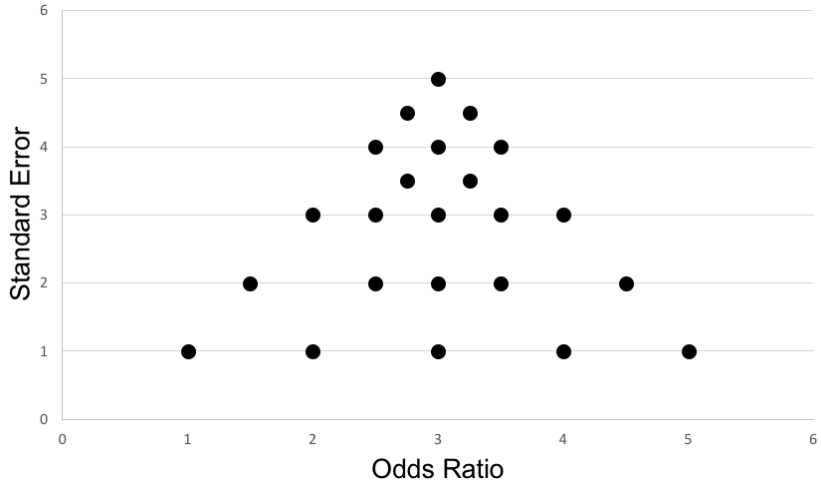
Publication bias is the tendency to submit or accept studies for publication based on the direction or strength of the study result. This means that positive studies tend to get published more than negative studies. The studies that are negative, or not as strong as the researchers would like, never get submitted for publication. The reason systematic reviews are done is to understand the totality of evidence on a given topic. If publication bias exists, and non-significant studies are suppressed, we will not be able to see all the evidence, and our systematic reviews and meta-analyses will yield a biased estimate of an intervention effect. Negative studies not being published leads to an overestimation of benefit and an underestimation of harm.

A commonly used visual method to assess publication bias is the funnel plot. A funnel plot is a scatter plot of effect size (x-axis) against some measure of study size or precision (y-axis). Each of the dots represents a study that was found by the researchers. If the funnel is symmetric then there is likely not significant publication bias. If the funnel is asymmetric, it suggests that there is possible publication bias. It is much more likely for small negative studies to not get published, and a funnel plot can visually display this. Figure 3.4 is an example of a symmetrical funnel plot, and Figure 3.5 is an example of an asymmetrical funnel plot which displays publication bias.

According to Egger et al. (1997)[102] there are five possible sources of asymmetry in funnel plots. The first is selection bias, which can include publication bias, language bias, location bias etc. The second is true heterogeneity, meaning that the included studies may not all be estimating the same effect or same intervention. This may lead to heterogeneous results, causing asymmetry in the funnel plot. A third possible reason for asymmetry is data irregularities. This can result from methodological quality differences in the included studies; it is known that smaller studies tend to be conducted not as meticulously as larger studies, and that lower quality trials are prone to showing larger effect sizes.[103–105] The fourth source of asymmetry may be due to artefactual bias. Artefactual bias may occur because of the statistic chosen to measure the effect size.

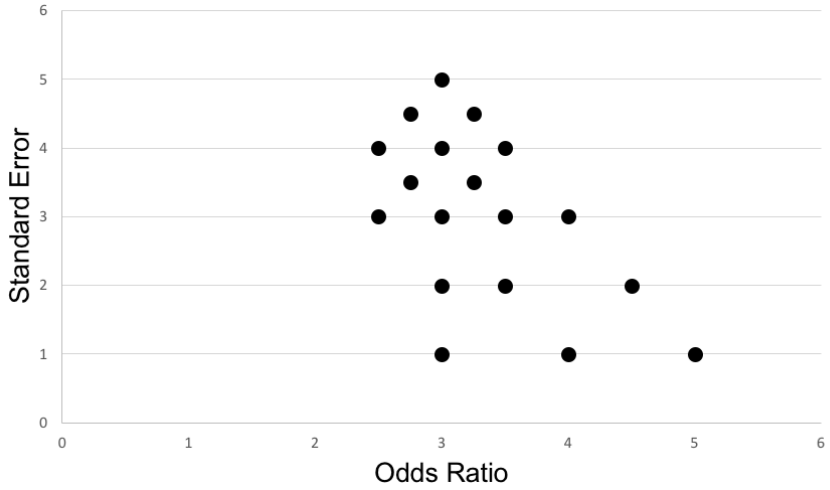
For example, if the event rate in a study is high and an odds ratio is calculated, the relative reduction in risk may be overestimated.[105] Lastly, an asymmetrical funnel plot may be purely due to chance.[102] It is important to take these possibilities into account when examining a funnel plot.

Figure 3.4: Symmetrical Funnel Plot



Source: Created by author.

Figure 3.5: Asymmetrical Funnel Plot



Source: Created by author.

3.14. Missing Data

A common issue when extracting data from a study is missing data. There are five types of missing data: missing studies (publication bias), missing outcomes (selective reporting bias), missing summary data (selective reporting bias), missing individuals (selecting reporting bias), and missing study-level characteristics (incomplete reporting).[98] There are many options to manage missing data. The Cochrane Handbook has dedicated an entire section to dealing with a common setback in meta-analyses which is missing standard deviations from the included studies. If the corresponding author from the study in question is not able to release the data from the paper, or no longer has access to it, there are a multitude of ways to calculate the standard deviation using available data in the study. This is known as imputation, and involves making assumptions about the missing data and statistics.[98] In instances where data was missing from the included studies, we consulted the Cochrane Handbook on their statistical methods to impute the data and an experienced researcher (WGH).

3.15. Risk of Bias Assessment

The Cochrane Collaboration is an international non-profit organization involving a global group of researchers, professionals, patients, and individuals interested in health and healthcare. It is a group of more than 37,000 individuals from 130 countries, working to produce credible and accessible evidence-based reports and information that is free from sponsorships and conflicts of interest.[106] This group has published over 7000 systematic reviews and reports, a 674-page handbook containing all the methodological guidance needed to conduct a systematic review of interventions, a data management program (Review Manager 5.3, also known as RevMan) that enables researchers to produce high quality systematic reviews, and various tools for systematic processes. One such tool is their *Assessment of Risk of Bias in Included Studies*, which has been implemented in RevMan, and described in Chapter 8.5 of the Cochrane Handbook.[98] This tool contains the seven categories that are assigned a judgement of either ‘yes’ meaning that i.e. allocation concealment was adequately conducted and there was a low risk of bias, “no” indicating a high risk of bias, or ‘unclear’ indicating that the risk of bias was unknown.

The first category is *random sequence generation (selection bias)*. This requires that allocating interventions to participants must be explicitly stated, and randomly processed. This prevents the researchers from selecting what intervention the participants receive.[98] The second category is *allocation concealment (selection bias)*. For the study to be at low risk, the individual who is randomizing the participant must not know what the next intervention allocation is. This prevents the individual randomizing the participants from selecting who gets what intervention.[98] The third category is *blinding of participants and personnel (performance bias)*, which occurs after the participants have received their allocation. Blinding means that neither the researchers or the participants are aware of which intervention they received. Blinding prevents researchers from treating patients that received a certain intervention differently, and vice-versa.[98] The fourth category is *blinding of outcome assessment (detection bias)*. The outcome assessor must be blinded to the intervention when assessing outcomes for the risk of bias to be low. For example, if a researcher knew what intervention was given, and was recording subjective patient pain levels, they may rate the patient's pain higher or lower than what it truly is. Blinding prevents this type of bias from occurring.[98] The fifth category is *incomplete outcome data (attrition bias)* – Attrition occurs from a loss of participants. This can cause biased effect estimates and results. If a participant's data is available yet knowingly excluded from an analysis, bias occurs. Additionally, if outcome data is not available (the participant dropped out, there was a nonresponse, or withdrew), it can cause biased results.[98] The sixth category is *selection reporting (reporting bias)* – This occurs when researchers do not report all the study results. For example, often only statistically significant results are reported, excluding the non-statistically significant results from the publication. Finally, the last category is *other bias.* Other biases can occur in specific circumstances. Recruitment bias, stopping a study early, or having a sequence generation for allocation that may be predictable can all contribute to bias.[98]

CHAPTER 4 Methods

4.1. Methods Introduction

This review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[107] (completed checklist in Appendix A).

4.2. Search Strategy

A comprehensive search strategy was created to locate the maximum return of relevant studies related to our question. Subject headings and keywords were tailored to each of the electronic databases. The search strategy was performed in collaboration with Dr. John Costella, a librarian with expertise in medical literature, and ophthalmologists specializing in cataract extraction at St. Joseph's Health Care in London, Ontario. The terms listed in Table 4.1 were used to develop a comprehensive search strategy with database and platform specific terminology and syntax for the following databases: Medline (OVID), Embase (OVID), Cochrane Library (Wiley), BIOSIS (Thomson-Reuters), Web of Science (Thomson-Reuters), and CINAHL (EBSCO). Grey literature was explored by searching dissertations, theses, reports, conference proceedings, clinical trials, as well as ophthalmology specific meeting abstracts such as the Association for Research in Vision and Ophthalmology (ARVO), Canadian Ophthalmology Society (COS), American Academy of Ophthalmology (AAO), and European Society of Ophthalmology (SOE). The Conference Proceedings Citation Index was also included as part of the Web of Science search. The appendix contains the complete search strategies used for the included databases with a detailed list of grey literature databases and websites explored (Appendix B). The original search was performed on September 7th and 8th, 2016, with weekly publication notifications until August 2017. To ensure all relevant studies were included, bibliographies of eligible studies retrieved in the literature were hand searched.

Table 4.1: Concepts, Keywords, and Phrases for Search Strategy

Concept	Subject Headings	Keywords
Cataract Surgery	Cataract Extraction, Cataract	Phacoemulsification, cataract extraction, cataract removal, cataract surgery, cataract operation
Anesthesia	Neuroleptanalgesia, anesthesia, local anesthesia, nerve block, intravenous anesthesia, cryoanesthesia, analgesia, anesthetics, perioperative care,	Block, anesthesia, infiltration, injection, orbicularis, subtenons, peribulbar, retrobulbar, topical, Intracameral, xylocaine, neuroleptics, benzodiazepine, lidocaine, procaine, proparacaine, oxybuprocaine, tetracaine, bupivacaine, etidocaine, lidocaine, prilocaine, ropicacaine, cryoanesthetics, midazolam, fentanyl, propofol, perifentanyl, gravol, dimenhydrinate, ondansetron, lorazepam, Ativan, valium, diphenhydramine, Benadryl
Pain	Pain, eye pain, postoperative pain, postoperative period, postoperative care, perioperative period, perioperative care, intraoperative period, intraoperative care	Pain, ache, discomfort, instillation, drop, dilation, manipulation, freeze, pressure, headache, postoperative, perioperative, intraoperative.
Complications	Intraoperative Complications/ or Postoperative Complications/ or Endophthalmitis/ or Keratitis/ or Lens Subluxation/ or Retinal Detachment/ or Vision Disorders/ or Eye Hemorrhage/ or Vitreous Hemorrhage/ or Retinal Hemorrhage/	Complication, broken capsule, posterior capsule rupture, endophthalmitis, keratitis, intraocular lens dislocation, lens subluxation, low ocular pressure, ocular hypotension, high ocular pressure, ocular hypertension, anesthetic allergy, ocular toxicity, or allergic reaction, vitreous hemorrhage, or retinal detachment, or choroidal hemorrhage, or suprachoroidal hemorrhage, or ocular hemorrhage, or eye hemorrhage, or retinal hemorrhage, or systemic hypertension, vision loss, vision disorder

4.3. Eligibility Criteria

With the expertise of ophthalmologists (WGH, CMLH) from the Ivey Eye Institute in London, Ontario, the study's eligibility criteria were established by identifying key components that needed to be fulfilled to answer our research question: how different anesthesia management strategies (IV vs non IV) in cataract extraction affect patient pain perception and intra-operative adverse effects. The P.I.C.O.S. model for clinical questions (patient, intervention, comparison, outcome, study design) was used.[108] The

P.I.C.O.S. tool allows researchers to focus their research on a specific question, and determine specific exclusion and inclusion criteria that is used when selecting studies to be included in the systematic review.

P.I.C.O.S. Tool

Participants: The study population included those with cataracts only and not cataracts combined with other surgical conditions (see Table 4.2 for the list of surgeries that were excluded). The included studies were also restricted to healthy adults (18+). This would ensure homogeneity within the study.

Intervention: Interventions involve a wide range of exposures such as pharmaceutical therapies, lifestyle changes, or social activities. In this study, the intervention was intravenous conscious sedation on patient pain perception, and surgical complications during phacoemulsification. Studies involving extracapsular cataract extraction (ECCE) or Intracapsular cataract extraction (ICCE) were excluded

Comparator: The comparator was any anesthesia technique that did not use intravenous sedation. This could include sublingual sedation, ocular blocks, intracameral injections, topical anesthetics, or combinations thereof.

Outcomes: The primary outcomes were patient pain perception and perioperative complications. These outcomes determine the effectiveness of the intervention and comparator for patients undergoing cataract extraction. Both outcomes were analyzed in a meta-analysis.

Study Design: Only randomized controlled trials were included in the study. Observational studies (cohort, case-control, and cross-sectional) were excluded. Case-series and case-reports were also excluded. Additionally, non-research articles such as commentaries, editorials, letters, methodology papers, and review articles were excluded.

Inclusion Criteria:

Articles were included if they: (i) were from any country, (ii) in English (iii) published from 1995 to present day (iv) were randomized control trials (v) had intravenous therapy as the intervention (vi) had all other non-IV anesthesia and sedation methods was the comparator (vii) had a study population of healthy adults with cataracts undergoing phacoemulsification (viii) included outcome measures of interest – pain perception, adverse complications or both.

Exclusion Criteria:

Articles were excluded if they: (i) were cohort, case-control, cross-sectional, commentaries, editorials, letters, methodology papers, review articles (ii) were not in English (iii) included patients who had combined surgical ocular conditions i.e. cataract extraction and trabeculectomy (iv) included children (v) did not use phacoemulsification as the surgery technique (vi) did not provide the outcome of interest (vii) were published prior to 1995.

Rationale for Date Restriction

The exclusion criteria consisted of articles published prior to 1995 since phacoemulsification is a relatively new procedure. It was not until 1967 that modern phacoemulsification was invented by Charles Kelman at the Manhattan Eye, Ear, and Throat Hospital in New York City. [46] However, even with the foundation of phacoemulsification laid out, Kelman still had to overcome surgical, instrument, and political problems before it would a widely performed procedure.[69] In 1996, 97% of all cataract operations in the United States were done by phacoemulsification. [48] For these reasons 1995 was selected as a cut-off year.

4.4. Article Screening

Screening was performed at two levels (citations and full text) by two reviewers (JJA and EK) to eliminate articles that did not meet the inclusion criteria. The screening was done twice to ensure this process was conducted with the utmost accuracy, and to reduce measurement bias. If a consensus was not reached during the article screening,

then an experienced ophthalmologist (WGH) intervened to solve disagreements on article eligibility. Level 1 consisted of simultaneously screening through titles and abstracts to locate articles that were potentially relevant to the study question. The screening questions for level 1 and 2 are listed in Table 4.2. If the answers to all the questions were “do not exclude”, then the study would go on to level 2 screening.

Table 4.2: Study Eligibility Criteria

Level 1 Screening Questions (Title and Abstract) *Covidence screening based on exclusion criteria
1) Exclude if the study does not look at uncomplicated cataract surgery in human adults. 2) Exclude if the cataract surgery performed is extracapsular extraction surgery (include phacoemulsification only) 3) Exclude if the study is not measuring effectiveness of anesthesia modalities such as sedation, intravenous therapy, blocks, topical drops, and local anesthesia. 4) Exclude if the study is not a primary study. 5) Exclude if the study is not in English. 6) Exclude if the study is not a comparative study.
Level 2 Screening Questions (Full Text) *Covidence screening based on exclusion criteria
1) Exclude the study if it consists of the following combined ocular surgeries: a. Combined cataract extraction and trabeculectomy b. Combined cataract extraction and vitrectomy 2) Exclude if the study does not compare intravenous sedation to non-intravenous sedation. 3) Exclude the study if it does not report on one of the following outcomes: a. Pain b. Complications c. Adverse events

4.5. Data Extraction for Qualitative Data

Upon completion of the article screening, a data extraction form was created on Microsoft excel. Two reviewers (EK and ST) independently extracted data using the form. Authors were emailed to obtain any missing information that was relevant to the study. The following information was collected in the final descriptive data extraction form:

Study Characteristics: citation, study design, location. This gives an idea of the types of studies being included in the analysis.

Participant Characteristics: sample size, mean age (and standard deviation/range of age if available), and the number of male and female patients. These characteristics are necessary to be able to compare patients from different intervention groups (intravenous sedation vs anesthetic techniques that did not use intravenous sedation). Additionally, it allows us to determine if the patient populations were homogenous.

Treatment: type of surgery. It is important that all included studies treated patients with the same surgery – phacoemulsification. This ensured homogeneity was present when looking at different interventions.

Sedation/Anesthesia: sedation type (intravenous, sublingual, oral, or none), sedation medication and dosage, topical anesthesia, gel anesthesia, and ocular/periocular injections. This information was vital so that sedation management strategies could be compared under the same surgical procedure.

Outcomes: The outcomes specifically looked at when comparing intravenous sedation vs. anesthetic techniques that do not use intravenous sedation were pain perception during surgery, and adverse events or complications that occurred perioperatively. For pain preference, the following was recorded: the pain scale used, the result in each group (mean, standardized difference, p-value), and the number of clinically-relevant adverse events in each group, and a description of what the adverse events were. These outcomes were extracted for the meta-analysis.

4.6. Data Extraction for Quantitative Data

Pain during surgical procedures is generally measured using a variation of pain scales, such as the Visual Analogue Scale (VAS), Verbal Pain Scale (VPS), or a Numeric Rating Scale (NRS). The mean and standard deviation of the pain levels in each group was extracted. When studies did not directly report the mean pain or their standard deviations, the authors were contacted. If the authors were unable to provide data or did not respond, these values were extrapolated from the graphs within the

studies, or with imputation techniques described in Chapter 16.1 of the Cochrane Handbook.[98]

Any adverse events or complications that occurred perioperatively were extracted from the studies. This included the number of complications, the number of patients who experienced complications, and a description of the adverse event. If complications were not reported, authors were contacted for information.

In the instance where a study has more than two groups (intervention group 1, intervention group 2, comparator group) the guidelines from Section 16.5 of the Cochrane Handbook[98] was used. The preferred methods of managing data from two intervention groups is to either combine groups for a single pair-wise comparison, select one intervention group and exclude the others, split the shared group to create two or more comparison groups, or undertake a multiple-treatments meta-analysis.[98]

4.7. Risk of Bias in Included Studies

Bias in a study can be described as systematic error in the results of interpretations. In other words, if a study with bias was repeated 1000 times in the exact same way, the results would be incorrect most of the time.[98] It is crucial to assess the studies for bias in a systematic review. If the included studies prove to have a high risk of bias, then the review's conclusions and results will be weak or incorrect. However, if there is a low risk of bias in the included studies, then the conclusions and results will be strong and correct. Two reviewers (EK and ST) judged each study to be either at a 'low', 'high', or 'un-clear' risk for seven categories (see Section 3.15) using Cochrane's *Assessment of Risk of Bias in Included Studies* in Review Manager 5.3 (RevMan). Disagreements were resolved through discussion, however if a consensus was not reached, an experienced researcher (WGH) intervened to solve disagreements. When an issue was 'un-clear', we would contact study authors for additional information. If there was no response, we would assess the bias based on what information was available. We used table 8.5.c in the Cochrane Handbook[98] to guide our judgements, as the criteria for correctly using their assessment tool is listed in detail.

4.8. Risk of Bias versus Study Quality

As mentioned in section 4.7, bias refers to systematic error in the conclusions and results of a study. Selection bias, performance bias, detection bias, attrition bias, and reporting bias can all result in incorrect results and interpretations. When assessing bias in a study, we are asking if the results of a study are true, and if we should believe them. Study quality, on the other hand, refers to if the study was conducted at the highest possible standard. This can refer to obtaining Research Ethics Board (REB) approval, performing a sample size calculation, registering an RCT, or reporting a study in line with recommendations such as the CONSORT[109] (Consolidated Standards of Reporting Trials) checklist or PRISMA[107] (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. An REB approval is unlikely to influence a study's risk of bias. Thus, risk of bias and study quality are distinctly different. For this reason, we have also assessed the study quality using the GRADE[110] (Grading of Recommendations, Assessment, Development, and Evaluation) guidelines.

4.9. Assessing Study Quality using GRADE

The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation guidelines.[111–124] The GRADE working group has created the GRADEpro tool on their website, allowing researchers to easily summarize and assess articles using the GRADE quality assessment evidence profiles and the Cochrane Summary of Findings tables. Two review authors (EK and ST) independently assessed the quality of evidence using the GRADEpro tool. Disagreements were resolved through discussion, however if a consensus was not reached, an experienced researcher (WGH) intervened to solve disagreements. This approach evaluates the overall quality of a body of evidence, assessing the risk of bias, inconsistency, indirectness, imprecision, and publication bias. These five categories are rated either as 'not serious', 'serious', or 'very serious', according to the reviewer's assessment, indicating any issues with the measurements. The articles published by the GRADE working group give categories that were used to guide judgements. The GRADEpro tool then summarized the ratings given on these five categories, and assigned the article to be either low, moderate, or high quality evidence.

4.10. Data Analysis

Primary Outcome – Pain Perception

Data analysis was conducted using STATA 13. In STATA, special syntax and options were used to conduct a random effects meta-analysis, (metan) for one of the primary outcomes – pain perception. All studies used meaningful scales, albeit with slight variations. For this reason, a meta-analysis was performed on the standardized mean difference. This is the standard method used when the included studies measure the same outcome, but with a variety of continuous scales.[125] This was conducted using a random effects model, as it was anticipated that there would be excess heterogeneity in the results due to the extensive variation of anesthetic techniques used in each study.

A sensitivity analysis was also conducted on the standardized mean difference to examine the robustness of the results. For this method, we omitted studies with effect sizes whose effect sizes were far from the rest of the data, and were clear outliers. Often, outliers can amplify or diminish the mean of a sample, influencing the overall treatment affect.[126] Once the studies were omitted, the analysis was re-run with the remaining studies. If the findings and conclusions were consistent with those from the primary analysis, then the primary analysis is used. In this situation, the outlying studies appear to have minimal impact on the primary conclusion, and the results are said to be robust.[126] Robust results can be described as strong results not affecting by outliers. A second sensitivity analysis was conducted in which the studies that used imputation techniques to estimate the missing standard deviations were omitted to investigate if these methods had an impact on the overall effect size. In this situation, if the findings are consistent with the primary analysis, then the results are said to be robust.

The results were also analyzed with a weighted mean difference meta-analysis. This is conducted when the outcome is measured using the same units/scales in all studies.[125] For the analysis to be possible, the included studies were converted to the same scale. This was done to highlight the clinical significance.

A sub-group analysis was conducted to identify differences in effect estimates in certain subgroups. It is important to conduct subgroup analyses, as treatment effects may vary according to intervention or patient characteristics. To determine the treatment effect of different types of intravenous medication, a subgroup analysis was conducted.

This analysis determined whether certain medications were more effective than others. A second subgroup analysis was conducted to determine the effect of intravenous sedation versus oral sedation. This analysis determined which sedation method was most effective. In both subgroup analyses, a fixed effects model was used to yield better precision, since it is assumed the subgroups are more homogenous.

A meta-regression was conducted to examine the relationship between certain covariates and the effect size. The covariates used in this univariate random-effects meta-regression to assess heterogeneity are as follows: location of study, year of publication, sex, and mean age. This was done using STATA13 by creating new variables that were coded to dichotomize the original data.[127]

Finally, a funnel plot was created using STATA13 to investigate publication bias.

Primary Outcome – Adverse Events

Data analysis was conducted using STATA 13. In STATA, special syntax and options were used to conduct a random effects meta-analysis, (metan) for the second primary outcome – adverse events and complications. This extracted data was utilized for a dichotomous random effects meta-analysis. Data was collected as the number of participants who experienced complications in each group, and the sample size. The risk ratio was the effect measure calculated, which describes the probability that an adverse event will occur with intravenous sedation, and non-intravenous sedation techniques.

When conducting a meta-analysis of dichotomous outcomes, zero cells (when there are no complications in one or both of the groups) do not allow the effect size to be calculated, as computation problems arise.[98] Since perioperative complications during cataract surgery are not common, this potential problem was anticipated. A correction factor of 0.5 was added to zero cells so effect sizes could be estimated for all studies.

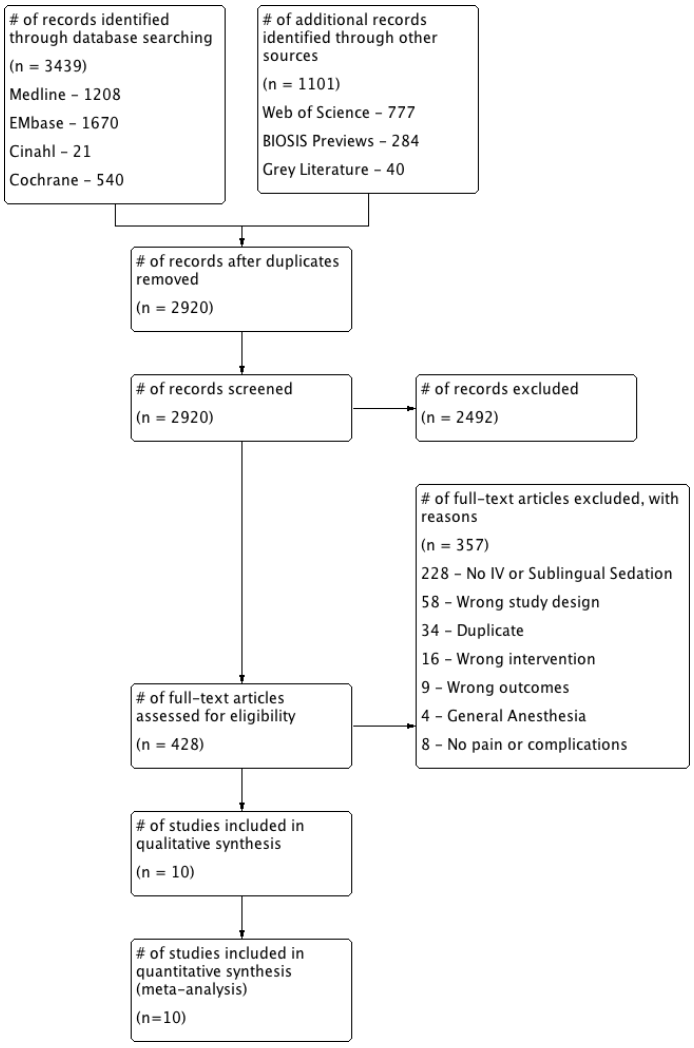
Finally, a funnel plot was created using STATA13 to investigate publication bias.

CHAPTER 5 Results

5.1. Study Selection

A total of 4541 articles were retrieved by searching the previously mentioned databases and grey literature, which were then imported into the Covidence screening tool. After removing duplicate articles, 2920 articles were included for screening. The full text of 428 articles were retrieved for level 2 screening. There were 10 articles eligible for data extraction. The PRISMA diagram demonstrating the selection process is displayed in Figure 5.1.

Figure 5.1: PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

5.2. Study Characteristics

A total of 4541 articles were retrieved from relevant databases and grey literature searches. After level 1 and 2 screening, 10[56,128–135] articles (985 participants) were included for quantitative synthesis in the meta-analysis. Table 5.1, 5.2, and 5.3 depict the baseline characteristics (demographic, intervention, and patient characteristics) of each study. Studies were conducted in 6 different countries. All articles were published between 2002 and 2015, and were randomized controlled trials. Of the 10 studies, 3 studies compared intravenous fentanyl to saline solution, 1 compared intravenous midazolam to saline solution, 2 compared intravenous midazolam to an oral sedative, 1 compared intravenous clonidine to saline solution, 2 compared intravenous dexmedetomidine to saline solution, and 1 compared intravenous remifentanil to saline solution. There was variation in the methods used for mydriasis, topical anesthesia, and ocular injection throughout the studies. There was no variation in study population; all were adult cataract patients. For pain measurement, 3 studies used a numeric rating scale (NRS) ranging from 0-10, 3 studies used a visual analogue scale ranging from 0-10, 2 studies used a visual pain scale ranging from 0-10, one study used a visual pain scale ranging from 0-3, and one study used a 5 point likert scale. All pain scales used in the randomized controlled trials have been validated.[136–139] The main outcome measures were pain perception and perioperative complications.

Table 5.1: Demographic Characteristics of Included Studies

Author (Year)	Location	Study Design	Sample Size	Population
Aydin et al. (2002)[128]	Turkey	RCT	68	Adult cataract patients
Inan et al. (2003)[129]	Turkey	RCT	120	Adult cataract patients
Laube et al. (2003)[130]	Germany	RCT	97	Adult cataract patients
Habib et al. (2004)[131]	England	RCT	100	Adult cataract patients
Leidinger et al. (2005)[132]	Germany	RCT	90	Adult cataract patients
Akgul et al. (2007)[133]	Turkey	RCT	120	Adult cataract patients
Erdurmus et al. (2008)[134]	Turkey	RCT	44	Adult cataract patients
Santiago et al. (2014)[135]	Brazil	RCT	40	Adult cataract patients
Chen et al. (2015)[56]	United States	RCT	156	Adult cataract patients
Ghodki et al. (2015)[140]	India	RCT	60	Adult cataract patients

Table 5.2: Intervention Characteristics of Included Studies

Author (Year)	Intravenous Sedation Group	Non-Intravenous Sedation Group	Dilation Drops (both groups)	Topical Anesthetic (both groups)	Ocular Injection (both groups)
Aydin et al. (2002)[128]	IV fentanyl 0.7 µg/kg PCA	IV balanced salt solution PCA	Cyclopentolate hydrochloride 1%, tropicamide 1%, phenylephrine hydrochloride 10%	Oxybuprocaine hydrochloride 0.4%, sponge soaked with lidocaine 2% and bupivacaine 0.5%	n/a
Inan et al. (2003)[129]	IV fentanyl 2 µg/kg	IV of 500 cc electrolyte solution	Phenylephrine hydrochloride 2.5%, tropicamide 0.5%, cyclopentolate hydrochloride 1%	Proparacaine hydrochloride	Retrobulbar block mixture of 1 mL (5 mg/mL) bupivacaine and 1.5 mL (20 mg/mL) of lidocaine 2%
Laube et al. (2003)[130]	IV midazolam 1 mg	Oral clorazepate dipotassium 10mg	n/a	n/a	Retrobulbar block of 6 to 8mL mepivacaine hydrochloride 2% with 75 IE hyaluronidase
Habib et al. (2004)[131]	IV midazolam 0.015 mg/kg	IV cannula inserted	n/a	Proxymetacaine hydrochloride 0.5% drops	Intracameral 1 to 2 mL preservative-free lidocaine 1%
Leidinger et al. (2005)[132]	IV remifentanil 0.3 µg/kg, Oral clorazepate dipotassium	IV saline, Oral clorazepate dipotassium	n/a	n/a	Retrobulbar nerve block
Akgul et al. (2007)[133]	IV fentanyl 0.7 µg/kg PCA OR remifentanil 0.3 µg/kg PCA. *Two intervention groups combined for a pair-wise comparison*	IV saline	Cyclopentolate hydrochloride 1%, tropicamide 1%, phenylephrine hydrochloride 10%	Oxybuprocaine hydrochloride 0.4% drops, a sponge soaked with lidocaine 2% and bupivacaine 0.5%	n/a
Erdurmus et al. (2008)[134]	IV dexmedetomidine 1 µg/kg	IV saline	Diclofenac sodium 0.1%, phenylephrine hydrochloride 2.5%, cyclopentolate 1%	Proparacaine 0.5% drops	n/a
Santiago et al. (2014)[135]	IV clonidine 4µg/kg	IV saline	phenylephrine 10%, tropicamide 1%	lidocaine 2% gel	n/a
Chen et al. (2015)[56]	IV midazolam 1.0 mg	Oral diazepam 5.0 mg	n/a	Tetracaine hydrochloride 1%, lidocaine hydrochloride 2% gel	Intracameral preservative-free lidocaine hydrochloride 1.0%
Ghodki et al. (2015)[140]	IV Dexmedetomidine 1 mcg/kg	IV saline	n/a	Paracaine 0.5%	n/a

*PCA = Patient controlled analgesia

Table 5.3: Participant Characteristics of Included Studies

Author (Year)	Sample Size	IV Sedation Group			No IV Sedation Group		
		Male	Female	Age (SD)	Male	Female	Age
Aydin et al. (2002)[128]	68	16	18	66.9 ±11.7	19	15	67.8 ±9.4
Inan et al. (2003)[129]	120	n/a	n/a	65.76 ±6.1	n/a	n/a	65.21 ±7.82
Laube et al. (2003)[130]	97	17	33	74 ±9.1	18	29	72 ±12.6
Habib et al. (2004)[131]	100	18	32	76.9 ±8.66	25	25	79.31 ±7.05
Leidinger et al. (2005)[132]	90	19	26	77 ±7.2	23	22	77 ±7.5
Akgul et al. (2007)[133]	120	42	38	66 ±9.04	22	18	68.6 ±8
Erdurmus et al. (2008)[134]	44	7	15	67.41 ±9.83	8	14	69.46 ±9.99
Santiago et al. (2014)[135]	40	7	13	64.3 ±8.2	9	11	65.5 ±10.7
Chen et al. (2015)[56]	156	26	57	69	35	38	69
Ghodki et al. (2015)[140]	60	11	19	62.6 ±6.5	10	20	61.4 ±6.9

5.3. Risk of Bias within Studies

Each study was thoroughly analyzed using the Cochrane risk of bias tool, and the following figures were generated. Figure 5.2 is a risk of bias graph, demonstrating what proportion of each study has a high, low, or unclear risk of bias. Figure 5.3 is a risk of bias summary; the judgements are shown in cross-tabulation.

In conclusion, eight studies had a low risk of bias, meaning that bias is unlikely to seriously alter the results of the studies. One study had an unclear risk of bias; it is possible that there may be some skepticism regarding the results. Lastly, one study had a high risk of bias; the result and interpretations may have been affected in this study. The bias across studies was mainly present in allocation concealment. However, we do not believe that this may have affected the outcome or results in a significant way. Thus, all studies were included in the statistical analysis, comparing intravenous sedation to non-intravenous techniques in cataract extraction.

Figure 5.2: Risk of Bias Graph (Percentages across all included studies)

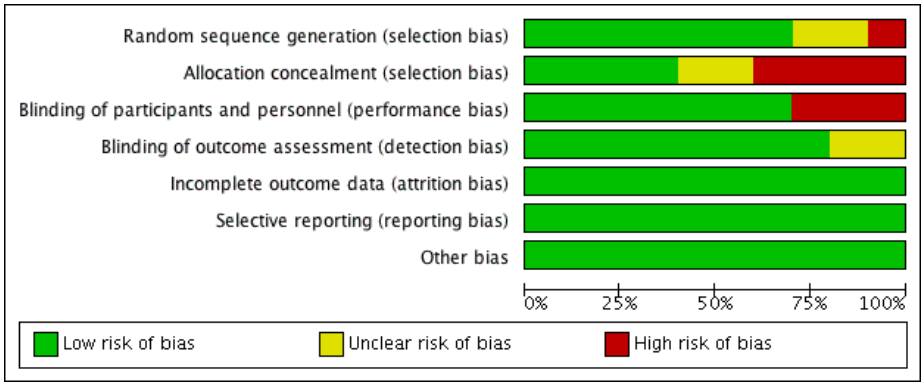
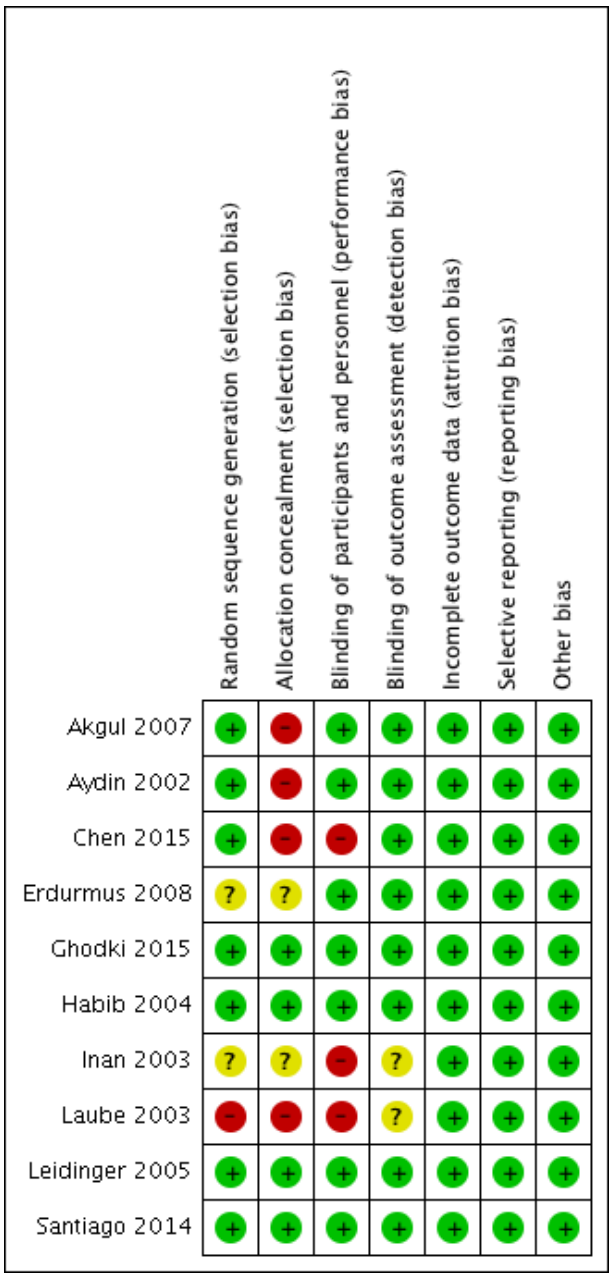


Figure 5.3: Risk of Bias Summary



5.4. GRADE Quality Assessment

The quality of the studies included in the systematic review were analyzed using the GRADE guidelines. The results indicate that eight articles were high quality, and two articles were moderate quality (Table 5.4). All articles were included in the analysis, which compares intravenous sedation to non-intravenous anesthesia techniques in cataract extraction.

Table 5.4: GRADE Evidence Profile

Study	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence
Aydin et al. (2002)[128]	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ HIGH
Inan et al. (2003)[129]	Serious	Not serious	Not serious	Not serious	None	⊕⊕⊕◯ MODERATE
Laube et al. (2003)[130]	Serious	Not serious	Not serious	Not serious	None	⊕⊕⊕◯ MODERATE
Habib et al. (2004)[131]	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ HIGH
Leidinger et al. (2005)[132]	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ HIGH
Akgul et al. (2007)[133]	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ HIGH
Erdurmus et al. (2008)[134]	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ HIGH
Santiago et al. (2014)[135]	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ HIGH
Chen et al. (2015)[56]	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ HIGH
Ghodki et al. (2015)[140]	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ HIGH

5.5. Primary Outcome – Pain

This section will be an overview on the analysis of pain perception when comparing intravenous sedation to non-intravenous techniques.

5.5.1. Data Extraction and Imputation

The sample size, mean, and standard deviations required for the meta-analyses were extracted from each study and are depicted in Table 5.5. Four studies had missing standard deviations. Although it is best to avoid using imputation techniques, it is often the only way to combine data with other studies. Before imputation was considered for the following studies, corresponding authors were contacted for more information and data. However, most of the authors did not get back to us, and those who did no longer had the data for the study of interest. For this reason, the standard deviations for the 4 studies were imputed using standard errors, confidence intervals, student's t values, and P values. When the articles were limited to the median, interquartile range, or range, the distribution was assumed to be normal and the SD was estimated. These methods are further described in the Cochrane Handbook[98]. If the statistics listed above were not available in the article, the standard deviations were imputed using novel methods. A detailed description of the calculations involved for the imputations in this study is listed in Appendix C.

Table 5.5: Extracted Data for Meta-Analysis

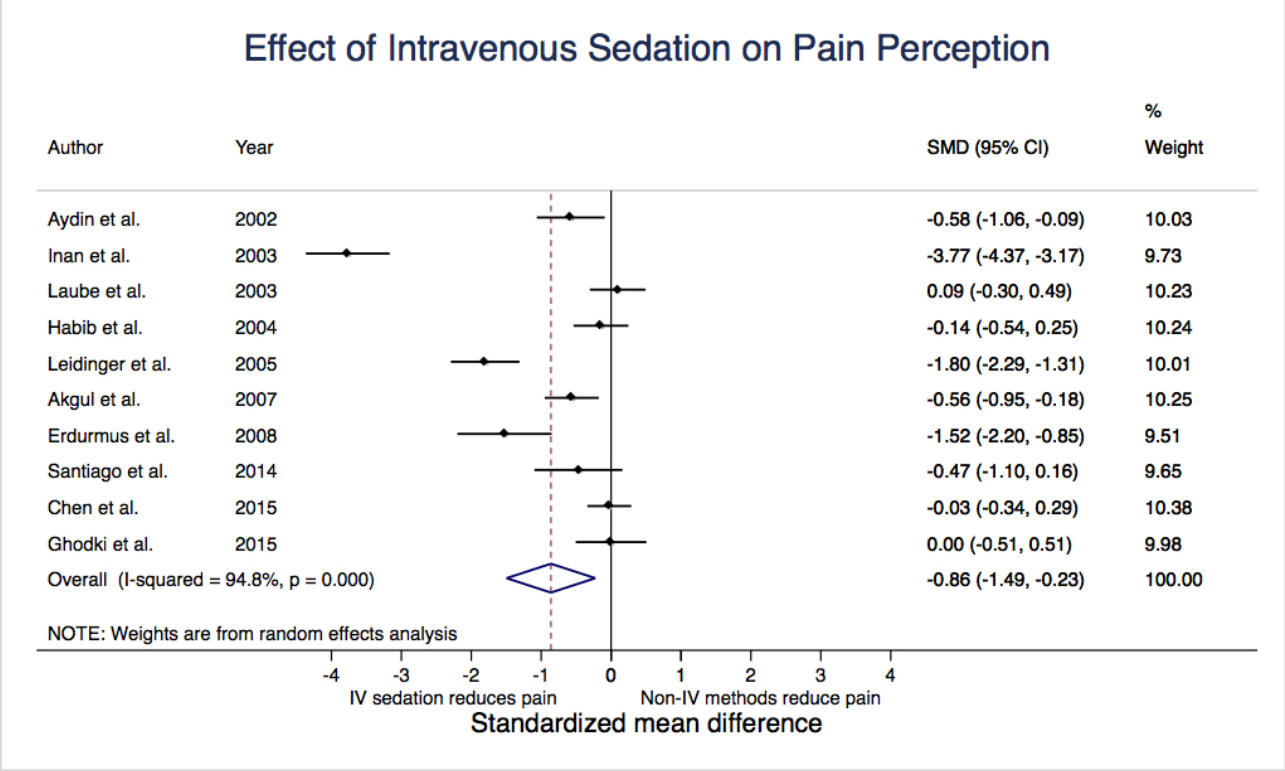
Author (Year)	Pain Scale	Intravenous Sedation			Non-Intravenous Group		
		Sample Size	Mean	SD	Sample Size	Mean	SD
Aydin et al. (2002)[128]	VPS (0-10)	34	0.52 §	± 1.11 *	34	1.16 §	± 1.11 *
Inan et al. (2003)[129]	VPS (0-3)	60	0.08	± 0.27	60	1.06	± 0.25
Laube et al. (2003)[130]	Likert Scale (0-4)	50	0.18	± 0.44	47	0.13	± 0.61
Habib et al. (2004)[131]	VAS (0-10)	50	0.29	± 0.65*	50	0.38	± 0.59 *
Leidinger et al. (2005)[132]	VAS 0-10	45	2.58 §	±1.06 §	45	5.53 §	± 2.06 §
Akgul et al. (2007)[133]	VPS (0-10)	80	0.25	± 0.80*	40	0.7	± 0.80*
Erdurmus et al. (2008)[134]	VAS (0-10)	22	1.23	± 1.72	22	3.64	± 1.43
Santiago et al. (2014)[135]	NRS (0-10)	20	0.81	±1.41	20	1.57	± 1.82
Chen et al. (2015)[56]	NRS 11 (0-10)	83	0.072	± 0.38	73	0.082	± 0.40
Ghodki et al. (2015)[140]	NRS (0-10)	30	3	± 0.29*	30	3	± 0.29*

*NRS = Numerical rating scale, VAS = Visual analogue scale, VPS = Verbal pain scale
§= extracted from graph or figure
*=imputed

5.5.2. Meta-Analysis – Standardized Mean Difference

Figure 5.4 below displays the forest plots of random effects pooled meta-analysis of the weighted standardized mean difference. The total sample size was 895 patients across all 10 analyzed studies. In the pooled random effects analysis, intravenous sedation was significantly associated with a decrease in pain (SMD = -0.86 with 95% CI of -1.49 to -0.23, p=0.0008) and the I_2 was 94.8%, p=0). It may be worthwhile to note that 7 studies (70%) reported that intravenous sedation significantly reduced pain perception. Stata code used is available in Appendix D.

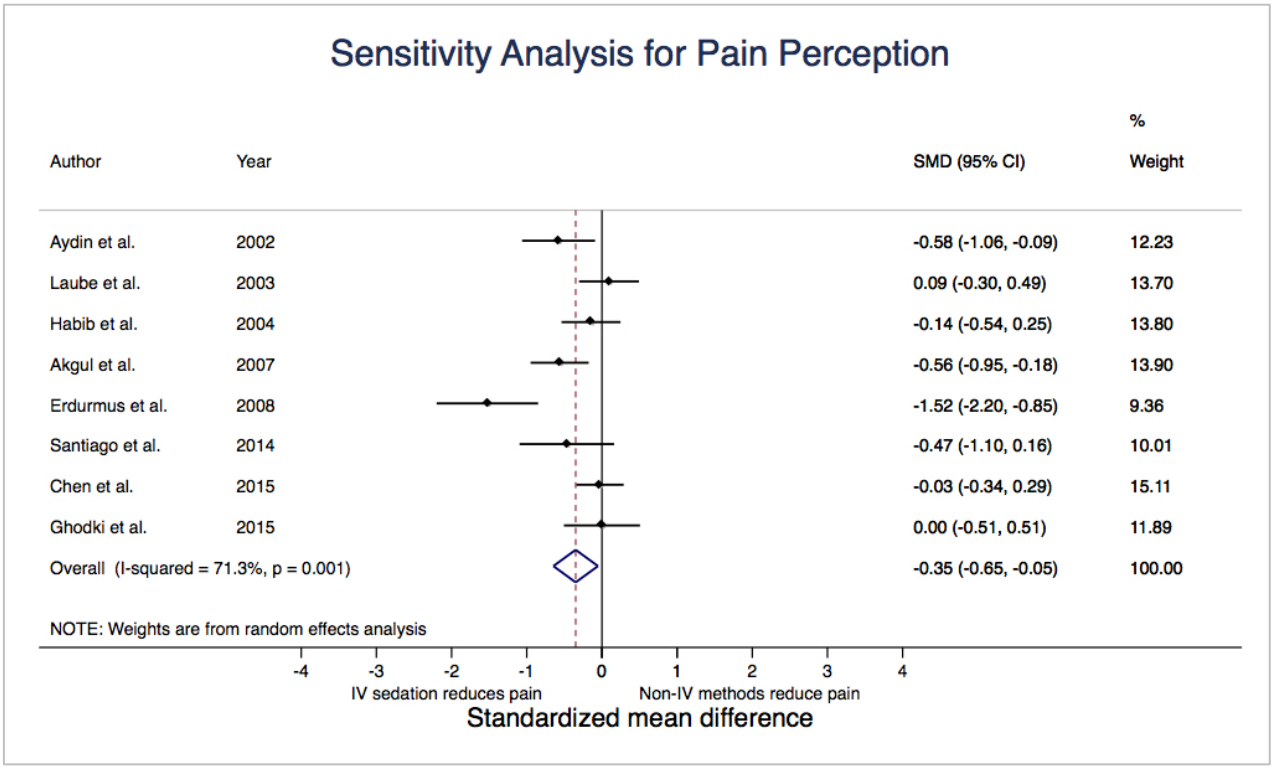
Figure 5.4: Pooled random effects meta-analysis for pain perception (SMD)



5.5.3. Sensitivity Analysis

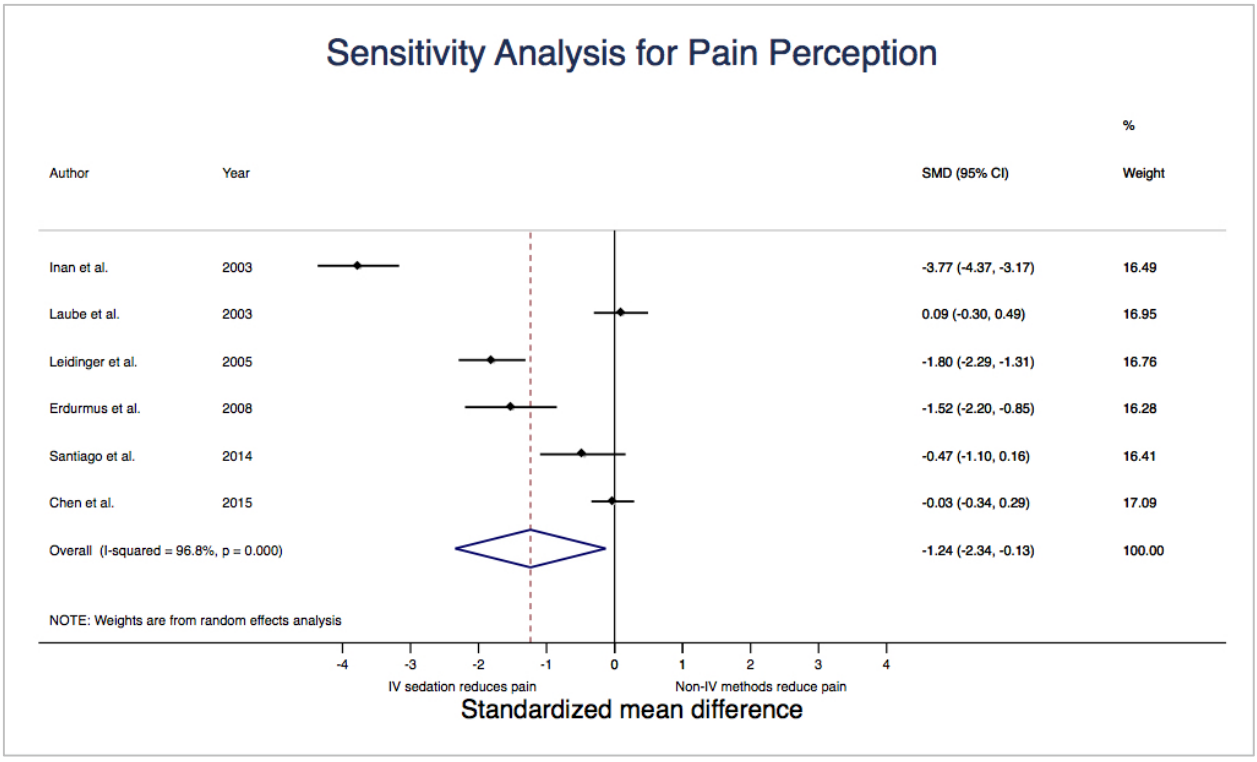
Although the included studies appear to be robust due to the narrow confidence intervals, the I^2 and p-value suggests there is considerable heterogeneity. Of the ten included studies, two studies[129,132] had effect sizes that were much larger than the rest. These studies were removed to conduct a sensitivity analysis. The adjusted forest plot for standardized mean differences is displayed in Figure 5.5 below. In the sensitivity analysis, intravenous sedation was still significantly associated with a decrease in pain (SMD = -0.35 with 95% CI of -0.65 to -0.05, p=0.021) and the I^2 was 71.3%, p=0.001. Even when the two outlier studies are excluded, the result is still the same; intravenous sedation significantly reduces pain perception, when compared to non-intravenous methods.

Figure 5.5: Sensitivity Analysis – Exclusion of Outlier Studies



A second sensitivity analysis was performed. Here, the studies in which imputation techniques were used to estimate the mean or standard deviation were omitted to investigate if the imputation methods had an impact on the overall effect size. Four studies[131,133,141,142] were excluded for the sensitivity analysis. The adjusted forest plot for standardized mean differences is displayed in Figure 5.6 below. In the sensitivity analysis, intravenous sedation was still significantly associated with a decrease in pain (SMD = -1.24 with 95% CI of -2.34 to -0.13, p=0.028) and the I^2 was 96.8%, p=0. Even when four studies with imputation techniques are excluded, the result is still the same; intravenous sedation significantly reduces pain perception, when compared to non-intravenous methods. This sensitivity analyses suggests that the effects of pain perception are robust across the imputation techniques used for missing standard deviations.

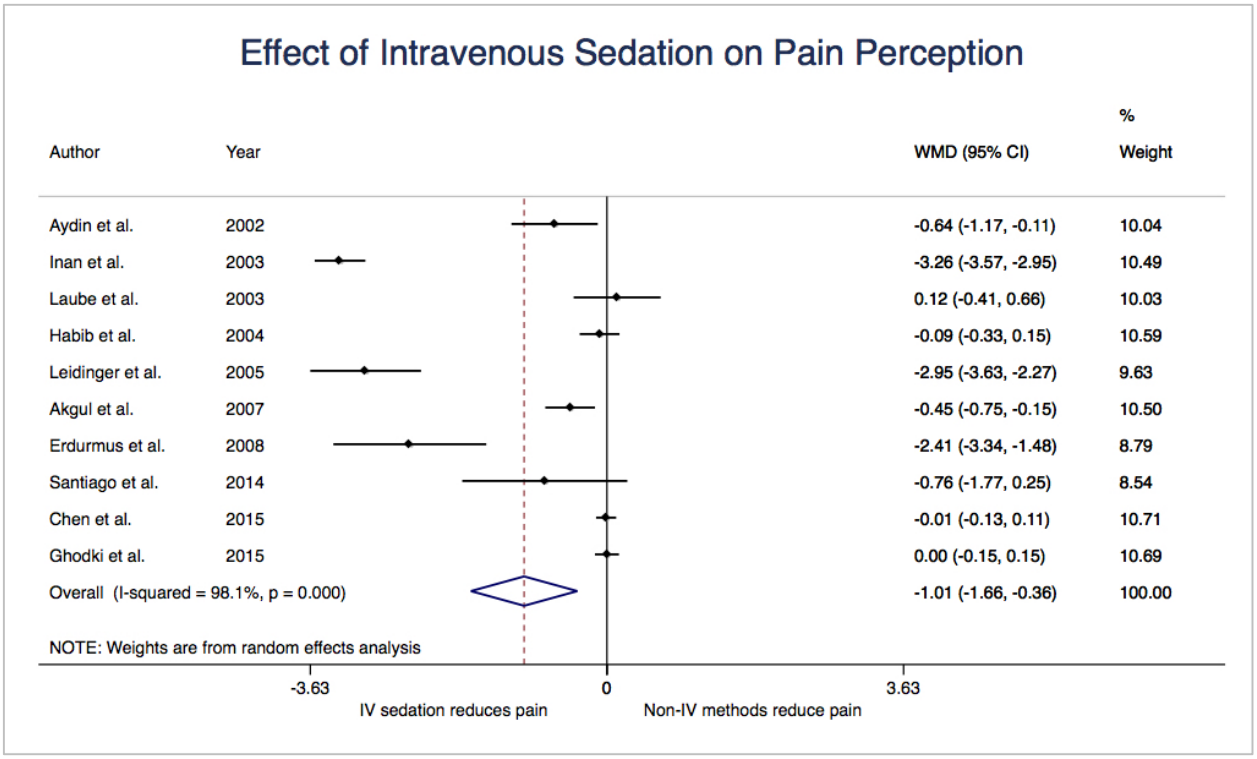
Figure 5.6: Sensitivity Analysis – Exclusion of Imputation Methods



5.5.4. Meta-Analysis – Weighted Mean Difference

A weighted mean difference meta-analysis was also conducted. The included studies were converted to the same scale for this analysis. Figure 5.7 below displays the forest plot of random effects pooled meta-analysis of the weighted mean difference in pain perception, where a negative change is a reduction of pain perception using intravenous sedation, and a positive change is a reduction of pain perception using non-intravenous sedation methods. A weighted mean difference was calculated to highlight the clinical significance of the results. In the pooled random effects meta-analysis, intravenous sedation was significantly associated with a decrease in pain (WMD= -1.01 with 95% CI of -1.66 to -0.36, p=0.002) and the I^2 was 98.1%, p=0. Overall, intravenous sedation reduced pain by 1.01 units on the 10-unit pain scale, when compared to non-intravenous anesthesia methods. This can be interpreted as a 10.1% decrease in pain.

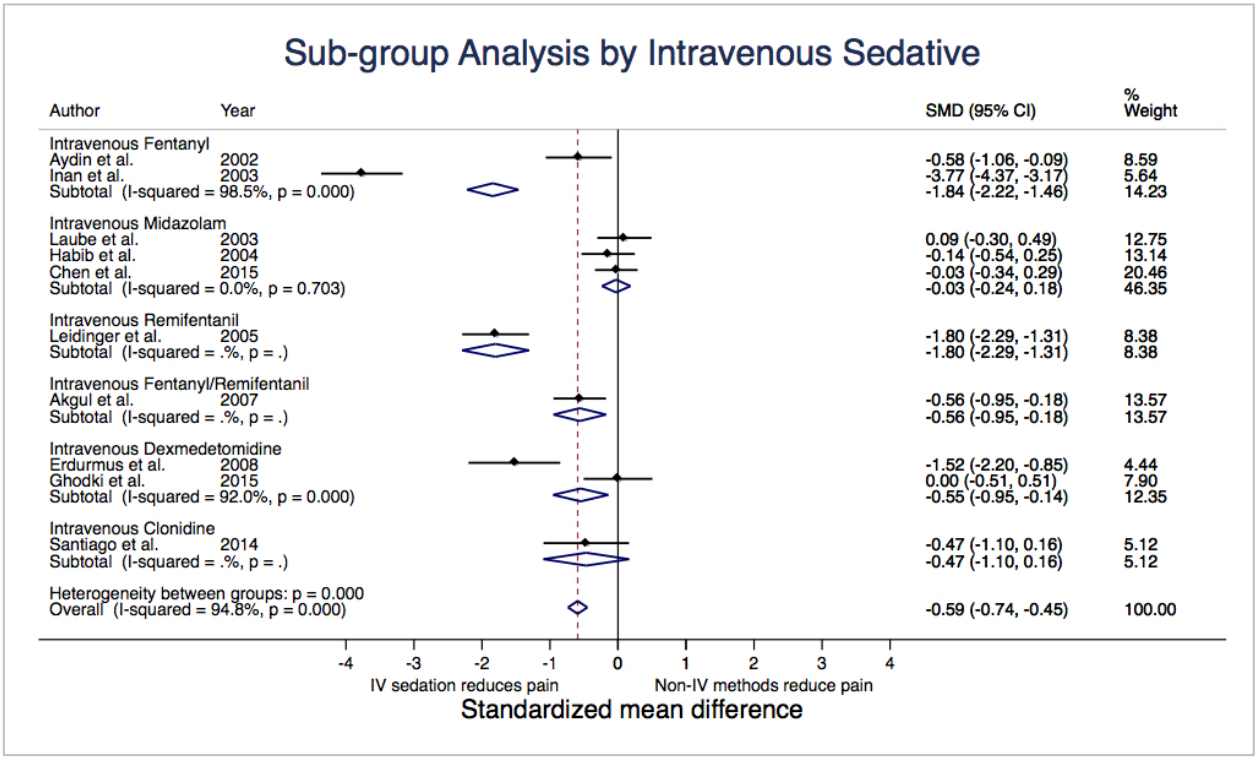
Figure 5.7: Pooled random effects meta-analysis for pain perception (WMD)



5.5.5. Sub-group Analysis by Intervention Sedation

The first fixed effects sub-group analysis was grouped by the intravenous medication used in the intervention groups. Two studies that used intravenous fentanyl as the intervention sedative indicated that patients did have a statistically significant reduction in pain, with a SMD of -1.84 (95% CI -2.22 to -1.46, p=0, i^2=98.5%). Three studies that used intravenous midazolam as the intervention sedative indicated that patients did not have a statistically significant reduction in pain, with a SMD of -0.03 (95% CI -0.24 to 0.18, p=0.804, i^2=0%). One study that used intravenous remifentanil as the intervention sedative indicated that patients did have a statistically significant reduction in pain, with a MD of -1.80 (95% CI -2.29 to -1.31, p=0). Since there is only one study in this subgroup, heterogeneity calculation is not possible. One study used both intravenous fentanyl and intravenous remifentanil as the intervention sedatives. The subgroup analysis indicates that patients did have a statistically significant reduction in pain, with a MD of -0.56 (95% CI -0.95 to -0.18, p=0.004). Since there is only one study in this subgroup, heterogeneity calculation is not possible. Two studies that used intravenous dexmedetomidine as the intervention sedative indicated that the patients did have a statistically significant reduction in pain, with a SMD of -0.55 (95% CI -0.95 to -0.14, p=0.0.008, i^2=92%). Lastly, one study that used intravenous clonidine as the intervention sedative indicated the patients did not have a statistically significant reduction in pain, with a MD of -0.47 (95% CI -1.10 to 0.16, p=0.146). This forest plot is graphically displayed in Figure 5.8.

Figure 5.8: Sub-group Analysis of Intervention Group by Intravenous Sedation

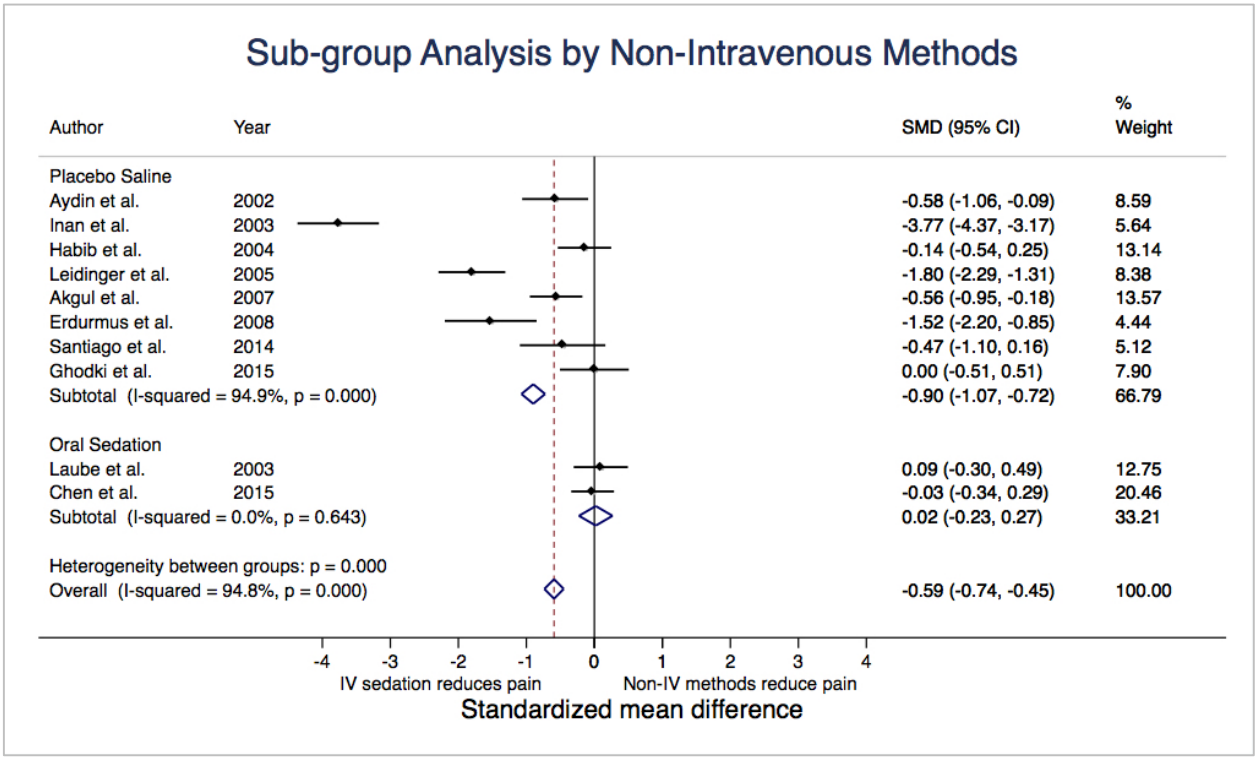


5.5.6. Sub-group Analysis by Non-Intravenous Sedation Method

The second fixed effects sub-group analysis is grouped by the non-intravenous sedation method used in the comparator group. Eight studies used a placebo saline drip, with various topical and injection anesthesia strategies (see Table 5.2 for anesthesia characteristics) as the comparator against an intravenous sedation strategy. The sub group analysis indicated that the patients did have a statistically significant reduction in pain when using intravenous sedation; a saline drip with topical and / or ocular injections did not control pain perception as well as intravenous sedation. The SMD was -0.90 (95% CI -1.07 to -0.72, p=0, i^2= 94.9%).

Two studies used an oral sedative, with various topical and injection anesthesia strategies (Table 5.2) as the comparator to an intravenous sedation method. The sub group analysis indicated that the patients did not have a statistically significant reduction in pain when using intravenous sedation over oral sedation. The SMD was 0.02 (95% CI -0.23 to 0.27, p=0.871, i^2=0%). Thus, when comparing intravenous sedation to oral sedation, they appear to be equivalent in terms of pain control. This is displayed in Figure 5.9.

Figure 5.9: Sub-group Analysis of Comparator Group by Non-IV Methods



5.5.7. Meta-regression

A meta-regression recognizes the reasons for heterogeneity and possible explanations for it in a meta-anlaysis.[125] A meta-regression examines the extent to which heterogeneity between results of multiple studies can be associated to characteristics of the studies. Since heterogeneity was present in the pooled meta-analysis, a univariate random effects meta-regression was conducted. The results can be found in Table 5.6. The covariates that were examined were the location of the study, year of publication, sex of participants, and the mean age of participants. Exact descriptions of how they were dichotomized are found in Table 5.6. No covariates were found to be significant, and heterogeneity was found in all covariates.

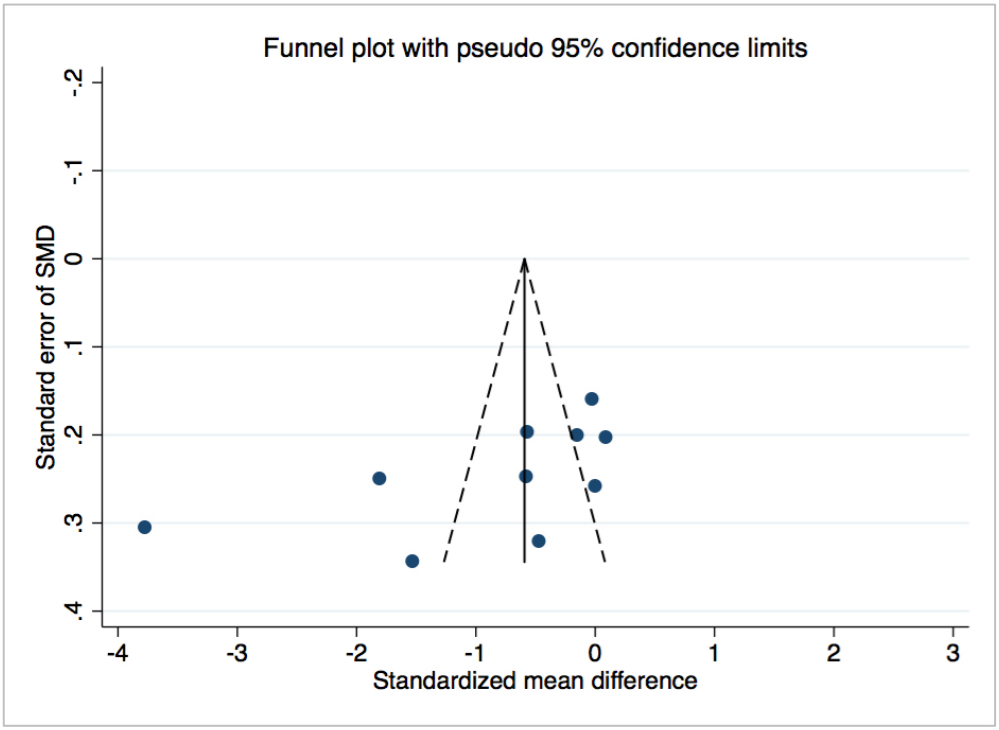
Table 5.6: Random Effects Meta-Regression Results

Meta-regression on:	Covariate	Regression Coefficient (95% CI)	P-value	I^2	Adjusted R^2	Tau^2
Location of Study	North America (1) vs. Other (0)	0.94 (-2.01 to 3.88)	0.485	94.90%	-6.06%	1.425
Year of study	After 2005 (1) vs. before or on 2005 (0)	0.71 (-1.03 to 2.47)	0.374	94.98%	-1.56%	1.365
Mean Age	Greater than or equal to 70 (1) vs. less than 70 years old (0)	0.36 (-1.62 to 2.35)	0.683	95.32%	-10.90%	1.49
Male/ Female	Higher proportion of males (1) vs. higher proportion of females (0)	-0.42 (-1.39 to 1.31)	0.944	87.72%	-17.22%	0.45

5.5.8. Funnel Plot

Funnel plots are a visual display that can be used to assess if the results of a meta-analysis are affected by bias and heterogeneity. In the absence of bias and heterogeneity, 95% of the included studies are expected to lie within the dashed triangular lines. The funnel plot for the studies included in the analysis of the pain perception in cataract extraction is displayed in Figure 5.10. The asymmetry of the funnel plot indicates the presence of publication bias and heterogeneity; on the left side, there are three studies that are widely scattered on the bottom of the triangle, and on the right side there are seven studies that are clustered together but still extended around the middle area of the triangle, closer to the center. As a trial's sample size increases, the precision of the effect estimate increases as well. Large, precise studies will localize to the top of the funnel plot, whereas small imprecise studies will have effect estimates that scatter widely at the bottom of the plot.[143] This premise supports the funnel plot depicted below, as all the included studies had a small number of participants, and the effect estimates are widely scattered across the bottom half of the funnel plot.

Figure 5.10: Funnel Plot for Pain Perception



5.6. Primary Outcome – Complications

This section will be an overview on the rate of adverse events when comparing intravenous sedation to non-intravenous techniques. Table 5.7 lists the quantitative data extracted from each study for analysis.

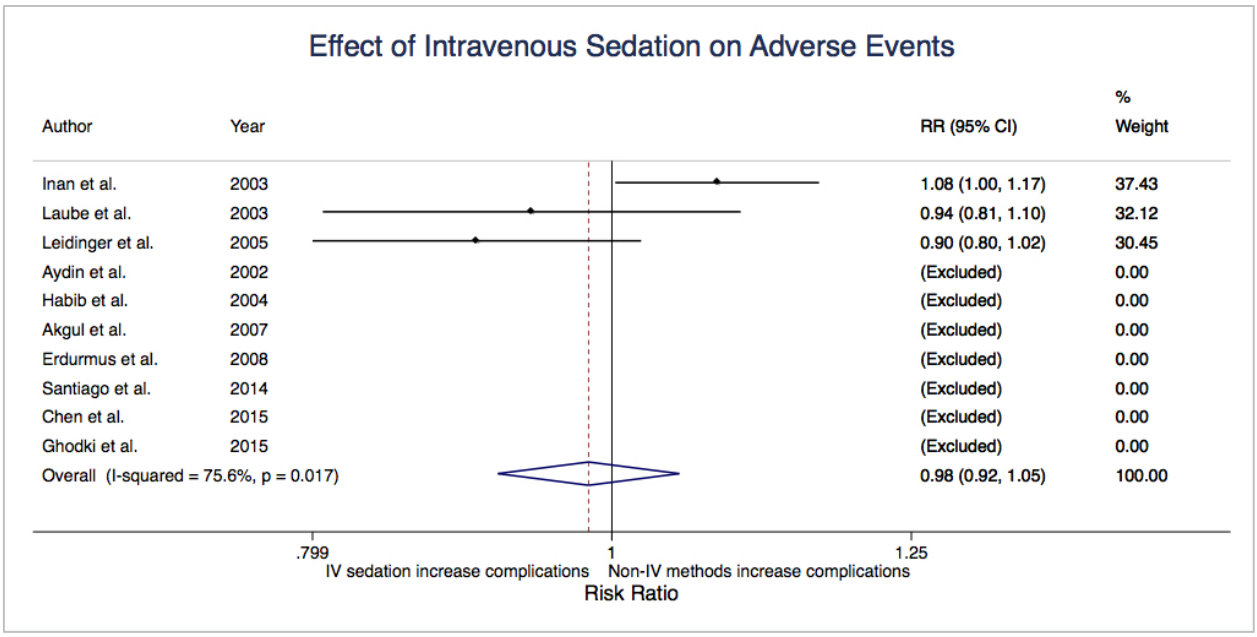
Table 5.7: Quantitative Data for Meta-Analysis

Author (Year)	Intravenous Sedation Patients with Complications			Non-IV Sedation Methods Patients with Complications		
	Sample Size	#	Description	Sample Size	#	Description
Aydin et al. (2002)[128]	34	0	n/a	34	0	n/a
Inan et al. (2003)[129]	60	0	n/a	60	5	5 patients with systemic hypertension requiring an anti-hypertensive drug
Laube et al. (2003)[130]	50	11	4 patients with posterior capsule rupture	47	7	2 patients with posterior capsule rupture
			3 patients with anterior vitrectomy			1 patient with bleeding
			4 patients with sulcus fixation of IOL			2 patients with anterior vitrectomy
						2 patients with sulcus fixation of IOL
Habib et al. (2004)[131]	50	0	n/a	50	0	n/a
Leidinger et al. (2005)[132]	45	7	3 patients with bradycardia	45	2	1 patient with tachycardia
			3 patients with nausea			1 patient with nausea
			1 patient with intraoperative sweating			
Akgul et al. (2007)[133]	80	0	n/a	40	0	n/a
Erdurmus et al. (2008)[134]	22	0	n/a	22	0	n/a
Santiago et al. (2014)[135]	20	0	n/a	20	0	n/a
Chen et al. (2015)[56]	83	0	n/a	73	0	n/a
Ghodki et al. (2015)[140]	30	0	n/a	30	0	n/a

5.6.1. Meta-Analysis

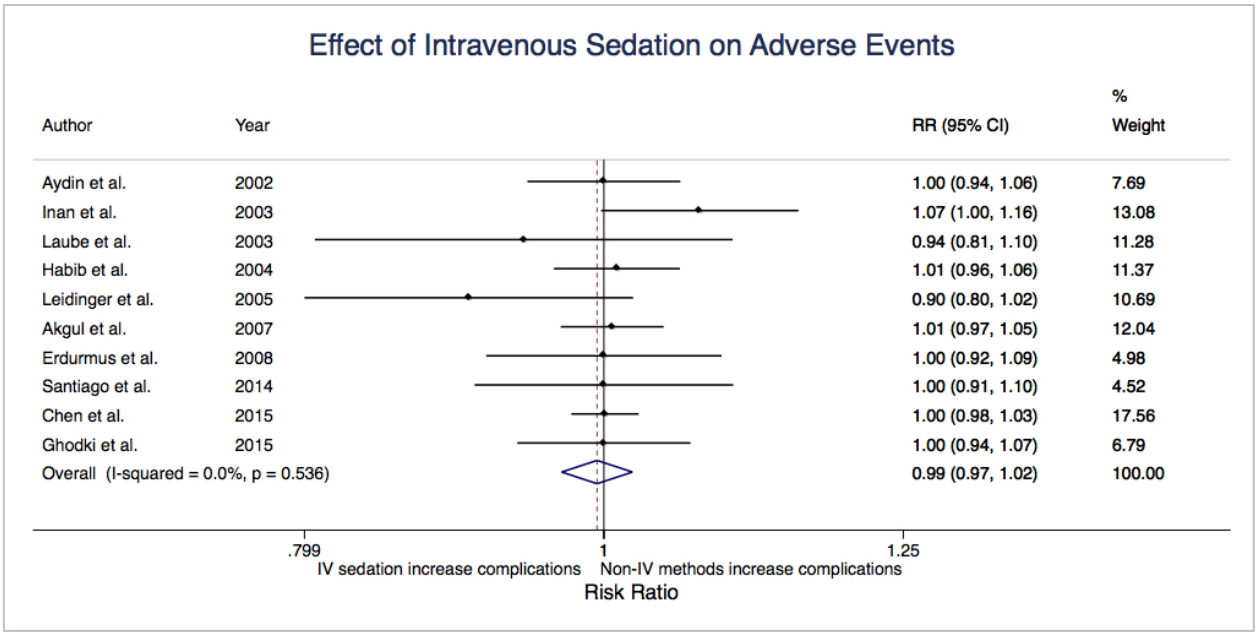
Figure 5.11 displays the forest plot for the meta-analysis for risk of complications. The total sample size was 895 patients across 10 analyzed studies. 18 patients in the intravenous sedation group had perioperative complications, and 14 in the non-intravenous sedation methods group had perioperative complications. It was found that intravenous sedation did not significantly increase complications (RR= 0.98 with 95% CI 0.92 to 1.05, p=0.614, i2=75.6%). A risk ratio of 1 indicates that there is no difference in risk between the two groups. Stata code used is available in Appendix D.

Figure 5.11: Meta-Analysis for Risk of Complications



Since 7 studies were excluded due to having 0 cell counts, we decided to add in a correction factor of 0.5 examine how the results may be affected (somewhat of a sensitivity analysis). Figure 5.12 displays the forest plot for the risk of complications with the correction factor. It was found that intravenous sedation did not significantly increase complications (RR= 0.99 with 95% CI 0.97 to 1.02, p=0.704, i2=0%). A risk ratio of 1 means there is no difference in risk between the two groups. The results of the meta-analysis with the correction factor are almost indistinguishable, showing that a directional bias was not introduced with the correction.

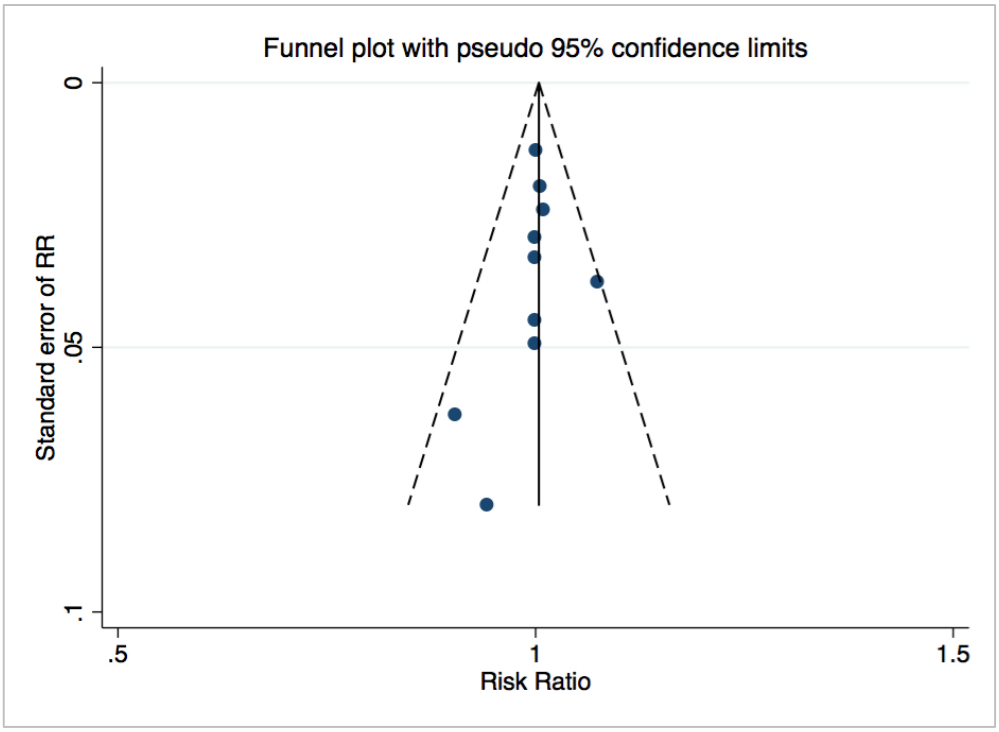
Figure 5.12: Meta-Analysis for Risk of Complications with Correction Factor



5.6.2. Funnel Plot

Funnel plots are a visual display that can be used to assess if the results of a meta-analysis are affected by publication bias and/or heterogeneity. The funnel plot for the risk of complications is displayed in Figure 5.13. This funnel plot appears to be nearly symmetrical (as can be seen from the lack of studies in the lower right quadrant), suggesting the presence of a small amount of potential publication bias. Possible explanations for this asymmetry include language bias (only English articles were included), small numbers of participants in the included randomized controlled trials, imprecise effect, and lastly, the asymmetry may simply be due to chance.

Figure 5.13: Funnel Plot of Risk of Complications



CHAPTER 6 Discussion

6.1. Overview

The final chapter of this document will outline the results, interpretations, and conclusions. In summary, the objectives of this thesis were to (1) determine the level of patient pain perception associated with cataract extraction by phacoemulsification, when administered under intravenous sedation versus non-intravenous anesthesia techniques and (2) determine the complication rate perioperatively when the patient is under intravenous sedation versus non-intravenous anesthesia techniques.

6.2. Systematic Review

This is the first study to conduct a systematic review and meta-analysis on the effects of intravenous sedation versus non-intravenous sedation methods during cataract extraction. There were 4541 citations and full texts screened using the P.I.C.O.S. model[98] and inclusion/exclusion criteria. There were 10 studies included in the review upon completion of level 1 and level 2 screening. They were found to be of high quality of evidence according to the GRADE tool, and to be at low risk of bias according to Cochrane's *Assessment of Risk of Bias in Included Studies.* There were 895 patients overall.

The patient characteristics were similar among the studies. All participants were adult patients (~65 years of age) undergoing phacoemulsification (Table 5.1 and Table 5.3). However, the study characteristics varied (Table 5.2). The sedation strategy and anesthesia techniques and pharmaceuticals differed in each study; each clinic had their own methods of achieving sedation and ocular anesthesia (whether that be with topical drops, topical gel, or ocular injections). Additionally, there was slight variations in the pain scale utilized. The intervention groups in the included studies varied with regards to the intravenous sedative used; intravenous fentanyl, midazolam, remifentanil, dexmedetomidine, clonidine, and a combination of fentanyl and remifentanil were used.

6.3. Meta-Analysis and Subgroup Analysis

Pain Perception

There were 10 studies included in the meta-analysis that compared pain perception under intravenous sedation and non-intravenous sedation methods during cataract extraction. Since standard deviations were not reported in four of the studies, imputation techniques were used to estimate the missing values, allowing the studies to be included in the analysis.

Results from the standardized mean difference meta-analysis indicate that intravenous sedation significantly reduces pain during cataract extraction (SMD= -0.86, 95% CI of -1.49 to -0.23, p=0.0008). A weighted mean difference meta-analysis was also conducted to highlight the clinical significance of this finding. The results indicate that intravenous sedation reduced pain by 1.01 unit on a 10-unit pain scale, when compared to non-intravenous sedation methods. This can be translated to an approximate 10% decrease in pain with IV sedation techniques.

Sensitivity analyses were conducted to ensure that the study results were robust. The first sensitivity analysis consisted of removing two outlier studies; the result remained the same. Intravenous sedation significantly reduced pain even when the two studies with the greatest variation were removed from the analysis. The second sensitivity analysis consisted of removing four studies with standard deviations that were estimated with imputation techniques. The overall effect size remained homogenous with the primary analysis; intravenous sedation was still significantly associated with a decrease in pain (SMD = -1.24 with 95% CI of -2.34 to -0.13, p=0.028). The sensitivity analysis suggests that the results from the primary analysis are robust. Although there was considerable heterogeneity in the primary analysis, the robustness of the sensitivity analysis and the narrow confidence intervals indicate that the combination of these studies for a meta-analysis is valid. Further, a meta-regression was conducted with the prospect of better understanding the heterogeneity. The covariates that analyzed were study location, study year, age, and sex. After running the meta-regression, none of the covariates were found to be significantly associated with a change in effect size. It is presumed that the heterogeneity in the study is due to the variation in anesthesia and sedation techniques found between the studies.

The first subgroup analysis conducted was a fixed-effects meta-analysis by intervention sedative. The purpose of this sub group was to establish which medication was most effective at reducing pain during phacoemulsification. The results indicate that intravenous fentanyl (SMD of -1.84,95% CI -2.22 to -1.46, p=0), intravenous remifentanil (MD of -1.80,95% CI -2.29 to -1.31, p=0), intravenous fentanyl/remifentanil (MD= -0.56, 95% CI -0.95 to -0.18, p=0.004), and intravenous dexmedetomidine (SMD of -0.55, 95% CI -0.95 to -0.14, p=0.0.008) significantly reduced pain during phacoemulsification, while intravenous clonidine and midazolam did not significantly reduce pain more than the non-intravenous sedation techniques. This has potential to impact cataract ambulatory care. For clinics that use intravenous sedation and will continue to do so, changing the intravenous sedative to one of the above medications that are more effective at reducing pain can benefit the patient experience.

The second subgroup analysis conducted was a fixed effects meta-analysis that examined the sedation technique of the comparator group. There were two subgroups created during this analysis. One subgroup compared placebo saline with various anesthetic methods to intravenous sedation, and the second subgroup compared oral sedation to intravenous sedation. The first subgroup (placebo saline versus intravenous sedation) indicated that patients have a statistically significant reduction in pain when using intravenous sedation; a saline drip with topical and / or ocular injections does not control pain perception as well as intravenous sedation (SMD= -0.90, 95% CI -1.07 to -0.72, p=0). The second subgroup (oral sedation versus intravenous sedation) indicated that oral sedation and intravenous sedation techniques were equivalent in pain control (SMD= 0.02, 95% CI -0.23 to 0.27, p=0.871). These results have potential to impact resource allocations in both publicly and privately funded environments, particularly the second subgroup analysis which compares oral sedation to intravenous sedation. The introduction of intravenous sedation requires tremendous resources; equipment, medication, nurse anesthetists, and the presence of anesthesiologist. A cost analysis study published in 2001[10] found that oral sedation cost $16.47 per procedure, while intravenous sedation could cost up to $324.72 per procedure; intravenous sedation was 19x more expensive than oral sedation in 2001. There is no doubt that the cost of

intravenous sedation in 2017 has increased with the cost inflation of equipment, medications, and personnel.

There are limitations associated with these subgroup analyses. First, subgroup analyses are entirely observational since they are not based on the pre-specified randomized comparisons (intravenous sedation versus non-intravenous sedation methods). Next, there were a few studies in each of the subgroups. Smaller numbers of studies may result in a less precise summary effect size. Specifically, there were only two studies that compared intravenous sedation to oral sedation. For this reason, we recommend further research in this area so that a more precise summary effect estimate can be determined.

Adverse Events

There were 10 studies included in the meta-analysis that compared the number of patients with adverse events under intravenous sedation and non-intravenous sedation methods during cataract extraction. There were 18 patients in the intravenous sedation group that had perioperative complications, and 14 in the non-intravenous sedation methods group that had perioperative complications. Many of the included studies had no adverse events or complications occur during the trial, resulting in many zero cells in the analysis. For this reason, two meta-analyses were conducted. The first meta-analysis included the three studies in which adverse events occurred. The results indicated that there was no difference in risk between the two groups (RR= 0.98 with 95% CI 0.92 to 1.05, p=0.614, i2=75.6%). The second meta-analysis was conducted with a correction factor of 0.5 added into the zero cells. The results indicated again that there was no difference in risk between the two groups (RR= 0.99, 95% CI 0.97 to 1.02, p=0.704). The nearly identical results indicate robustness in the analysis. To reiterate the cost summary above, in 2001 it was found that intravenous sedation could cost upwards of $324.72 per procedure, 19x more expensive than non-intravenous sedation.[10] The risk ratio of intravenous sedation versus non-intravenous sedation should be considered by anesthesiologists and surgeons when determining which anesthesia/sedation technique to utilize. Since there is not an increase in risk with non-

intravenous sedation techniques, and it is a far more economical option, it is evident that using non-intravenous sedation strategies is a feasible option.

6.4. Publication Bias

The funnel plot for pain perception is displayed in Figure 5.10. The presence of asymmetry in this funnel plot is evident, indicating publication bias. The funnel plot for the risk of complications is displayed in Figure 5.13. This funnel plot appears to be nearly symmetrical (as can be seen from the lack of studies in the lower right quadrant). There are several possibilities to explain the funnel plot's asymmetry. First, language bias was present, as the search strategy was limited to English articles. Second, publication bias may be present. A study which reviewed publication bias from the Cochrane database of systematic reviews found that when a meta-analyses of efficacy was conducted, outcomes that were statistically significant were 27%[144] more likely to be included in the review. Further, it has been reported that statistically significant results are three times more likely to be accepted for publication than papers with non-significant results.[145] Third, the funnel plot may be asymmetrical simply due to chance. Fourth, all the included studies were small randomized controlled trials with a range of 40 to 156 participants. It is possible that these studies were conducted with less methodological rigor than larger scale randomized controlled trials resulting in imprecise effect estimates.[103–105] Lastly, we know from the meta-analysis conducted that heterogeneity is present, which may cause the funnel to be asymmetrical. Funnel plots are not without their limitations. Since funnel plots are purely visual and not a statistical test, their interpretations are subjective, especially when there are few studies. They do not accurately predict publication bias[146], therefore treatment decisions should not be based on the symmetry of a funnel plot.

6.5. Limitations

In our inclusion/exclusion criteria, one of the components was to limit the included studies to English speaking articles only, since we did not have translational services available. This could be a factor that resulted in the presence of publication

bias in our study, as displayed by the funnel plot for pain perception (Figure 5.7). It is recommended that future reviews attempt to include non-English articles.

Another limitation was insufficient data reported in the included articles. Four of the articles did not have standard deviations explicitly stated, and even though authors were contacted for original datasets and information, none were provided. The standard deviations were generated via imputation techniques to make meta-analysis possible. However, this can be a risky process because assumptions are being made about the data, which could result in bias or narrow confidence intervals.[98] It is recommended that more trials are done comparing intravenous sedation to non-intravenous sedation techniques, and that the authors publish complete data with respect to effect sizes.

Many researchers agree that only two studies[147] are required for a meta-analysis, however the Cochrane Handbook[98] states that the minimum number of studies in a meta-analysis should be 10. More studies result in smaller confidence intervals and higher statistical power, and less studies in a review may introduce bias. It is therefore a limitation that this systematic review and meta-analysis is comprised of 10 studies. This can be viewed as an opportunity for future research to expand the body of knowledge in this topic area.

Lastly, there was considerable heterogeneity present in all the analyses. However, the sensitivity analyses conducted demonstrates that the results are robust, and even when outlier studies are removed, or studies whose statistics have been estimated with imputation techniques are removed, the conclusion remains the same. Additionally, the confidence intervals of the included studies are narrow, implying that the accuracy is also high. The presence of heterogeneity is likely from the variation of the intravenous sedative used in the included studies, and the variation in the non-intravenous anesthesia techniques. It would be extremely difficult to find studies with homogenous sedation and anesthesia techniques, as there are no guidelines currently available with recommendations on which methods to use. The sedation and anesthesia techniques rely solely on the preference of the operating surgeon or overseeing anesthesiologist.

6.6. Strengths

A meta-analysis is a powerful statistical procedure that allows research to combine all the information present on a topic or research question, and investigate the discrepancies between their results. This tool allows the researcher to calculate a single effect estimate, allowing professionals in health care, medicine, and other fields to generalize the results to a larger population and use evidence based medicine. However, utmost care must be taken when performing a meta-analysis; if conducted with even the slightest mistake, or error in methodology, it can result in incorrect, biased, or misleading results. When conducted this systematic review and meta-analysis, we adhered to every guideline available. The Cochrane Handbook and PRISMA checklist was referred to at every step in the process; search strategy formulation, article extraction from databases, screening, data extraction, quality assessment, and analysis. A strength of this study is unquestionably the high standards of methodological rigor that was upheld.

Another strength of this systematic review and meta-analysis is the study design of the included studies. All included studies are randomized controlled trials. RCT's by nature are of higher quality, and contain less bias than other study designs. The observed effect size of an RCT will generally be closer to the true effect size than an observational study, for example. Since all studies are RCT's, the summary effect estimate will have high accuracy and precision, ensuring the integrity of the results.

The studies were evaluated on quality and risk of bias using the GRADE tool and Cochrane's Risk of Bias tool. The two reviewers determined with the GRADEpro tool that 8 studies were of high quality, and two were of moderate quality. The Cochrane bias tool determined that there were eight studies were a low risk of bias, and two with a high risk of bias. These results suggest that the overall quality of the included studies was high, which increases the validity of the results.

Lastly, this was the first meta-analysis done to address the question of intravenous sedation versus non-intravenous sedation. Articles were collected from 6 databases and grey literature searches using a meticulous search strategy created with the help of an information technician. Strict inclusion and exclusion criteria were adhered to, ensuring all relevant articles were obtained. Since this review was

completed with such rigorous attention to detail, we feel it is a valuable addition to the literature, that will inspire future research in this topic area.

6.7. Recommendations for Future Research

Future research should focus on examining the effectiveness of intravenous sedation versus oral sedation, as there is insufficient research in this area. In this systematic review and meta-analysis, there were only two randomized controlled trials that evaluated this relationship. Oral sedation appears to be just as effective at controlling pain as intravenous sedation, is significantly less costly, and does not appear to have any associated increases in complications. Investigating the effects of oral sedation during phacoemulsification may benefit the allocation of resources in both publically and privately funded clinics. In addition to randomized controlled trials that evaluate the effects of oral sedation, future studies should also survey patient's preferences regarding sedation methods during cataract extraction. An updated cost-analysis model to reflect the cost of intravenous sedation versus oral sedation in present time will also be of great value to the literature. Finally, future research should focus on creating guidelines and recommendations for anesthesia and sedation strategies in North America.

6.8. Conclusion

This systematic review was conducted with the utmost accuracy and methodological rigor. The results indicate that intravenous sedation is more effective at controlling patient pain compared to non-intravenous sedation methods. Subgroup analysis indicated that oral sedation and intravenous sedation techniques were equivalent in controlling patient pain. The rate of adverse events was found to be equivalent in both sedation groups. This thesis has identified crucial gaps in the literature, which will guide future research, allowing us to generate better conclusions regarding the most effective sedation method for phacoemulsification.

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Appendices

Appendix A: Preferred Reporting Item for Systematic Reviews and Meta-analysis (PRISMA) guidelines

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	i
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	ii
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	49
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	--
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	49-50
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	47
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	101-108
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	50-51
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	51
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	51-52
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this	54

		information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	55-56
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	36-39
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	45-46
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	55-56
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	57
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	58-60
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	60-62
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	63-76
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	63-76
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	60-62
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	63-76
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	77-84

Appendix B: Systematic Review Search Strategies

DATABASE		SEARCH TERMS
OVID Medline	1	exp Cataract Extraction/ or exp Cataract/
	2	(Phacoemulsif* or Phakoemulsif* or Phaco-emul* or Phako-emul* or Cataract extrac* or Cataract remov* or Cataract surg* or Cataract operat*).mp
	3	1 or 2
	4	neuroleptanalgesia/ or anesthesia/ or anesthesia, local/ or nerve block/ or anesthesia, intravenous/ or cryoanesthesia/ or analgesia/ or exp Anesthetics/ or exp Perioperative care/
	5	(((block or anesthe* or anaesthe* or infiltrat* or inject*) adj3 (orbicularis or subtenon or peribulbar or retrobulbar or topical or intracameral or intracameral)) or Xylocaine or Neurolept* or Benzodiazep* or Lidocaine or Intracameral or Intracameral* Procaine or Proparacaine or Oxybuprocaine or Tetracaine or Bupivacaine or Etidocaine or Lidocaine or Prilocaine or Ropicacaine or Cryoanalg* or cryoanalg* or Cryoanesthes* or Cryoanaesthes* or midazolam or Fentanyl or Propofol or Perifentanyl or Gravol or dimenhydrinate or ondansetron or lorazepam or Ativan or valium or diphenhydramine or benadryl).mp.
	6	4 or 5
	7	pain/ or eye pain/ or pain, postoperative/ or Postoperative/ or Postoperative Period/ or Perioperative Care/ or Perioperative Period/ or Intraoperative Care/ or Intraoperative Period/ or hyphema/
	8	((pain or ache or aching or discomfort or instil* or drop or dilat* or manipulation or manipulat* or freez* or pressure or headache) adj3 (postop* or post-op* or periop* or peri-op* or Intraop* or intra-op*)).mp.
	9	7 or 8
	10	Intraoperative Complications/ or Postoperative Complications/ or Endophthalmitis/ or Keratitis/ or Lens Subluxation/ or Retinal Detachment/ or Vision Disorders/ or Eye Hemorrhage/ or Vitreous Hemorrhage/ or Retinal Hemorrhage/
	11	(complication* or broken capsul* or posterior capsule ruptur* or endophthalmitis or keratitis or intraocular lens dislocation* or lens subluxat * or low ocular pressure or ocular hypotens* or high ocular pressure or ocular hypertens* or anesthetic allergy or ocular toxicit* or allergic reaction* or vitreous hemorrhag* or retinal detachment* or choroidal hemorrhag* or suprachoroidal hemorrhag* or ocular hemorrha* or eye hemorrhag* or retinal hemorrhag* or systemic hypertension or vision loss* or vision

		disorder*).mp.
	12	10 or 11
	13	3 and 6 and 9
	14	3 and 6 and 12
	15	13 or 14
	16	limit 15 to (human and english language and yr="1995 - Current")
	RESULTS	**1208**
		Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
OVID Embase	1	exp Cataract Extraction/ or exp Cataract/
	2	(Phacoemulsif* or Phakoemulsif* or Phaco-emul* or Phako-emul* or Cataract extrac* or Cataract remov* or Cataract surg* or Cataract operat*).mp.
	3	1 or 2
	4	neuroleptanalgesia/ or anesthesia/ or anesthesia, local/ or nerve block/ or anesthesia, intravenous/ or cryoanesthesia/ or analgesia/ or exp Anesthetics/ or exp Perioperative care/
	5	(((block or anesthe* or anaesthe* or infiltrat* or inject*) adj3 (orbicularis or subtenon or peribulbar or retrobulbar or topical or intracameral or intracameral)) or Xylocaine or Neurolept* or Benzodiazep* or Lidocaine or Intracameral or Intracameral* Procaine or Proparacaine or Oxybuprocaine or Tetracaine or Bupivacaine or Etidocaine or Lidocaine or Prilocaine or Ropicacaine or Cryoanalg* or cryoanalg* or Cryoanesthes* or Cryoanaesthes* or midazolam or Fentanyl or Propofol or Perifentanyl or Gravol or dimenhydrinate or ondansetron or lorazepam or Ativan or valium or diphenhydramine or benadryl).mp.
	6	4 or 5
	7	pain/ or eye pain/ or pain, postoperative/ or Postoperative/ or Postoperative Period/ or Perioperative Care/ or Perioperative Period/ or Intraoperative Care/ or Intraoperative Period/ or hyphema/
	8	((pain or ache or aching or discomfort or instil* or drop or dilat* or manipulation or manipulat* or freez* or pressure or headache) adj3 (postop* or post-op* or periop* or peri-op* or Intraop* or intra-op*)).mp.
	9	7 or 8
	10	Intraoperative Complications/ or Postoperative Complications/ or Endophthalmitis/ or Keratitis/ or Lens Subluxation/ or Retinal Detachment/ or Vision Disorders/ or Eye Hemorrhage/ or Vitreous Hemorrhage/ or Retinal

		Hemorrhage/
	11	(complication* or broken capsul* or posterior capsule ruptur* or endophthalmitis or keratitis or intraocular lens dislocation* or lens subluxat* or low ocular pressure or ocular hypotens* or high ocular pressure or ocular hypertens* or anesthetic allergy or ocular toxicit* or allergic reaction* or vitreous hemorrhag* or retinal detachment* or choroidal hemorrhag* or suprachoroidal hemorrhag* or ocular hemorrha* or eye hemorrhag* or retinal hemorrhag* or systemic hypertension or vision loss* or vision disorder*).mp.
	12	10 or 11
	13	3 and 6 and 9
	14	3 and 6 and 12
	15	13 or 14
	16	limit 15 to (human and english language and yr="1995 - Current")
	RESULTS	**1670**
		Embase Classic+Embase <1947 to 2017 September 8>
CINAHL	1	(MH "Cataract Extraction+") or (MH "Cataract")
	2	Phacoemulsif* or Phakoemulsif* or Phaco-emul* or Phako-emul* or Cataract extrac* or Cataract remov* or Cataract surg* or Cataract operat*
	3	S1 OR S2
	4	(MH "Anesthesia") OR (MH "Anesthesia, Local") OR (MH "Nerve Block") OR (MH "Anesthesia, Intravenous") OR (MH "Analgesia") OR (MH "Anesthetics") OR (MH "Anesthetics, Local") OR (MH "Anesthetics, Intravenous") OR (MH "Analgesia") OR (MH "Anesthesia and Analgesia")
	5	((block or anesthe* or anaesthe* or infiltrat* or inject*) N3 (orbicularis or subtenon or peribulbar or retrobulbar or topical or intracameral or intracameral)) or Xylocaine or Neurolept* or Benzodiazep* or Lidocaine or Intracameral or Intracameral* Procaine or Proparacaine or Oxybuprocaine or Tetracaine or Bupivacaine or Etidocaine or Lidocaine or Prilocaine or Ropicacaine or Cryoanalg* or cryoanalg* or Cryoanesthes* or Cryoanaesthes* or midazolam or Fentanyl or Propofol or Perifentanyl or Gravol or dimenhydrinate or ondansetron or lorazepam or Ativan or valium or diphenhydramine or benadryl
	6	S4 OR S5
	7	(MH "Pain") OR (MH "Postoperative Pain") OR (MH "Eye Pain") OR (MH "Postoperative Period") OR (MH "Postoperative Care") OR (MH "Intraoperative Care") OR (MH "Intraoperative Period") OR (MH "Perioperative Care")

		OR (MH "Eye Hemorrhage")
	8	(pain or ache or aching or discomfort or instil* or drop or dilat* or manipulation or manipulat* or freez* or pressure or headache) N3 (postop* or post-op* or periop* or peri-op* or Intraop* or intra-op*)
	9	S7 OR S8
	10	(MH "Postoperative Complications") OR (MH "Intraoperative Complications") OR (MH "Endophthalmitis") OR (MH "Keratitis") OR (MH "Keratitis, Fungal") OR (MH "Keratitis, Bacterial") OR (MH "Corneal Ulcer") OR (MH "Retinal Detachment") OR (MH "Eye Hemorrhage") OR (MH "Vision Disorders")
	11	complication* or broken capsul* or posterior capsule ruptur* or endophthalmitis or keratitis or intraocular lens dislocation* or lens subluxat* or low ocular pressure or ocular hypotens* or high ocular pressure or ocular hypertens* or anesthetic allergy or ocular toxicit* or allergic reaction* or vitreous hemorrhag* or retinal detachment* or choroidal hemorrhag* or suprachoroidal hemorrhag* or ocular hemorrha* or eye hemorrhag* or retinal hemorrhag* or systemic hypertension or vision loss* or vision disorder*
	12	S10 OR S11
	13	S3 AND S6 AND S9
	14	S3 AND S6 AND S12
	15	S13 OR S14
	16	Limit - Published Date: 19950101-20160931; English Language; Human
	RESULTS	**21**
		Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
WEB OF SCIENCE	1	Phacoemulsif* or Phakoemulsif* or Phaco-emul* or Phako-emul* or Cataract extrac* or Cataract remov* or Cataract surg* or Cataract operat*
	2	((block or anesthe* or anaesthe* or infiltrat* or inject*) NEAR/3 (orbicularis or subtenon or peribulbar or retrobulbar or topical or intracameral or intracameral)) or Xylocaine or Neurolept* or Benzodiazep* or Lidocaine or Intracameral or Intracameral* Procaine or Proparacaine or Oxybuprocaine or Tetracaine or Bupivacaine or Etidocaine or Lidocaine or Prilocaine or Ropicacaine or Cryoanalg* or cryoanalg* or Cryoanesthes* or Cryoanaesthes* or midazolam or Fentanyl or Propofol or Perifentanyl or Gravol or dimenhydrinate or ondansetron or lorazepam or Ativan or valium or diphenhydramine or benadryl

	3	pain or ache or aching or discomfort or instil* or drop or dilat* or manipulation or manipulat* or freez* or pressure or headache or eye pain
	4	complication* or broken capsul* or posterior capsule ruptur* or endophthalmitis or keratitis or intraocular lens dislocation* or lens subluxat* or low ocular pressure or ocular hypotens* or high ocular pressure or ocular hypertens* or anesthetic allergy or ocular toxicit* or allergic reaction* or vitreous hemorrhag* or retinal detachment* or choroidal hemorrhag* or suprachoroidal hemorrhag* or ocular hemorrha* or eye hemorrhag* or retinal hemorrhag* or systemic hypertension or vision loss* or vision disorder*
	5	#3 AND #2 AND #1
	6	#4 AND #2 AND #1
	7	#6 OR #5
	8	(#6 OR #5) AND LANGUAGE: (English)
	RESULTS	**777**
		Timespan=1995-2016 Indexes=Science Citation Index Expanded (SCI-EXPANDED) --1945-present, Social Sciences Citation Index (SSCI) --1900-present, Conference Proceedings Citation Index- Science (CPCI-S) --1990-present, Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) 1990-present, Emerging Sources Citation Index (ESCI) --2015-present
BIOSIS Previews	1	Phacoemulsif* or Phakoemulsif* or Phaco-emul* or Phako-emul* or Cataract extrac* or Cataract remov* or Cataract surg* or Cataract operat*
	2	((block or anesthe* or anaesthe* or infiltrat* or inject*) NEAR/3 (orbicularis or subtenon or peribulbar or retrobulbar or topical or intracameral or intracameral)) or Xylocaine or Neurolept* or Benzodiazep* or Lidocaine or Intracameral or Intracameral* Procaine or Proparacaine or Oxybuprocaine or Tetracaine or Bupivacaine or Etidocaine or Lidocaine or Prilocaine or Ropicacaine or Cryoanalg* or cryoanalg* or Cryoanesthes* or Cryoanaesthes* or midazolam or Fentanyl or Propofol or Perifentanyl or Gravol or dimenhydrinate or ondansetron or lorazepam or Ativan or valium or diphenhydramine or benadryl
	3	pain or ache or aching or discomfort or instil* or drop or dilat* or manipulation or manipulat* or freez* or pressure or headache or eye pain
	4	complication* or broken capsul* or posterior capsule ruptur* or endophthalmitis or keratitis or intraocular lens

		dislocation* or lens subluxat* or low ocular pressure or ocular hypotens* or high ocular pressure or ocular hypertens* or anesthetic allergy or ocular toxicit* or allergic reaction* or vitreous hemorrhag* or retinal detachment* or choroidal hemorrhag* or suprachoroidal hemorrhag* or ocular hemorrha* or eye hemorrhag* or retinal hemorrhag* or systemic hypertension or vision loss* or vision disorder*
	5	#3 AND #2 AND #1
	6	#4 AND #2 AND #1
	7	#6 OR #5
	8	(#6 OR #5) Refined by: LANGUAGES: (ENGLISH) Previews Timespan=1995-2016
	RESULTS	**284**
		Indexes=BIOSIS Previews
Cochrane	1	[Cataract Extraction] explode all trees
	2	[Cataract] explode all trees
	3	(Phacoemulsif* or Phakoemulsif* or Phaco-emul* or Phako-emul* or Cataract extrac* or Cataract remov* or Cataract surg* or Cataract operat*)
	4	#1 or #2 or #3
	5	[Anesthesia] this term only
	6	[Neuroleptanalgesia] this term only
	7	[Anesthesia, Local] this term only
	8	[Nerve Block] this term only
	9	[Anesthesia, Intravenous] this term only
	10	[Cryoanesthesia] this term only
	11	[Analgesia] this term only
	12	[Anesthetics] explode all trees
	13	[Perioperative Care] explode all trees
	14	(((block or anesthe* or anaesthe* or infiltrat* or inject*) adj3 (orbicularis or subtenon or peribulbar or retrobulbar or topical or intracameral or intracameral)) or Xylocaine or Neurolept* or Benzodiazep* or Lidocaine or Intracameral or Intracameral* Procaine or Proparacaine or Oxybuprocaine or Tetracaine or Bupivacaine or Etidocaine or Lidocaine or Prilocaine or Ropicacaine or Cryoanalg* or cryoanalg* or Cryoanesthes* or Cryoanaesthes* or midazolam or Fentanyl or Propofol or Perifentanyl or Gravol or dimenhydrinate or ondansetron or lorazepam or Ativan or valium or diphenhydramine or benadryl)
	15	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
	16	[Pain] this term only
	17	[Pain, Postoperative] this term only

	18	[Eye Pain] this term only
	19	[Facial Pain] this term only
	20	[Headache] this term only
	21	[Pain Management] this term only
	22	[Pain Measurement] this term only
	23	[Eye Injuries] this term only
	24	[Dizziness] this term only
	25	((pain or ache or aching or discomfort or instil* or drop or dilat* or manipulation or manipulat* or freez* or pressure or headache) adj3 (postop* or post-op* or periop* or peri-op* or Intraop* or intra-op*))
	26	#16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
	27	[Intraoperative Complications] this term only
	28	[Postoperative Complications] this term only
	29	[Endophthalmitis] this term only
	30	[Eye Infections] this term only
	31	[Corneal Ulcer] this term only
	32	[Eye Infections, Bacterial] this term only
	33	[Eye Infections, Fungal] this term only
	34	[Keratitis] this term only
	35	[Retinal Detachment] this term only
	36	[Retinal Hemorrhage] this term only
	37	[Eye Hemorrhage] this term only
	38	[Choroid Hemorrhage] this term only
	39	[Vitreous Hemorrhage] this term only
	40	[Vision Disorders] explode all trees
	41	[Ocular Hypertension] this term only
	42	[Ocular Hypotension] this term only
	43	[Eye Diseases] explode all trees
	44	(complication* or broken capsul* or posterior capsule ruptur* or endophthalmitis or keratitis or intraocular lens dislocation* or lens subluxat* or low ocular pressure or ocular hypotens* or high ocular pressure or ocular hypertens* or anesthetic allergy or ocular toxicit* or allergic reaction* or vitreous hemorrhag* or retinal detachment* or choroidal hemorrhag* or suprachoroidal hemorrhag* or ocular hemorrha* or eye hemorrhag* or retinal hemorrhag* or systemic hypertension or vision loss* or vision disorder*)
	45	#27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44
	46	#4 and #15 and #26
	47	#4 and #15 and #45
	48	#46 or #47 Publication Year from 1995 to 2016

	RESULTS	**540**
		Cochrane Reviews, Other Reviews, Trials, Methods Studies, Technology Assessments, Economic Evaluations, Cochrane Groups
TYPE	RESULT	DATABASE/WEBSITE
Grey Literature (General)	4	Grey Matters (CADTH - Canadian Agency for Drugs and Technologies in Health)
	n/a	Open Grey
	n/a	Grey Literature Report
Clinical Trials	3	ClinicalTrials.gov
	33	International Clinical Trials Registry
	n/a	UK Clinical Trials Gateway
	n/a	UK Clinical Research Network Study Portfolio
Conference Proceedings	n/a	World Cat
Reports	n/a	Centers for Disease Control and Prevention
	n/a	Health Canada
	n/a	World Health Organization
Theses and Dissertations	n/a	Electronic Thesis Online Service (EThoS)
	n/a	NDLTD http://serach.ndltd.org/
	n/a	Theses Canada Portal http://amicus.collectionscanada.gc.ca/thesescanada-bin/Main/Ba sicSearch?coll=18&l=0&v=1
	n/a	Western Theses and Dissertations (UWO Catalogue)
Ophthalmo-logy Specific	n/a	Association for Research in Vision and Ophthalmology (ARVO) Conference Abstracts
	n/a	American Academy of Ophthalmology (AAO)
	1	Canadian Society of Ophthalmology (COS)
	n/a	European Society of Ophthalmology (SOE)

Appendix C: Imputation Calculations

Aydin et al. (2002)

To impute the standard deviation of Intravenous Fentanyl Group and control group using the mean and p values:

- Mean for intervention = 1.16, mean for control= 0.52
- The P Value for the comparison is 0.02, obtained using a two sample t-test.
- Degrees of freedom = n1-1 + n2-1 = (34-1) + (34-1) = 66
- t is 2.38418574. Obtained from a table of the t distribution with 66 degrees of freedom or an excel spreadsheet (enter =tinv(0.02,66)

NOTE: The calculated standard deviation is the average of the standard deviations of the intervention and comparator arms, and should be entered into the analysis software for the intervention and comprator.

$$\boldsymbol{SE = MD/t = (1.16 - 0.52)/2.38418574 = 0.26843546}$$

$$\boldsymbol{SD = \frac{SE}{\sqrt{\frac{1}{Ne} + \frac{1}{Nc}}} = \frac{0.26843546}{\sqrt{0.0588}} = 0.10678776}$$

Leidinger et al. (2005)

The following data and calculations were done based on Figure 1(a) in the article, which plots the distribution of the visual analogue scores 3 minutes after retrobulbar block – the x-axis is the visual analogue score and the y-axis is the number of patients.

Saline

- Numbers in the data set = 2, 2, 2, 3, 3, 3, 3, 3, 3, 3, 3, 4, 4, 4, 5, 5, 5, 5, 5, 5, 5, 5, 6, 6, 6, 6, 6, 7, 7, 7, 7, 7, 7, 7, 7, 8, 8, 8, 8, 8, 8, 8, 8, 10
- Mean = $\sum X/n$ = 5.53333
- Standard Deviation = $\sqrt{\sum(X-M)^2/n}$ = 2.06265

IV Remifentanil

- Numbers in the data set = 1, 1, 1, 1, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 4, 4, 4, 5, 5, 6
- Mean = $\sum X/n$ = 2.57778
- Standard Deviation = $\sqrt{\sum(X-M)^2/n}$ = 1.05505

Score	Saline # of patients	Remifentanil # of patients
0	0	0
1	0	4
2	3	21
3	8	14
4	3	3
5	8	2
6	5	1
7	9	0
8	8	0
9	0	0
10	1	0

Akgul et al. (2007)

This study has two intervention groups and one comparator group. We have decided to combine the two intervention groups into one so that a pair-wise comparison is possible in the meta-analysis. 15 minutes after the surgery had begun, pain score ratings were taken. Group: Fentanyl – VPS 0.2, p=0.014, Remifentanil – VPS 0.3, p=0.021, Control – VPS 0.7

Impute SD of IV Fentanyl to Control

- The P Value for the comparison is 0.014 @ 15 minutes, obtained using a two sample t-test. The t value that corresponds with a P value of 0.014
- Degrees of freedom = n1-1 + n2-1 = (40-1) + (40-1) = 78
    - T Procedure for two independent populations = conservative approximation https://www.thoughtco.com/how-to-find-degrees-of-freedom-3126409
- t = 2.5139004. Obtained from a table of the t distribution with 78 degrees of freedom or an excel spreadsheet (in a cell enter =tinv(0.014,78)

$$SE = MD/t = (0.7 - 0.2)/2.5139004 = 0.19889412$$

$$SD = \frac{SE}{\sqrt{\frac{1}{Ne} + \frac{1}{Nc}}} = \frac{0.19889412}{\sqrt{0.05}} = \frac{0.19889412}{0.2236068} = 0.88948155$$

Impute SD of IV Remifentanil to Control

- The P Value for the comparison is 0.021 @ 15 minutes, obtained using a two sample t-test.The t value that corresponds with a P value of 0.021
- Degrees of freedom = n1-1 + n2-1 = (40-1) + (40-1) = 78
- t is 2.5139004. Obtained from a table of the t distribution with 78 degrees of freedom or Microsoft excel (=tinv(0.014,78)

$$SE = MD/t = (0.7 - 0.3)/2.5139004 = 0.15911529$$

$$SD = \frac{SE}{\sqrt{\frac{1}{Ne} + \frac{1}{Nc}}} = \frac{0.15911529}{\sqrt{0.05}} = \frac{0.15911529}{0.2236068} = 0.711585$$

The standard deviations were combined according to the Cochrane Handbook:

$$SD = \sqrt{\frac{(N1-1)SD1^2 + (N2-1)SD2^2 + \frac{N1N2}{N1+N2}(M1^2 + M2^2 - 2M1M2)}{N1+N2-1}}$$

$$\sqrt{\frac{(39)0.889481^2 + (39)0.711585^2 + \frac{1600}{80}(0.2^2 + 0.3^2 - 2x0.2x0.3)}{79}}$$

$$\sqrt{\frac{30.8558815 + 19.7477753 + 0.2}{79}}$$

=0.80192535

Santiago et al. (2014)

This research study reports the mean and standard deviation of the intravenous and placebo group at 9 stages throughout the procedure. To get an overall effect estimate, we averaged the mean's and standard deviation's. The following chart depicts the process of averaging the standard deviation.

Formula: Average SD = $\sqrt{\left(\frac{SD1^2+SD2^2+\cdots+SDn^2}{n}\right)}$

Stage of Cataract Extraction	Placebo			IV Clonidine		
	Mean	Standard Deviation	Variance (SD^2)	Mean	Standard Deviation	Variance (SD^2)
1	0.2	0.7	0.49	0.3	0.9	0.81
2	0.2	0.7	0.49	0.3	0.9	0.81
3	0.2	0.7	0.49	0.3	0.9	0.81
4	0.2	0.5	0.25	0.3	0.9	0.81
5	0.9	1.3	1.69	0.5	1.1	1.21
6	3.9	3.2	10.24	1.4	1.6	2.56
7	3.1	2.7	7.29	1.4	2	4
8	3.6	2.4	5.76	1.7	2	4
9	1.8	1.8	3.24	1.1	1.7	2.89
SUM	14.1		29.94	7.3		17.9
/9	**1.57**		3.326666667	**0.81**		1.988888889
Square Root			**1.82**			**1.41**

Chen et al. (2015)

There were 6 cases of pain in the study:

- 3 patients in the IV midazolam group reported a level 1 (mild) on NRS-11 scale
- 4 patients in the oral diazepam group reported a level 1 (mild) on NRS-11 scale
- Since level 1 on the NRS-11 scale is a rating of 1-3, we will use a rating of 2 to calculate the mean and standard deviation.

Oral Diazepam

- Numbers in the data set = 2, 2, 2, and 70 ratings of 0
- Mean = $\sum X/n$ = 0.082
- Standard Deviation = $\sqrt{\sum(X-M)^2/n}$ = 0.3998

IV Midazolam

- Numbers in the data set = 2, 2, 2, and 80 ratings of 0
- Mean = $\sum X/n$ = 0.072
- Standard Deviation = $\sqrt{\sum(X-M)^2/n}$ = 0.3756

Ghodki et al. (2015)

To impute the standard deviation of Intravenous Dexmedetomidine Group and control group using the mean and p values:

- Mean for intervention = 3, mean for control= 3
- The P Value for the comparison is 0.182, obtained using a two sample t-test.
- Degrees of freedom = n1-1 + n2-1 = (30-1) + (30-1) = 58
- t is 1.35081913. This can be obtained from a table of the t distribution with 66 degrees of freedom or from a computer (entering =tinv(0.182,58) into any cell in a Microsoft Excel spreadsheet.

$$\boldsymbol{SE = MD/t = (3-3)/1.35081913 = \text{Not Estimiable}}$$

Added in a correction factor of 0.1

$$\boldsymbol{SE = MD/t = (0.1)/1.35081913 = 0.07402916}$$

$$\boldsymbol{SD = \frac{SE}{\sqrt{\frac{1}{Ne}+\frac{1}{Nc}}} = \frac{0.07402916}{\sqrt{0.0667}} = 0.2867}$$

Habib et al. (2004)

Lastly, Habib et al. (2004) was the most challenging study to impute the standard deviation. P values, confidence intervals, and numbers in the dataset were absent from the article and not available through the corresponding author. An experienced researcher suggested the following method: Calculate the standard deviation as a percentage of mean, and use the average of that for all the other studies. Then, apply that no to the mean of the missing study.

	IV Sedation Group			**Non-IV Sedation Group**		
Study ID	**Mean**	**SD**	**% SD/mean**	**Mean**	**SD**	**% SD/mean**
Aydin et al. (2002)[116]	0.52	1.11	2.134615385	1.16	1.11	0.956896552
Inan et al. (2003)[117]	0.08	0.27	3.375	1.06	0.25	0.235849057
Laube et al. (2003)[118]	0.18	0.44	2.444444444	0.13	0.61	4.692307692
Leidinger et al. (2005)[120]	2.58	1.06	0.410852713	5.53	2.06	0.372513562
Akgul et al. (2007)[121]	0.25	0.8	3.2	0.7	0.8	1.142857143
Erdurmus et al. (2008)[122]	1.23	1.72	1.398373984	3.64	1.43	0.392857143
Santiago et al. (2014)[123]	0.81	1.41	1.740740741	1.57	1.82	1.159235669
Chen et al. (2015)[56]	0.072	0.38	5.277777778	0.082	0.4	4.87804878
Ghodki et al. (2015)[124]	3	0.29	0.096666667	3	0.29	0.096666667
Average			2.230941301			1.547470252
Habib et al. (2004)[131]	0.29		0.29 * 2.230941301 = **0.646**	0.38		0.38 * 1.547470252 = **0.588**

Appendix D: Stata Code

Outcome	Analysis	Stata Code
Pain Perception	Meta-analysis SMD	metan n1 m1 sd1 n2 m2 sd2, random xlabel(-4,-3,-2,-1,0,1,1,2,3,4) title("Effect of Intravenous Sedation on Pain Perception") xtitle("Standardized mean difference") textsize(150) favours(IV sedation reduces pain # Non-IV methods reduce pain) lcols(author year) boxsca(0) xsize(5) ysize(3) graphregion(color(white))
	Sensitivity analysis	drop in 2 drop in 4 metan n1 m1 sd1 n2 m2 sd2, random xlabel(-4,-3,-2,-1,0,1,1,2,3,4) title("Sensitivity Analysis for Pain Perception") xtitle("Standardized mean difference") textsize(150) favours(IV sedation reduces pain # Non-IV methods reduce pain) lcols(author year) boxsca(0) xsize(5) ysize(3) graphregion(color(white))
	Sensitivity Analysis	drop in 1 drop in 3 drop in 4 drop in 7 metan n1 m1 sd1 n2 m2 sd2, random xlabel(-4,-3,-2,-1,0,1,1,2,3,4) title("Sensitivity Analysis for Pain Perception") xtitle("Standardized mean difference") textsize(150) favours(IV sedation reduces pain # Non-IV methods reduce pain) lcols(author year) boxsca(0) xsize(5) ysize(3) graphregion(color(white))
	Meta-analysis WMD	**converted scale** metan n1 m1 sd1 n2 m2 sd2, nostandard random title("Effect of Intravenous Sedation on Pain Perception") textsize(150) favours(IV sedation reduces pain # Non-IV methods reduce pain) lcols(author year) boxsca(0) xsize(5) ysize(3) graphregion(color(white))
	Subgroup Analysis (Intravenous Sedative)	metan n1 m1 sd1 n2 m2 sd2, fixed xlabel(-4,-3,-2,-1,0,1,1,2,3,4) title("Sub-group Analysis by Intravenous Sedative") xtitle("Standardized mean difference") textsize(125) favours(IV sedation reduces pain # Non-IV methods reduce pain) lcols(author year) boxsca(0) xsize(5) ysize(3) by(intervention) graphregion(color(white))
	Subgroup Analysis (Non-IV Methods)	metan n1 m1 sd1 n2 m2 sd2, fixed xlabel(-4,-3,-2,-1,0,1,1,2,3,4) title("Sub-group Analysis by Non-Intravenous Methods") xtitle("Standardized mean difference") textsize(125) favours(IV sedation reduces pain # Non-IV

		methods reduce pain) lcols(author year) boxsca(0) xsize(5) ysize(3) by(comparator) graphregion(color(white))
	Meta-regression	metan n1 m1 sd1 n2 m2 sd2, random xlabel(-4,-3,-2,-1,0,1,1,2,3,4) title("Effect of Intravenous Sedation on Pain Perception") xtitle("Standardized mean difference") textsize(150) favours(IV sedation reduces pain # Non-IV methods reduce pain) lcols(author year) boxsca(0) xsize(5) ysize(3) graphregion(color(white)) metareg _ES reglocation, wsse(_seES) metareg _ES regyear, wsse(_seES) metareg _ES regage, wsse(_seES) metareg _ES regsex, wsse(_seES)
	Funnel Plot	metafunnel _ES _seES, xlab(-4 -3 -2 -1 0 1 2 3) ylab(-.2 -.1 0 .1 .2 .3 .4) xtitle(Standardized mean difference) ytitle(Standard error of SMD) graphregion(color(white))
Adverse Events	Meta-analysis RR	metan n1 comp1 n2 comp2, rr title("Effect of Intravenous Sedation on Adverse Events") xtitle("Risk Ratio") textsize(150) favours(IV sedation increase complications # Non-IV methods increase complications) lcols(author year) boxsca(0) xsize(6) ysize(3) graphregion(color(white))
	Meta-analysis RR with correction factor	metan n1 comp1 n2 comp2, rr nointeger title("Effect of Intravenous Sedation on Adverse Events") xtitle("Risk Ratio") textsize(150) favours(IV sedation increase complications # Non-IV methods increase complications) lcols(author year) boxsca(0) xsize(6) ysize(3) graphregion(color(white))
	Funnel plot complications	metafunnel _ES _selogES, xlab(0.5 1 1.5) ylab(0 0.05 .1) xtitle(Risk Ratio) ytitle(Standard error of RR) graphregion(color(white))

Curriculum Vitae

Name:	Efstathia Kiatos
Post-secondary Education and Degrees:	Schulich School of Medicine and Dentistry; London, Canada Master of Science (MSc) Epidemiology and Biostatistics 2015-2017 Western University; London, Ontario Honours Specialization Bachelor of Health Science (BHSc) 2010-2014
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Peer Reviewed Abstracts	OPHTHALMOLOGY RESEARCH DAY 11/03/17 – ST JOSEPH'S HOSPITAL: ORAL PRESENTATION. Title: A Systematic Review and Meta-Analysis of Intravenous Sedation in Modern Cataract Surgery CANADIAN OPHTHALMOLOGICAL SOCIETY ANNUAL MEETING AND EXHIBITION 06/17/201 – MONTREAL, QC: ORAL PRESENTATION. Title: The Value of Corneoscleral Rim Cultures in Keratoplasty: A Systematic Review and Cost-Effectiveness Analysis LAWSON HEALTH RESEARCH DAY 03/28/2017 – LONDON, ON: POSTER PRESENTATION. Title: The Value of Corneoscleral Rim Cultures in Keratoplasty: A Systematic Review and Cost-Effectiveness Analysis

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