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Is the use of a sustained-release intracanalicular dexamethasone depot an effective treatment for pain reduction following cataract surgery?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not "Is the use of a sustained-release intracanalicular dexamethasone depot an effective treatment for pain reduction following cataract surgery?"

Study Design: A systematic review of three randomized controlled trials (RCTs) all published between 2015 and 2019.

Data Sources: Two RCTs were discovered using PubMed, and one RCT was discovered using Semantic Scholar. The articles were published in peer-reviewed journals in the English language and selected based on relevance to the clinical question.

Outcome Measured: Absence of pain at day 8 following cataract surgery was a primary outcome measured in all three studies using the Ocular Pain Assessment Scale. Patient-rated pain scores ranged 0-10 with higher scores representing severe, disabling pain.

Results: All three studies found that intracanalicular dexamethasone depots provide a significant reduction of ocular pain in patients following cataract surgery compared to the control group. The RCT conducted by Walters et al. (2016) found a NNT of three and a calculated p-value of < 0.0001. This study was found to have a large treatment effect and is statistically significant. The RCT led by Tyson et al. (2019) found a NNT of six and p-value of < 0.0001. This study was found to have a large treatment effect and is statistically significant. Lastly, the RCT led by Walters et al. (2015) found a NNT of three and p-value of < 0.0001. This study was found to have a large treatment effect and is statistically significant. Additionally, in all three studies, patients receiving intracanalicular dexamethasone required the use of additional anti-inflammatory rescue drops far less than patients in the placebo group.

Conclusion: All three studies in this review demonstrated that the use of intracanalicular dexamethasone depots provides a statistically significant reduction of pain severity following cataract surgery. This suggests that it is an effective and advantageous treatment method for post-cataract surgery ocular pain.

Key Words: Dexamethasone, cataract surgery, intracanalicular

INTRODUCTION:

Cataracts are defined as an ocular condition in which the lens of the eye gradually becomes opacified.[1] Patients with visually significant cataracts suffer from blurred vision, difficulty seeing in dim light, seeing halos around lights, vision loss, or total blindness.[1] Cataracts are most commonly developed as a result of the natural aging process.[1] Over time, protein begins to accumulate and clump together in the lens. This gives the lens a cloudy appearance and hinders light from passing through to the retina clearly. Cataracts can also be acquired as a result of congenital abnormalities, systemic disease, medications, or trauma.[1]

Cataracts are the most common cause of blindness worldwide and the most common cause of vision loss in the US.[2] The number of patients needing cataract surgery is increasing yearly due to our aging population.[2] In the United States alone, cataracts affect approximately 22 million people over the age of 40.[1] While there is an estimated $6.8 billion in direct medical costs for the treatment of cataracts annually, an exact estimate for healthcare visit costs as a result of this condition is unknown. However, it is known that in the United States, nearly 1.5 million people have cataract surgery annually.[1]

Topical steroid and topical NSAID medications are typically used for prophylactic treatment of postoperative pain and inflammation that may follow cataract surgery.[2-4] However, patient compliance is oftentimes suboptimal for various reasons, and proper instillation techniques are frequently lacking with the use of topical agents.[2-4] Patients, particularly the elderly, often fail to remember to take the drops as scheduled due to a complex, tapered dosing regimen.[2,3] Patients also struggle with properly instilling the drops as the bottles the medications are dispensed in can be difficult for them to handle.[2,3] These factors negatively affect the efficacy of the drug and can potentially put patients at increased risk for developing postoperative

complications.[2-4] A study was conducted where investigators asked cataract surgery patients to self-administer antibiotic and steroid drops five times per day for two weeks. It was discovered that only half of the patients were compliant with the medication schedule.[5] The one-time administration of sustained-release intracanalicular dexamethasone depots may be used as an option to eradicate the concerns of patient compliance and inaccurate drop administration, subsequently leading to enhanced efficacy of the drug's ability to reduce postoperative pain and complications following cataract surgery.

This paper evaluates three randomized control trials assessing the efficacy of sustained-release intracanalicular dexamethasone depots in the treatment of pain reduction following cataract surgery. In all three studies, the dexamethasone as well as placebo was suspended in a dried polyethylene glycol (PEG) hydrogel device and placed in the inferior canaliculus.[5-7] The rod shaped device was designed to expand once in contact with fluid from the ocular surface so that it may stay securely placed inside the punctum.[5-7] For up to 30 days, the depot releases a sustained and tapered dose of preservative free dexamethasone or placebo to the ocular surface.[5-7] The device then gradually liquifies, and dissipates through the nasolacrimal duct.[5-7] Each device was conjugated with fluorescein dye for the purpose of visualization and confirmation of correct placement of the depot when viewed through a slit lamp.[5-7]

Previous studies have been conducted using hydrogel sustained-release depots. The Singapore National Eye Center conducted a study evaluating the efficacy of moxifloxacin in a hydrogel sustained-release depot.[6] There have also been studies conducted in canines evaluating the efficacy of travoprost as well as dexamethasone when suspended in a hydrogel sustained-release depot.[6] Each of these previous studies support this method of delivering medications to the ocular surface as being exceptionally efficacious.[6]

OBJECTIVE:

The objective of this systematic EBM review is to determine "Is the use of a sustained-release intracanalicular dexamethasone depot an effective treatment for pain reduction following cataract surgery?"

METHODS:

The population targeted in this selective EBM review were patients undergoing cataract surgery. The intervention used in each study was a sustained-release dexamethasone depot placed in the canaliculus of the operated eye. The comparison used in each study was a similar-appearing placebo depot placed in the canaliculus of the operated eye. The outcome measured that is being examined in this review is the absence of pain in the operated eye at day 8.

Studies were selected based on relevance and ability to answer the clinical question: "Is the use of a sustained-release intracanalicular dexamethasone depot an effective treatment for pain reduction following cataract surgery?". Furthermore, articles were chosen if they contained patient-oriented outcomes (POEMS) and fulfilled criteria based on intervention, comparison, and outcome measured. It was required that all articles conducted randomized, placebo-controlled clinical trials on patients undergoing cataract surgery without current ocular disease and using intracanalicular dexamethasone depots for post-op ocular pain. The studies selected for this review were found on PubMed and Semantic Scholar using keywords "cataract surgery", "intracanalicular", and "dexamethasone". In order for the articles to be selected, they must have been published in peer-reviewed journals in the English language after 2010. Studies also must have been randomized controlled trials and conducted on humans. Articles that were not randomized, not published in a peer-reviewed journal, secondary studies, or published prior to

2010 were excluded. Statistics reported in this review include Experimental Event Rate (EER), Control Event Rate (CER), Relative Benefit Increase (RBI), Absolute Benefit Increase (ABI), Number Needed to Treat (NNT), and p-values derived from patient-rated Ocular Pain Assessment Scores. Demographics and characteristics of each study are included below in Table 1.

OUTCOME MEASURED:

The outcome measured in this review is the absence of ocular pain at day 8 following cataract surgery.[5-7] All three studies utilized patient-rated Numeric Ocular Pain Assessment Rating Scales where 0 = no pain, 1 to 3 = mild pain (nagging, annoying, minimally interferes with ADLs), 4 to 6 = moderate pain (significantly interferes with ADLs), and 7 to 10 = severe pain (disabling, unable to perform ADLs).[5-7] Patients completed the one question assessment pertaining to their pain level at each follow up visit in the presence of a study investigator.[5-7]

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Walters[6] (2015)	RCT	60	21+ years old	Cataractous lens undergoing clear corneal cataract surgery with phacoemulsification and implantation of PCIOL, potential post-op pin-hole Snellen visual acuity $\geq$ 20/200 in operative eye, and > 20/200 in the fellow eye	Intraocular inflammation, score > 0 on the Ocular Pain Assessment, compromised immune system, or autoimmune disease, obstructed nasolacrimal duct	2	0.4mg intracanalicular dexamethasone insert vs. intracanalicular placebo insert, both suspended in a dried polyethylene glycol (PEG)-based hydrogel device

Walters[5] (2016)	RCT	247	18+ years old	Visually significant cataract with plans to undergo clear corneal cataract surgery with phacoemulsification and PCIOL, potential post-op pinhole corrects Snellen visual acuity $\geq$ 20/200 in both eyes	Intraocular inflammation, score > 0 on Ocular Pain Assessment, inflammatory eye disease, significant macular pathology, glaucoma, ocular HTN, corneal or retinal surgery in past 6 months	3	0.4mg intracanalicular dexamethasone insert vs. intracanalicular placebo insert, both suspended in a dried polyethylene glycol (PEG)-based hydrogel device
Tyson[7] (2019)	RCT	438	18+ years old	Presence of a cataract with plans to undergo clear corneal cataract surgery with phacoemulsification and PCIOL, potential post-op Snellen pin-hole CDVA $\geq$ 20/200 in both eyes	Intraocular inflammation, score > 0 on Ocular Pain Assessment, diabetic retinopathy, significant macular pathology, certain ocular surgeries or procedures during study period or in prior 6 months, glaucoma, or ocular HTN	3	0.4mg intracanalicular dexamethasone insert vs. intracanalicular placebo insert, both suspended in a dried polyethylene glycol (PEG)-based hydrogel device

RESULTS:

Walters et al.[6] (2015) conducted a randomized double-blind RCT for a total of 30 days to assess the efficacy and safety of dexamethasone as a biodegradable sustained-release depot when placed in the canaliculus for the treatment of ocular pain in cataract surgery patients. A total of 60 individuals aged 21 and older, who were undergoing clear corneal cataract surgery with phacoemulsification and implantation of a posterior chamber intraocular lens (PCIOL) were selected to participate in the study across four sites in the US.[6] Participants were selected according to certain inclusion and exclusion criteria noted in Table 1. Participants were randomized 1:1 to either receive 0.4 mg of preservative free sustained-release dexamethasone suspended in a PEG-based hydrogel device, or an identical-appearing placebo vehicle device inserted intraoperatively into the inferior distal canaliculus of the operated eye.[6] Patients

experiencing moderate to severe pain (pain score ≥ 4) after surgery were allowed the use of additional anti-inflammatory (rescue) drops.[6] Patients who used rescue medication before the primary endpoint of day 8 were considered treatment failures.[6] The treatment groups consisted of 30 patients each. There was one patient who was not treated from the intervention group for unknown reasons, so data from 59 patients was used in the statistical analysis.

There were two primary outcomes studied in this RCT though, the outcome being analyzed in this review is the absence of ocular pain 8 days after cataract surgery.[6] Ocular pain severity was assessed using the Ocular Pain Assessment Scale. Patients rated their pain on a scale 0-10, where 0 represented no pain, and 10 represented severe pain. Of the participants receiving sustained-release dexamethasone, 79.3% of the patients were pain free compared to 30% in the placebo group at day 8 (Table 2).[6] The difference between the two groups was 49.3% (Table 2).[6] Additionally, a significantly lower proportion of patients in the sustained-release dexamethasone group compared to the placebo group received rescue medication at day 8.[6] Of 29 patients, 5 (17.2%) patients in the intervention group received rescue medication compared to 16 (55.2%) out of 29 in the placebo group.[6] Using dichotomous data from the study, a NNT of three was calculated (Table 5), meaning that for every three cataract surgery patients receiving a sustained-release dexamethasone depot, ocular pain for one more patient will be prevented compared to the placebo. The study reported a p-value of < 0.0001 between the intervention and control groups (Table 2).[6] 80% and 95% confidence intervals were constructed around the difference in proportions for the outcome.[6] Given the reported p-value and a low NNT, it can be concluded that there is a large treatment effect that is statistically significant. Resultant values from this study are shown below in Tables 2 and 5.

Table 2. Occurrence of Ocular Pain in Walters et al.[6] (2015) Study at day 8

Sustained-release dexamethasone (n=29)	Placebo (n=30)	Difference between two groups	P-value
23 (79.3%)	9 (30%)	49.3%	< 0.0001

Walters et al.[5] (2016) conducted a randomized double-blind RCT for a total of sixty days to assess the efficacy and safety of dexamethasone as a sustained-release intracanalicular biodegradable depot for the treatment of postoperative ocular pain in patients having cataract surgery. A total of 247 patients participated in this study across 32 different private practice sites in the US.[5] Participants were selected based on certain inclusion and exclusion criteria that can be found as listed in Table 1. All participants were older than 18 years of age and were receiving clear corneal cataract surgery with phacoemulsification and implantation of a PCIOL.[5] Participants were randomized 2:1 where 163 participants received a sustained-release dexamethasone depot and 83 participants received a placebo vehicle placed immediately following surgery.[5] Dexamethasone containing 0.4 mg was delivered to the ocular surface via PEG-based hydrogel depot placed in the inferior punctum.[5] The placebo consisted of a similar-appearing device, but without the active ingredient of dexamethasone.[5] The use of additional anti-inflammatory drops were allowed per investigators discretion, particularly if patients were experiencing moderate to severe pain (pain score $\geq$ 4).[5] Patients who received rescue medications were deemed treatment failures after the visit in which they were prescribed the medication.[5]

The primary outcome measured being analyzed in this review from the Walters et al.[5] (2016) study is absence of pain 8 days after receiving cataract surgery. Pain was assessed by patients reporting their pain levels using Numeric Rating Scales where 0 represented no pain, and 10 represented severe pain.[5] Far fewer patients in the sustained-release dexamethasone group required rescue medication compared to the placebo group.[5] At day 8, 7.4% of patients in the intervention group received rescue medication while 28.9% of patients in the placebo group

received rescue medications (p=0.0321).[5] A significantly higher amount of patients in the intervention group compared to the placebo group reported an absence of pain 8 days after cataract surgery.[5] 80.4% of the patients receiving sustained-release dexamethasone reported no pain while 43.3% of patients receiving placebo reported no pain (Table 3).[5] A p-value of < 0.0001 was reported between the intervention and control groups (Table 3).[5] A 95% confidence interval was constructed around the difference in proportions for the outcomes.[5] A NNT of three was calculated using dichotomous data from the study (Table 5). For every three cataract surgery patients receiving a sustained-release dexamethasone depot, ocular pain for one more patient will be prevented compared to the placebo. The reported p-value and calculated NNT indicates a large treatment effect that is statistically significant. Values for this study are summarized below in Tables 3 and 5.

Table 3. Occurrence of Ocular Pain in Walters et al.[5] (2016) Study at day 8

Sustained-release dexamethasone	Placebo	Difference between two groups	P-value
80.4%	43.4%	37%	< 0.0001

The final study analyzed in this review was conducted by Tyson et al.[7] as a double blind RCT for a total of six weeks across 21 sites throughout the US to evaluate the efficacy and safety of a sustained-release intracanalicular dexamethasone depot for the treatment of postoperative ocular pain in cataract surgery patients. Patients were selected according to certain inclusion and exclusion criteria that is outlined above in Table 1. A total of 438 patients were enrolled into the study and randomized 1:1 with 216 patients in the intervention group receiving 0.4 mg of sustained-release dexamethasone depot, and 222 patients in the control group receiving a placebo depot placed into the inferior vertical canaliculus of the study eye immediately following cataract removal and PCIOL placement.[7] The need for additional anti-inflammatory medication was assessed on visit days and administered to patients exhibiting an ocular pain score $\geq$ 4 at

investigators discretion.[7] Patients who received rescue medication were considered treatment failures after the visit in which they were prescribed the medication.[7]

Absence of pain in the study eye at Day 8 was one of the primary endpoints for this study, and was also assessed using the same patient-reported numerical rating scale as the other two previous studies discussed above.[7] Considerably more patients reported an absence of pain in the study eye that were in the intervention group compared to the control group at Day 8, 79.6% and 61.3%, respectively (Table 4).[7] According to the study, approximately twice as many patients in the placebo group required additional anti-inflammatory drops compared to patients treated with sustained-release dexamethasone by the primary endpoint of day 8.[7] A 95% confidence interval was also constructed around the difference in proportions in this study.[7] Dichotomous data from the study was used to compute a NNT value of six (Table 5), so for every six cataract surgery patients receiving a sustained-release dexamethasone depot, ocular pain for one more patient will be prevented compared to the placebo. The study reported a p-value of < 0.0001 (Table 4).[7] It can be concluded that there is a large treatment effect that is statistically significant given the p-value and calculated NNT. Tables 4 and 5 below summarize the values from this study.

Table 4. Occurrence of Ocular Pain in Tyson et al.[7] Study at day 8

Sustained-release dexamethasone	Placebo	Difference between two groups	P-value
79.6%	61.3%	18.3%	< 0.0001

Table 5. Calculations for NNT in Both Walters et al. and Tyson Studies

Study	EER	CER	RBI	ABI	NNT
Walters[6] (2015)	0.793	0.310	1.56	0.483	3
Walters[5] (2016)	0.804	0.434	0.853	0.37	3
Tyson[7]	0.796	0.613	0.299	0.183	6

DISCUSSION:

The trauma to ocular tissues that occurs during cataract surgery oftentimes leads to pain and inflammation following the procedure. The amount of pain and inflammation a patient experiences postoperatively directly impacts patient outcomes, satisfaction, and overall surgical success.[2,4] Modern interventions, such as the intracanalicular dexamethasone depot discussed in this review, can significantly reduce, and potentially eliminate postoperative complications due to pain and inflammation. The dexamethasone depot does not require any action or participation from the patient, eliminating the noncompliance component that may adversely affect outcomes. Furthermore, the depot optimizes the delivery of the medication, so that more of its affects and benefits can be appreciated.[4]

This review evaluated the efficacy of intracanalicular dexamethasone depots for the treatment of postoperative pain associated with cataract surgery. In all three studies, sustained-release intracanalicular dexamethasone was superior over placebo in reducing postoperative ocular pain. All three studies were designed similarly, and found a statistically significant reduction of ocular pain in the study eye that received intracanalicular dexamethasone following cataract surgery as determined by the reported p-values. In each study, more patients in the intervention group reported a score of zero on the Ocular Pain Assessment Scale compared to the placebo group on post-op day 8. Additionally, in all three studies, patients receiving intracanalicular dexamethasone required the use of additional anti-inflammatory rescue drops far less than patients in the placebo group, indicating that the intracanalicular depot was more effective in preventing and eradicating postoperative ocular pain early on. The studies conducted by Walters et al.[6] (2015) and Walters et al.[5] (2016) both demonstrated a NNT of three, while the

study conducted by Tyson et al.[7] produced a NNT of six. Based on these NNTs, the treatment affect was considered to be large in all three studies.

All three studies used in this review were subject to limitations in their research. In all three studies, patients were allowed the use of systemic NSAIDs for comorbidities throughout the duration of the study.[5-7] This could have further contributed to the reduction of postoperative pain and skewed the results in favor of the effectiveness of the intracanalicular dexamethasone depot's ability to reduce postoperative ocular pain. Additionally, the study conducted by Walters et al.[6] (2015) had a small sample size of 60 participants, which affects the validity and reliability of the results from the study. Lastly, none of the studies performed worst-case analyses for missing outcome data from participants who were lost to follow-up. This determinant makes the studies less valid as it potentiates bias.

CONCLUSION:

All three studies utilized for this systematic review demonstrated that the use of a sustained-release intracanalicular dexamethasone depot is an effective treatment for pain reduction following cataract surgery. The treatment affect was determined to be large in each study based on the calculated NNT. Additionally, the reported p-values in each study indicate that the results are statistically significant.

Future studies should be conducted to evaluate the efficacy of intracanalicular dexamethasone when compared to an active control such as topical steroid medications. If possible, it may be beneficial for future investigators to take into account baseline pain tolerance levels of participants and the circumstances that may influence their tolerance and subsequently their self-reported pain scores. This will allow for a more accurate picture of its effectiveness in reducing postoperative ocular pain. It may also be worth exploring the use of intracanalicular

dexamethasone for ocular procedures other than cataract surgery as well as for ocular diseases or conditions that require a prolonged, tapered course of steroids. Future studies may also investigate the use of intracanalicular depots that contain other ocular medications such as antibiotics or Glaucoma medications. While current ongoing studies of sustained-release intracanalicular dexamethasone depots were not found during the preparation of this systematic review, hopefully future studies will identify additional advantageous uses for intracanalicular depots that more providers can adopt as a treatment method that is not so onerous, but instead more auspicious for patients.

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