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Comparative study between the analgesic effect of ketorolac when administrated intravenous preoperatively versus when added to local anesthesia in squint surgery

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ABSTRACT

Background: This study aimed to investigate the safety and the analgesic and anesthetic efficacy of preoperative intravenous ketorolac as well as combined ketorolac with local anesthesia (LA) for peribulbar block.

Methods: This trial enrolled adults scheduled for strabismus surgery under peribulbar block who were allocated into three groups (n = 30). The control group (C) received LA mixture containing lidocaine (2%, 10 ml) and hyaluronidase (5 IU/ml). The ketorolac group (K) received ketorolac (30 mg, intravenously) 30 minutes before LA injection. The ketorolac local group (KL) received an LA mixture to which ketorolac (4 mg/ml) was added.

Results: The onset of anesthesia was significantly shorter in the KL group than in the K group (39.3 ± 6.9 versus 58.5 ± 13.4 sec, $p < 0.001$), and each was also significantly shorter compared to the control group (67.8 ± 16.1). The onset of akinesia was significantly shorter in the KL group than in the K group (95.2 ± 14.0 versus 106.5 ± 14.9, $p < 0.001$). The block duration was significantly longer in the KL group than in the K group and the control group. The pain was less in the KL group than in the K group with significant differences between the medians of VAS score. The time to the 1st analgesic dose was significantly longer in the KL group compared to the K group (5.4 ± .7 versus 4.9 ± .5, $p < 0.001$).

Conclusions: The combination of ketorolac with LA mixture in the peribulbar block was effective; providing better anesthesia, increasing the duration of the block, reducing intraoperative and postoperative pain, and delaying the need for postoperative supplementary analgesia. Both intravenous preoperative ketorolac administration and its addition to the LA mixture were safe with minimal side effects.

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1. Introduction

In recent years, local anesthesia (LA) has replaced general anesthesia for most ophthalmic surgeries, particularly in the setting of day-case surgery. Retrobulbar, peribulbar and sub-Tenon blocks are forms of LA that can provide the required akinesia and anesthesia [1,2].

Local anesthesia is associated with lower incidences of oculocardiac reflex and emergence agitation, quicker recovery, and lower medical costs in comparison with general anesthesia. Though LA provides postoperative analgesia, many patients experience perioperative pain and discomfort [3].

Analgesics as adjuvants to LA provide better anesthesia and analgesia for strabismus surgery [4]. Ketorolac is a non-narcotic, nonsteroidal anti-inflammatory drug that inhibits the cyclooxygenase enzyme in the arachidonic acid cascade and interferes with prostaglandin production. It has a rapid analgesic effect that reaches its maximum within one to two hours following its administration [5]. Additionally, ketorolac has shown comparable efficacy to narcotic analgesics with fewer side effects, particularly less sedation and respiratory depression [6].

Ketorolac has been used intravenously (IV) to relieve postoperative pain after renal surgery [7], and it has been added to LA for ankle block in foot surgery [8]. It has shown improved anesthetic efficacy when administered before inferior alveolar nerve block in mandibular surgery [9]. The analgesic efficacy of ketorolac with perioperative pain control has been shown in different eye procedures such as levator advancement, laser-assisted subepithelial keratectomy, and retinal detachment surgeries [10–12].

Earlier studies reported promising analgesic effects for intraoperative or preoperative IV ketorolac in pediatric patients with strabismus. However, no previous studies in adults with strabismus compared the analgesic properties of preoperative ketorolac administration or when added to LA. Therefore, this study aimed to compare the analgesic and the anesthetic efficacy and the

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safety of preoperative IV ketorolac as well as combined ketorolac with lidocaine for a peribulbar block in adults undergoing strabismus surgery.

2. Methods

2.1. Ethical considerations

This study obtained ethical approval from the Ethics Committee of the Research Institute of Ophthalmology, Egypt. Informed written consent was obtained from each patient. Confidentiality of the data was preserved by making a code number for each participant. The trial was registered at the Iranian Registry of Clinical Trials (Registry ID: IRCT20210106049952N2, Date: 14–11-2021).

2.2. Study design, setting, and date

This randomized, controlled trial was carried out at the Anesthesia Department, Research Institute of Ophthalmology, Egypt, from February 2021 to April 2021.

2.3. Sample size calculation

The sample size was calculated using the G*power 3.1.9.2 software. The alpha error level was set at 0.05 and the power was set at 0.80. The allocation ratio was decided to be 1:1:1. The effect size was calculated based on the difference in the mean of the time to the first analgesic requirement between the two study groups. The sample size was 27 per group and we added 10% to compensate for the loss to follow-up. So, the sample size was 30 patients per group.

2.4. Randomization and allocation concealment

We used the sealed, opaque, sequentially numbered envelopes method for randomization and allocation concealment of the study participants. We used 90 identical, opaque, letter-sized envelopes each containing a sheet of white paper and another sheet of single-sided carbon paper. We wrote, "Treatment A" on 30 paper sheets, "Treatment B" on another 30 sheets, and "Treatment C" on the last 30 sheets. All the envelopes were sealed, combined, and shuffled thoroughly. Then, using a pen we marked a number on the front of each envelope sequentially from 1 to 90. The carbon paper inside the envelope transferred this number to the allocation paper inside. Finally, the envelopes were placed into a container in numerical order.

2.5. Eligibility criteria

The study included male and female adults, aged 30 to 70 years old who were American Society of Anesthesiologists (ASA) physical status I, II, or III and were scheduled for strabismus surgery using peribulbar block anesthesia.

We excluded ASA IV patients on anticoagulant therapy and those who had coagulopathy, bronchial asthma, chronic kidney diseases, bradyarrhythmia, allergy to the used LA agents, and infection at the site of the block, or posterior staphyloma. Uncooperative patients and those who refused to participate in the study were also excluded.

2.6. Study procedures

All patients were fasting for 6 hours preoperatively. In the operating room, a 22 G cannula was inserted, and the patient was attached to a multichannel monitor that recorded the baseline ECG, heart rate (HR), systolic (SBP), and diastolic blood pressures (DBP), and oxygen saturation. The patient was placed in the supine position with a nasal cannula that delivers oxygen at 3 liters per minute. The patient received 2 mg of midazolam + 20 mg of propofol as sedation before the performance of the block.

2.7. Interventions

Ninety eligible patients were randomly allocated into three groups. The control group (Group C) received a local anesthetic mixture containing 10 ml of lidocaine 2% and 5 IU/ml of hyaluronidase. The ketorolac group (Group K) received 30 mg of ketorolac IV, 30 minutes before the local anesthetic injection. The ketorolac local group (Group KL) received the local anesthetic mixture to which 4 mg/ml of ketorolac was added.

2.8. Outcomes

The primary outcome was the analgesic efficacy evaluated by the postoperative pain that was assessed by asking the patient to grade it on the Visual Analogue Scale (VAS) from 0 to 10 (0 = no pain and 10 = severe pain) immediately after the surgery and at 1, 2, 4, and 6 hours later, and by recording the time to the first analgesic dose (h). The secondary outcomes included the onset of anesthesia (sec) assessed by gentle touching of the cornea with a cotton swab from time of injection till complete loss of sensation; the onset of akinesia (sec), assessed by the 3-point score in four directions (0 = no movement, 1 = partial movement, and 2 = complete movement from finishing of injection till complete akinesia); the duration of the block

(min), calculated from the time of injection till full recovery of the movement; and the assessment of the baseline HR (beat/min), SBP and DBP (mmHg), and oxygen saturation (%), then at 10, 20, 30, 40, and 50 min after the interventions throughout the surgery. At the end of the surgery, patient and surgeon satisfaction scores were assessed. Each patient was asked to rate his maximum intraoperative pain on a score that ranged from 0 to 4 (1: no pain felt, 2: no comment, 3: moderate discomfort, and 4: severe pain), and the surgeon was asked, and his answer was given a sore (0: unsuccessful, 1: poor, 2: acceptable, 3: perfect). All patients were monitored for any adverse events, and they were recorded (if any).

2.9. Statistical analysis

Data were analyzed by using the Statistical Package for Social Sciences (IBM SPSS Statistics) for Windows, version 26 (IBM Corp., Armonk, N.Y., USA). Numerical variables were checked for distribution by the Shapiro Wilk test. Normally distributed variables were presented as mean ± SD, and differences between the three groups were tested by One-Way ANOVA. Significant results were followed by post hoc analysis using either Tukey or Games-Howell test. Abnormally distributed variables were expressed as the median and interquartile range (25^{th} – 75^{th} percentile), and the Kruskal-Wallis test was applied, followed by the Dunn-Bonferroni post hoc test. Categorical variables were summarized as frequencies and percentages, and the associations between variables were tested using X^2 tests (Pearson's Chi-square for independence or Fisher Exact Test as appropriate). A p-value of < 0.05 was considered statistically significant.

3. Results

This randomized, controlled clinical trial enrolled 90 adult patients who were scheduled for surgical correction of squint. All patients received the allocated intervention, completed their follow-up at the designed time intervals, and were included in the final analysis (Figure 1).

There were homogenous distributions of the age and sex of the patients among the studied groups with no significant differences (all $p > 0.05$) (Table 1).

The onset of sensory block was significantly more rapid in the KL group than in the K group (39.3 ± 6.9 versus 58.5 ± 13.4 sec, $p < 0.001$). The onset of sensory block was also significantly more rapid in each of the K (58.5 ± 13.4 sec) and the KL (39.3 ± 6.9 sec) groups in comparison with the control group (67.8 ± 16.1 sec). The onset of motor block was significantly more rapid in the KL group than in the K group (95.2 ± 14.0 versus 106.5 ± 14.9 sec, $p < 0.001$). The KL group showed a significantly more rapid onset of motor block (95.2 ± 14.0 sec) than the control group (114.8 ± 14.9 sec). Furthermore, the mean duration of the block was significantly longer in the KL group (107.0 ± 15.6 min) compared to the K group (87.0 ± 13.4 min) and the control group (77.5 ± 15.5 min). At 1 and 2 h after surgery, the pain was less in the KL group than in the K group with

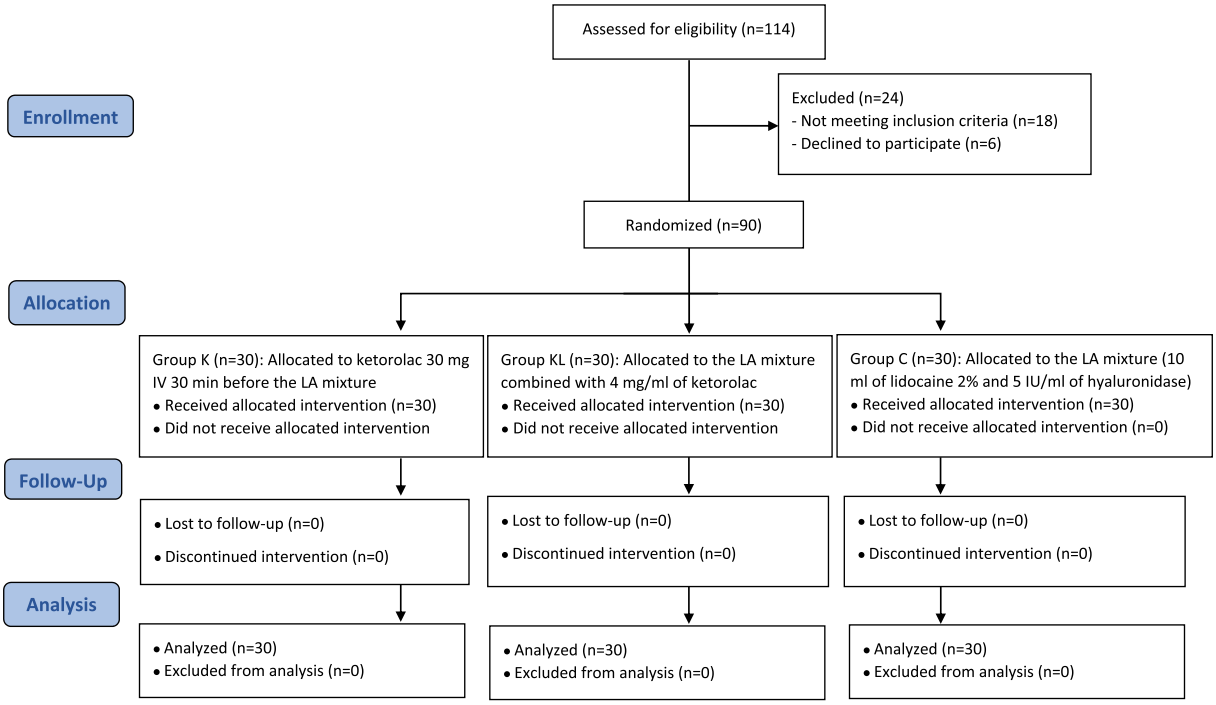

Figure 1. The trial flow diagram.

Table 1. Demographic characteristics of the studied groups.

			Group K N = 30	Group KL N = 30	Group C N = 30	P-value
Sex	Female	N	14	15	17	0.733
		%	46.7	50.0	56.7	
	Male	N	16	15	13	
		%	53.3	50.0	43.3	
Age (Year)	Minimum-Maximum		20.0–41.0	19.0–45.0	20.0–41.0	0.120
	Mean ± SD		30.9 ± 5.7	30.8 ± 6.5	28.0 ± 5.9	

SD: standard deviation

significant differences between the medians (IQR) of VAS score [0.0 (.0–1.0) versus 1.0 (1.0–2.0) at 1 h, and 1.0 (1.0–1.0) versus 2.0 (2.0–3.0) at 2 h, respectively] (Figure 2). The analgesic effect of ketorolac was comparable with no significant difference between the KL and K groups at 4 and 6 h after the surgery. The mean time of 1st analgesic dose was significantly longer in the KL group in comparison to the K group (5.4 ± .7 versus 4.9 ± .5, p < 0.001) as demonstrated in Table 2.

The hemodynamics of the studied groups are illustrated in Table 3 and Figure 3. At 20, 30, and 40 min following the interventions, the HR mean values were comparable in the three studied groups (p > 0.05). At 50 minutes, the KL group showed significantly higher HR mean values compared to the control group (79.1 ± 8.7 versus 73.1 ± 8.8, p = 0.028). The mean values of mean arterial pressure (MAP) were significantly lower in the K and KL groups in comparison to the control group at 30, 40, and 50 min after the intervention (p < 0.05). Alternatively, no significant differences were found between the K and KL groups regarding the mean MAP at all time intervals (p > 0.05). There were no significant differences between the K and KL groups regarding the median oxygen saturation at all time intervals. The K group showed significantly higher mean oxygen saturation than the control group at the baseline reading and 10 and 30 min after IV administration of ketorolac.

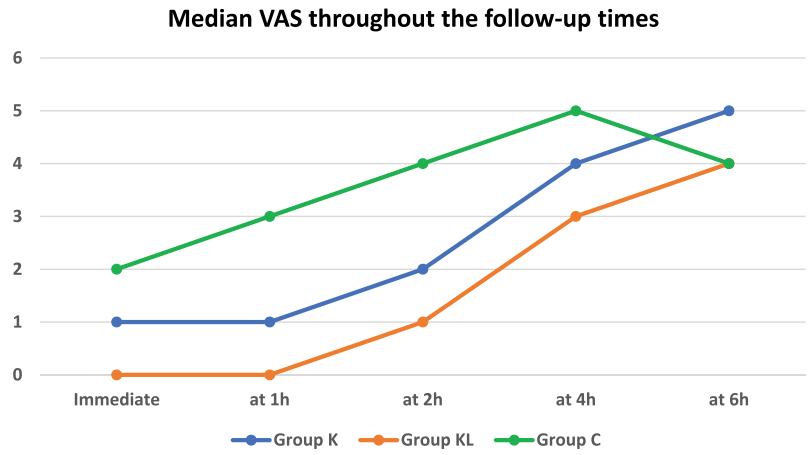

Figure 2. Comparison between the studied groups regarding the medians of the visual analogue scale at different times intervals.

Table 2. Comparison of the primary outcomes between the studied groups.

		Group K N = 30	Group KL N = 30	Group C N = 30	P-value
The onset of sensory block (sec)	Mean ± SD	58.5 ± 13.4[a]	39.3 ± 6.9[c]	67.8 ± 16.1[b]	<0.001*
The onset of motor block (sec)	Mean ± SD	106.5 ± 14.9 [a]	95.2 ± 14.0 [c]	114.8 ± 14.9	<0.001*
Duration of the block (min)	Mean ± SD	87.0 ± 13.4 [a]	107.0 ± 15.6 [c]	77.5 ± 15.5 [b]	<0.001*

SD: standard deviation
*Significant at p < 0.05
[a]: Significant difference between group K and group KL; [b]: significant difference between group K and group C; [c]: significant difference between group KL and group C

Table 3. Comparison between the studied groups regarding the oxygen saturation recorded at different times intervals.

		Group K N = 30	Group KL N = 30	Group C N = 30	P-value
Baseline oxygen saturation	Median (IQR)	100.0 (99.0–100.0)	99.5 (99.0–100.0)	99.0 (98.0–100.0) [b]	0.017*
Oxygen saturation 10 min	Median (IQR)	99.5 (99.0–100.0)	99.0 (98.0–100.0)	99.0 (98.0–99.0) [b]	0.018*
Oxygen saturation 20 min	Median (IQR)	99.0 (99.0–100.0)	99.0 (98.0–100.0)	99.0 (98.0–99.0)	0.265
Oxygen saturation 30 min	Median (IQR)	99.0 (99.0–100.0)	99.0 (99.0–100.0)	99.0 (99.0–100.0) [b]	0.033*
Oxygen saturation 40 min	Median (IQR)	99.0 (99.0–99.0)	99.0 (98.0–99.0)	99.0 (98.0–99.0)	0.124
Oxygen saturation 50 min	Median (IQR)	99.0 (99.0–99.0)	99.0 (98.0–100.0)	99.0 (98.0–100.0)	0.474

IQR: interquartile range
*Significant at p < 0.05
[b]: significant difference between group K and group C

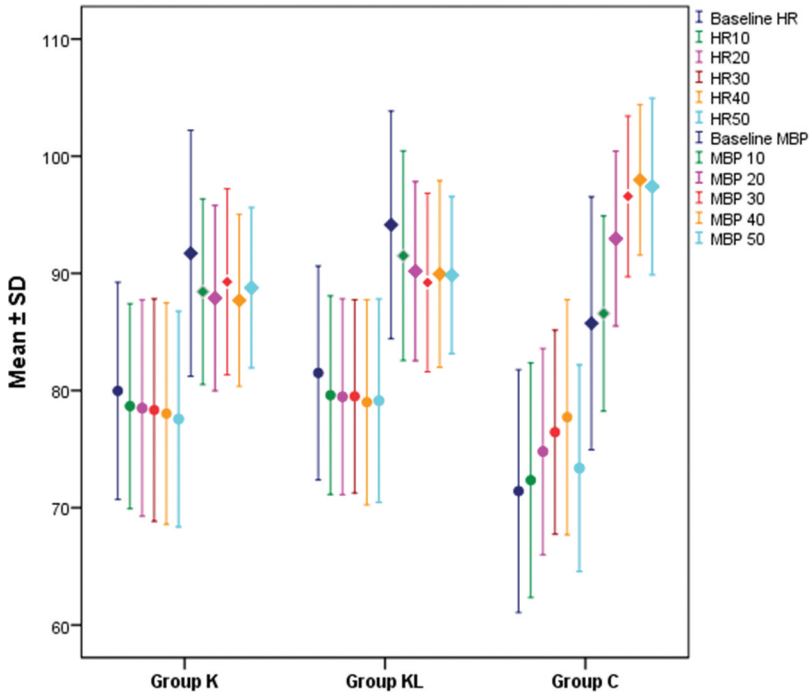

Figure 3. Comparison between the studied groups regarding the means of heart rate and mean blood pressure at different times intervals.

A comparison of the patients' satisfaction scores revealed better satisfaction in the KL than in the K groups (1.0 versus 2.0, $p < 0.001$). The surgeon satisfaction was comparable in the K and the KL groups with no significant difference, while the KL group showed significantly higher satisfaction in comparison to the control group (3.0 versus 2.5, $p = 0.003$). The documented adverse effects were subconjunctival hemorrhage, dizziness, and hypotension which were evenly distributed in the three groups ($p > 0.999$) (Table 4).

4. Discussion

This study explored the analgesic efficacy of both the preoperative IV ketorolac before LA administration and the combined ketorolac-local anesthetic injection for strabismus surgery in adults. The reduced postoperative pain was significantly more evident with ketorolac added to the LA mixture than when given IV 30 minutes before the LA injection during the first 2 hours after the surgery. After that, analgesia was comparable with no significant difference between either group. The potent analgesic effect of the added ketorolac to the LA mixture significantly delayed the need for postoperative rescue analgesic drugs with an observed longer time of analgesia in the ketorolac local group in comparison to the ketorolac group. Further, reflections made by the patients on the intraoperative pain experienced at the end of the surgery revealed less pain and better satisfaction scores in the ketorolac local group.

Previous research on patients premedicated with 60 mg ketorolac IV versus placebo who underwent a single-stage adjustable strabismus surgery under topical anesthesia showed significantly reduced intraoperative and postoperative pain. However, the patient satisfaction assessed by a five-point analogue scale was comparable in both groups [13].

The efficacy of IV Ketorolac administered at the induction of anesthesia in controlling perioperative pain with strabismus and vitreoretinal surgeries in pediatric patients has been previously reported [14,15]. Furthermore, the combination of ketorolac with LA exhibited better postoperative pain control in scleral buckling surgery than in LA alone [11].

In patients aged 12 years or older who underwent correction of squint under general inhalational anesthesia or local periocular lidocaine anesthesia, IV ketorolac given at the end of the surgery was more effective in diminishing postoperative pain than either oral acetaminophen or oral ibuprofen given 30–45 min after the surgery. Intravenous ketorolac attained pain relief earlier than the oral analgesic agents that were continued for 5 h after the surgery, with easier suture adjustment and shorter hospital stay [16].

The analgesic efficacy of ketorolac was proven to be equal to that of pethidine in children who underwent strabismus surgery. The pain was assessed by the validated objective pain score at 0 h, 1/2 h, and 1 h after arrival at the post anaesthesia care unit as well as the postoperative analgesic requirement was similar in ketorolac and pethidine groups [14]. As well, it has been reported that ketorolac reduced the morphine

Table 4. Comparison of the patient and surgical satisfaction and adverse effects between the studied groups.

			Group K N = 30	Group KL N = 30	Group C N = 30	P-value
Patient satisfaction	Median (IQR)		2.0 (1.0–2.0) [a]	1.0 (1.0–2.0) [c]	2.0 (1.0–2.0)	<0.001*
Surgeon satisfaction	Median (IQR)		3.0 (2.0–3.0)	3.0 (3.0–3.0) [c]	2.5 (2.0–3.0)	0.003*
Adverse effects	Dizziness	N	1	1	1	>0.999
		%	3.3	3.3	3.3	
	Hypotension	N	1	1	1	
		%	3.3	3.3	3.3	
	Subconjunctival hemorrhage	N	1	1	1	
		%	3.3	3.3	3.3	
	None	N	27	27	27	
		%	90.0	90.0	90.0	

IQR: interquartile range
*Significant at $p < 0.05$
[a]: Significant difference between group K and group KL [c]: significant difference between group KL and group C

doses when combined with them to treat postoperative pain in pediatric surgical patients with no significant increase in bleeding or nephrotoxicity [17]. As narcotics can cause extreme sedation and respiratory depression with delayed discharge, ketorolac is favored for the prevention and treatment of postoperative pain in strabismus patients.

In this study, during the first 2 hours after the surgery, patients in the ketorolac local group experienced less pain than those in the ketorolac group. After that, the analgesic effects of ketorolac were comparable with no significant differences between either group. Previous studies showed that the analgesic effect of ketorolac starts within 10 min, becomes effective 30 min after administration, and reaches its maximum effect at 2 h [15,18].

High quality ophthalmic anesthesia is an important component of the surgical procedure and has an important impact on the rate of surgical complications [19]. In the current study, ketorolac improved the anesthetic properties of the LA mixture. It significantly enhanced the onset of anesthesia and akinesia with a more prolonged duration of the block in comparison to the control group. The anesthetic efficacy of ketorolac was greater when added to the LA mixture than when given before the LA injection. However, the surgeon satisfaction scores were comparable in the K and the KL groups, with no significant difference. These findings are in line with Howaidy, Eldaly [5] who reported that the addition of ketorolac to the LA mixture in peribulbar anesthesia of patients who underwent cataract surgery showed a statistically significant reduction in the time of onset of globe anesthesia. However, ketorolac showed no significant effect on globe akinesia or the duration of motor block. Better anesthesia has been also experienced when ketorolac was combined with the LA in scleral buckling surgeries as reported by Chen, Liu [11].

In the present study, intraoperative monitoring of the vital signs at 10 minutes intervals revealed stable HR, blood pressure, and oxygen saturation where the observed alterations were minimal throughout the surgery. Furthermore, follow-up of the participants in our study for any adverse effects revealed subconjunctival hemorrhage, dizziness, and hypotension that were detected in 3 patients in each studied group with no significant differences. These complications were well treated with no adverse outcomes. Similarly, the combination of ketorolac with LA for pain control in retinal detachment surgery did not reveal any serious complications [11]. Being a nonsteroidal anti-inflammatory drug, ketorolac might be associated with side effects, such as nausea, vomiting, dyspepsia, inhibition of platelet aggregation, gastrointestinal hemorrhage, drowsiness, and headache [20]. These adverse effects are usually dose-dependent with increased risk at higher doses [21].

This was a well-designed randomized, controlled trial that compared two different regimens of ketorolac administration in adults scheduled for strabismus surgery. The study assessed both intraoperative and postoperative pain as well as the analgesic efficacy and safety of ketorolac. However, there were some limitations; the enrolled patients were from a single center and the trial was open-label.

5. Conclusions

During strabismus surgery in adults, the combination of ketorolac with LA mixture for the peribulbar block was effective in providing better anesthesia, reducing intraoperative and postoperative pain, and delaying the need for postoperative supplementary analgesics. Moreover, both IV preoperative ketorolac administration and its addition to the LA mixture were safe with minimally resolved adverse effects.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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