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Comparison of Ketorolac Tromethamine and Prednisolone Acetate in Preventing Surgically Induced Miosis during Cataract Surgery

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مقارنة بين كيتورولاك ترومیثامين وأسيتات البريدنيزولون في منع تقلص الحدقة المحفّز بالجراحة أثناء جراحة الساد

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الملخص: الهدف: مقارنة فعالية وسلامة استعمال أسيتات البريدنيزولون 1% والكيتورولاك ترومیتامين 0.5% موضعياً للمحافظة على توسّع الحدقة خلال جراحة الساد. **الطريقة:** شملت هذه الدراسة الاستباقية العشوائية المقنّعة جزئياً خمسين مريضاً، حيث تم تطبيق معالجة موضعية بالبريدنيزولون أسيتات (25 مريضا) أو بالكيتورولاك ترومیتامين (25 مريضا) بدءاً من 24 ساعة قبل استخراج الساد، سواء بالطريقة التقليدية باستخراج العدسة أو باسْتِحْلاَبُ العَدَسَة). كانت تُعطى قطرة كل 6 ساعات من كل دواء وحتى الوصول إلى جرعة كلية تعادل 4 قطرات، وكان سائل الإرواء خالياً مِنَ الإيبنفرين. تم قياس قطر الحدقة في ثلاثة أوقات أثناء العمل الجراحي، وللتأكد من سلامة المرضى تم مراقبتهم عبر التنظير المجهري الحيوي وتنظير قعر العين والضغط داخل المقلة والآثارُ الضائرَة وحدة الإبصار. **النتائج:** كان متوسط تغير قطر الحدقة من مرحلة ما قبل الشق إلى مرحلة ما بعد إرواء وغسل القشرة والشفط وزرع العدسةَ أقل وبشكل جوهري مع الكيتورولاك منه مع البريدنيزولون(P=0.003). وبالنتيجة كان متوسط قطر الحدقة بعد غسل القشرة والشفط وزرع العدسة أكبر وبشكل جوهري مع الكيتورولاك مقارنة مع البريدنيزولون(P<0.0001). لم تلاحظ أية فروق جوهرية بين المجموعتين في قطر الحدقة سواء قبل الشق الأول (P=0.244)، أو بعد إعطاء مقبّض الحدقة (P=0.505). أما متغيرات الأمان فقد كانت متقاربة بين المجموعتين ولم تسجل آثارٌ ضائرَة لكلا الدوائين. **الخلاصة:** كان تحمّل المرضى للكيتورولاك ترومیثامين ولأسيتات البريدنيزولون جيدا وبشكل متساوي وبدون آثارٌ ضائرَة، لكن الكيتورولاك ترومیثامين كان أفضل في منع تقلص الحدقة الناتج عن الجراحة.

مفتاح الكلمات: كيتورولاك ترومیتامين، أسيتات البريدنيزولون، استخراج الساد، تقلص الحدقة، توسع الحدقة.

ABSTRACT: ***Objectives:*** The aim of this study was to compare the efficacy and safety of topical prednisolone acetate 1% and topical ketorolac tromethamine 0.5% in the maintenance of pupillary mydriasis during cataract surgery. ***Methods:*** Fifty patients were enrolled in this prospective, partially masked and randomised study. They were assigned to receive topical treatment with either prednisolone acetate (n = 25) or ketorolac tromethamine (n = 25), starting 24 hours before cataract extraction (either routine extracapsular cataract extraction or phacoemulsification). One drop of the study medication was instilled every 6 hours for a total of 4 drops. No epinephrine was used in the intraoperative irrigation solution. Pupil diameter was measured three different times during surgery. To ensure participant safety, biomicroscopy, ophthalmoscopy, intraocular pressure, adverse events and visual acuity were also monitored. ***Results:*** The mean pupil diameter change from the time of the pre-incision until after cortical irrigation and aspiration and lens implantation was significantly less with ketorolac than with prednisolone (P = 0.003). Consequently, mean pupil diameter after cortical irrigation and aspiration and lens implantation was significantly greater with ketorolac than with prednisolone (P <0.0001). No significant differences between groups were observed in the pupil diameter before the first incision (P = 0.244), nor after administration of a miotic agent (P = 0.505). Safety variables were comparable and no drug-related adverse events were reported. ***Conclusion:*** Ketorolac tromethamine 0.5% and prednisolone acetate 1% solutions were equally well tolerated without related adverse events, but ketorolac was better in preventing surgically induced miosis.

Keywords: Ketorolac tromethamine; Prednisolone acetate; Cataract extraction; Miosis; Mydriasis.

Advances in Knowledge

1. *Ketorolac tromethamine and prednisolone acetate are well tolerated when applied topically before cataract extraction.*
2. *Ketorolac tromethamine is very effective in preventing surgically induced miosis, while prednisolone acetate is not, despite the fact that both drugs inhibit the liberation of prostaglandins which are believed to be the main cause of surgically induced miosis and postoperative inflammation during cataract surgery.*
3. *Many previous studies have demonstrated that both drugs are equally effective in preventing and treating postoperative inflammation.*

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Therefore, these findings suggest that there are other factors, rather than prostaglandins, that interfere in surgically induced miosis.

APPLICATION TO PATIENT CARE

1. *Ketorolac has many advantages over prednisolone, such as preventing surgically induced miosis and its complications, avoiding the possible steroid-induced pressure increase, and avoiding other steroid-related side effects. These advantages, together with the good efficacy in controlling postoperative inflammation and lowering costs, may make ketorolac a good choice before and after cataract extraction, especially if a patient is a known steroid responder.*

Techniques for extracapsular cataract extraction (ECCE) have improved tremendously in the past few decades, with small-incision surgery nowadays being the standard treatment. Nevertheless, ocular tissue is traumatised during surgery leading to the activation of phospholipase A2,[1] and the liberation of two groups of lipid molecules: arachidonic acid (AA) metabolites, and platelet-activating factors (PAFs).[2] Arachidonic acid forms the substrate for further reactions mainly by the cyclo-oxygenase and the lipoxygenase pathways. The main products of the cyclo-oxygenase pathway are prostaglandins (PGs), and the main products of the lipoxygenase pathway are leukotrienes (LTs). Endogenous PGs produce many effects such as: miosis during surgery, postoperative inflammation, increased permeability of the blood-ocular barriers, conjunctival hyperaemia and change in intraocular pressure.[1-3] Platelet-activating factors induce an impressive repertoire of responses *in vitro* and seem to be a major regulator of cell adhesion and vascular permeability in many forms of acute inflammation, trauma, shock, and ischaemia, but their precise role is still under investigation.[2]

The decrease in pupil diameter can make cataract removal more difficult and increases the risk of surgical trauma, postoperative ocular inflammation,[4] and posterior capsule rupture.[5] Thus, maintaining adequate pupil dilation is considered an important part of ensuring that cataract removal proceeds smoothly.

Inhibition of PGs' biosynthesis inhibits intraoperative miosis during cataract surgery, reduces the vascular permeability of the blood-ocular barrier, and modifies inflammation.[3]

Non-steroid anti inflammatory drugs (NSAIDs) inhibit the cyclo-oxygenase enzyme, so inhibiting the biosynthesis of PGs but not LTs.[2-3] Topical ophthalmic NSAIDs have been shown to be effective in treating a variety of conditions in which prostaglandins are believed to play a causative role,[3] including surgically induced miosis,[6-7] postoperative inflammation,[8-9] treatment and prevention of cystoid macular oedema (CME),[3-10] and control the pain of refractive surgery.[11] The NSAID ketorolac tromethamine has demonstrated efficacy in the prevention of surgically induced miosis,[12] in the treatment of postoperative ocular pain,[13] in the treatment of chronic aphakic and pseudophakic CME[14] and in the prevention and suppression of ocular inflammation after cataract surgery.[15]

Glucocorticoids inhibit the phospholipase A2 enzyme and consequently inhibit the biosynthesis of both platelet-activating factors and arachidonic acide.[2] This results in the inhibition of the biosynthesis of both PGs and LTs.[3] Topical steroids like prednisolone acetate have been the standard regimen postoperatively for many years and are known to prevent inflammatory reactions after cataract extraction.

Previous studies have not mentioned the role of corticosteroids in preventing surgically induced miosis, despite that corticosteroids inhibit PGs liberation. However, important side effects of topical steroids are increased intraocular pressure (IOP), impairment of wound healing and postoperative ocular infection.[16-17]

The present study compared the efficacy and safety profile of ketorolac tromethamine 0.5% ophthalmic solution with that of prednisolone acetate 1% ophthalmic solution in maintaining the pupillary mydriasis during cataract surgery. The primary efficacy variable was the change in pupil diameter during surgery.

Methods

This prospective, partially masked and randomised study was performed in the Ophthalmology Department, Al-Assad Hospital, Tishreen University, Latakia, Syria during the period March 2008 to March 2009. Patients who were scheduled to undergo unilateral cataract surgery (either routine ECCE or phacoemulsification) and posterior

Table 1: Patients characteristics of the two study groups

		Prednisolone group n = 25	Ketorolac group n = 25	*P* value
Age by Year	Mean ± SD	70.56 ± 8.39	65.68 ± 10.52	0.076*
	Range	47—84	42—80	
Sex	Female	13 (52%)	14 (56%)	> 0.1**
	Male	12 (48%)	11 (44 %)	
Pre-surgery IOP (mmHg)	Mean ± SD	13.88 ± 3.47	13.49 ± 5.20	0.752*
Operated eye	Right	14 (56%)	14 (56%)	1**
	Left	11 (44%)	11 (44%)	
Procedure	ECCE	15 (60%)	15 (60%)	1**
	Phaco	10 (40%)	10 (40%)	

Legend: ** = Analysis of variance test; ** = χ2 test.; IOP = intraocular pressure; ECCE = extra capsular cataract extraction; Phaco = phacoemulsification*

chamber-intraocular lens (PC-IOL) implantation were enrolled in the study. The study protocol was approved by the appropriate institutional review board and written informed consent was obtained from all patients before enrollment in the study. Some cases were excluded according to the study protocol. Patients were not enrolled if they had any of the following features: were pregnant or lactating; only one eye with good visual acuity; any uncontrolled systemic or ocular disease; a history of uveitis or glaucoma; pseudoexfoliation syndrome; a history of any ocular disorder or surgery that might interfere with the surgical procedure or interpretation of the study results; a known sensitivity to any of the components of the study medication; use of systemic steroids or NSAIDs within 2 weeks before study entry, or topical ophthalmic drugs in the eye to be operated within 1 month before study entry. After this process, fifty patients were enrolled in the study. Randomly, 25 patients were given ketorolac tromethamine 0.5% and 25 patients were given prednisolone acetate 1% by the study executor, while the surgeon was masked to patient randomisation.

Patient characteristics of the two groups are shown in Table 1. No significant differences in age, sex, pre-surgery IOP, operated eye or procedure were observed between the two groups ($P \geq 0.076$). All patients in the two groups completed the study and were included in the efficacy and safety analysis.

Patients were assigned to receive either ketorolac tromethamine 0.5% solution (ROLAC® Oubari Pharma, Aleppo, Syria) or prednisolone acetate 1% solution (PRED-ALPHA-FORT® ALPHA-Ind., Aleppo, Syria) according to a randomisation schedule, starting 24 hours before surgery. One drop of study medication was instilled every 6 hours, for a total of 4 drops.

Topical pupillary dilating agents (tropicamide 0.5% and phenylephrine 10 %) were used, starting one hour before surgery, to induce operative mydriasis. Antimicrobial agents were used starting 24 hours before surgery, and retrobulbar anaesthesia was used in all patients. The intraocular irrigating solutions did not contain epinephrine, rather viscoelastics were used by all surgeons. A miotic agent (carbachol) was used after intraocular lens (IOL) implantation, only when the pupil was still markedly dilated, to study the effect of ketorolac and prednisolone on the carbachol efficacy. Any non-study medications that could interfere with interpretation of the study results (e.g. affect pupil diameter) were specifically prohibited by the study protocol. The surgery then proceeded as scheduled and all patients received a subconjunctival dexamethasone plus gentamycin injection at the end of the surgery.

Intraoperative pupil diameter was measured at three different times during surgery using a Castroviejo caliper and standard microscope at 10x magnification under full illumination. The first measurement (preincision [pre-I]) provided the baseline value and was taken immediately before the first incision. The second measurement was

Table 2: Angiographic characteristics of both groups

	Ketorolac group n = 25	Prednisolone group n = 25	*P* value
Pre-I pupil diameter (Mean ± SD)	7.72 ± 0.54	7.52 ± 0.65	0.244*
Post I/A pupil diameter (Mean ± SD)	6.28 ± 0.74	5.34 ± 0.72	< 0.0001*
Change in pupil diameter from pre-I to post I/A (Mean ± SD)	1.44 ± 0.96	2.18 ± 0.70	0.003*
Patients needing mydriatic agent during surgery	4 (16%)	14 (56%)	< 0.005**
Patients who received carbachol	21 (84%)	13 (52%)	< 0.025**
Post M pupil diameter (Mean ± SD)	3.76 ± 0.77	3.92 ± 0.49	0.505*
Change in pupil diameter from post I/A to Post M (Mean ± SD)	2.55 ± 1.18	1.61 ± 0.96	0.014*

*Legend: * = Analysis of variance test; ** = χ2 test; Pre-I = preincision; Post I/A = Post irrigation & aspiration; post M = post miotic*

Note: Post M pupil diameter and change in pupil diameter from post I/A to Post M concerns only the eyes which received carbachol at the end of surgery.

taken at the end of surgery, after cortical irrigation and aspiration, and PC-IOL implantation, before postoperative administration of a miotic agent (post-irrigation and aspiration [post-I/A]). The final measurement was taken at the end of surgery, but only for the patients who had postoperative administration of a miotic agent (postmiotic [post-M]). Care was taken to avoid the presence of viscoelastic in the anterior chamber prior to measurements. The change in pupil diameter during the most traumatic part of the surgical procedure was determined by subtracting the post-I/A value from the pre-I value. The change in pupil diameter caused by the postoperative use of a miotic agent was determined by subtracting the post-M value from the post-I/A value. The safety variables included the results of slit-lamp biomicroscopy and ophthalmoscopy, intraocular pressure, and visual acuity (Snellen chart). Adverse events were recorded and graded for severity.

Microsoft Excel (2003 Version) was simply used to manipulate the data and the available analysis of variance test was used to analyse the continuous variables (such as pupil diameter, changes in pupil diameter, intraocular pressure and age). Treatment differences in nominal categorical variables (such as sex, operated eye and surgical procedure) were analysed using (χ 2) test. All tests were two sided, and the probability values of ≤0.05 were considered as statistically significant.

Results

The efficacy analysis revealed the following results with the mean pupil diameter during the three stages and the changes in pupil diameter shown in Table 2. The (mean ± SD) pre-I pupil diameter was (7.72 ± 0.54 mm) in the ketorolac group and (7.52 ± 0.65 mm) in the prednisolone group. No significant differences in pre-I pupil diameter were observed between the two groups (P = 0.244). The (mean ± SD) Post I/A pupil diameter was greater in the ketorolac group (6.28 ± 0.74 mm) than in the prednisolone group (5.34 ± 0.72 mm) and the difference was statistically significant(P < 0.0001). The mean pupil diameter change from pre-I to post I/A and PC-IOL implantation was significantly less (P = 0.003) in the ketorolac group (1.44 ± 0.96 mm) than in the prednisolone group (2.18 ± 0.70 mm). The number of patients requiring additional mydriatic medication during surgery was significantly greater (P < 0.005) in the prednisolone group (n = 14) than in the ketorolac group (n = 4). The number of patients who received a miotic agent at the end of surgery was significantly greater (P < 0.025) in the ketorolac group (21) than in the prednisolone group (13). The (mean ± SD) post-M pupil diameter was (3.76 ± 0.77 mm) in the ketorolac group and (3.92 ± 0.49 mm) in the prednisolone group. The difference was not significant (P = 0.505). The mean change in the pupil diameter from post I/A to post-M was significantly greater (P = 0.014) in the ketorolac group (2.55 ± 1.18 mm) than in the prednisolone group (1.61 ± 0.96 mm).

The safety analysis revealed no significant differences between groups in slit-lamp biomicroscopy and ophthalmoscopy results, intraocular pressure or visual acuity. In addition, no

treatment-related adverse events occurred. Adverse events occurred in 12% of patients in each group, but no event was considered to be related to the study medication.

Discussion

Surgically induced miosis is a well known event during cataract surgery and believed to be related to the stimulation of PGs release following surgical trauma. The first NSAIDs approved by the FDA for use as intraoperative inhibitors of miosis during cataract surgery were 0.03% flurbiprofen and 1% suprofen. They decrease the synthesis of PGs in the ocular tissues by inhibiting the cyclo-oxygenase pathway, thus reducing miosis. All commercially available topical NSAIDs appear to share this therapeutic benefit.[1]

One previous study has demonstrated the efficacy and safety profile of 0.5% ketorolac compared with its vehicle on maintaining intraoperative mydriasis.[18] The results showed that the mean pupil diameter after cortical irrigation and aspiration was significantly greater (P = 0.03) with 0.5% ketorolac than with its vehicle. Many other previous studies have demonstrated the efficacy of ketorolac in preventing surgically induced miosis.[12-19] In addition, many previous studies have compared the efficacy of NSAIDs and corticoids in ocular inflammation after cataract surgery, [8,9, 20-23] but the role of cocorticoids, which inhibit the biosynthesis of both PGs and LTs, in preventing surgically induced miosis seems not to have been investigated.

Our study demonstrated that ketorolac was significantly better than prednisolone in maintaining mydriasis during surgery. Patients in the ketorolac group had smaller mean decreases in pupil diameter than did patients in the prednisolone group. Many previous studies have demonstrated no significant differences between ketorolac and prednisolone in controlling postoperative inflammation. These findings, considering the fact that both study medications inhibit the biosynthesis of PGs, can probably be attributed to a diminished role of PGs in surgically induced miosis. This suggests that the ketorolac-treated eyes were less susceptible to prostaglandin-independent factors contributing to surgically induced miosis.

Our study also demonstrated no significant differences between ketorolac and prednisolone in the response to the mydriatic agents applied preoperatively, or to the miotic agent applied at the end of surgery. Previous studies have demonstrated that no differences between ketorolac and its vehicle were observed in the response to miotic agents administered at the end of surgery, or in the response to the mydriatic agents applied preoperatively,[18] suggesting that neither ketorolac nor prednisolone has direct antimiotic or mydriatic properties.

In our study, the number of patients requiring additional mydriatics was significantly greater in the prednisolone group ($P < 0.025$) compared to the ketorolac group, while others demonstrated that no differences between ketorolac and its vehicle were observed in the need for additional mydriatics during surgery.[18] This means that patients in the prednisolone group in our study required more additional mydriatics than patients in ketorolac vehicle group in the other comparable study. These findings support more the hypothesis that there are other factors responsible for reducing miosis which are altered by prednisolone, and that ketorolac decreases surgically induced miosis through inhibition of routes other than inhibition of prostaglandin synthesis.

A previous study showed that ketorolac had significantly greater efficacy than the glucocorticoids against blood-aqueous barrier breakdown at day 5 and week 2, as demonstrated by the difference in fluorescein concentration between the operated and nonoperated eyes. That is the median fluorescein concentration in the anterior chamber in the gluococorticoid-treated eyes was significantly elevated during the first two weeks after surgery and then began to decrease.[20] Another previous study also demonstrated comparable results.[24] That is during the first two postoperative weeks, the fluorescein leakage was significantly greater in the steroid-treated eyes than in the indomethacin+steroid-treated eyes. After the second postoperative week, the fluorescein leakage in the steroid-treated eyes continued to decrease. These findings suggest that prednisolone takes more time to act than ketorolac thereby having less efficacy in the intraoperative period.

However, these two studies, and others,[21,22] have demonstrated that prednisolone and ketorolac were equally effective in regard of cells and flare in the anterior chamber during the early postoperative period. Another previous study demonstrated

that fluorescein concentration in placebo-treated eyes was significantly elevated during the first two postoperative weeks (comparable to fluorescein concentration in prednisolone-treated eyes in other studies) then began to decrease and the anterior chamber reaction (cells and flare) was also intensive.[25] This means that prednisolone seems to be similar to the placebo regarding the effect on fluorescein leakage. Moreover the decrease in fluorescein concentration after the second postoperative week in the prednisolone-treated eyes seems not to be related to a delayed prednisolone efficacy. This means that prednisolone is also effective in the early postoperative period as regards the clinical anterior chamber reaction. It appears that although fluorescein is the most sensitive technique for demonstrating breakdown of blood-aqueous barrier (BAB), it may not always be an indicator of large molecule permeability.[26] These findings disprove the hypothesis that prednisolone takes more time to act than ketorolac and suggest that ketorolac is effective against even small-molecule permeability (fluorescein) while prednisolone is effective only against large molecule permeability (cells, protein).

The differences in the efficacy between ketorolac and prednisolone may be due to their differing effects on platelet activating factors, which are inhibited by glucocorticoids, but not by NSAIDs; however, this hypothesis needs to be verified.

In the present study, the use of ketorolac and prednisolone was not associated with any significant adverse effects. This is consistent with previous studies that have documented the comparable tolerability of ketorolac and prednisolone in the treatment of postoperative ocular inflammation.[20-22]

Conclusion

Ketorolac tromethamine 0.5% ophthalmic solution seems to be more effective in preventing surgically induced miosis during cataract surgery compared to prednisolone acetate 1% ophthalmic solution. Consequently, topical ketorolac administered 24 hour before cataract surgery, reduces the complications of miosis during surgery and the need for intraoperative epinephrine which has been linked to CME.[27-28] We therefore advise to apply ketorolac 24 hours before cataract surgery.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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