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Research article

Ketamine versus fentanyl as an adjuvant to local anesthetics in the peribulbar block for vitreoretinal surgeries: Randomized controlled study

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ABSTRACT

Background: The use of an adjuvant to local anesthetics in the peribulbar block may improve the block characteristics. This study aimed to evaluate the effect of the addition of either ketamine or fentanyl to local anesthetics in single injection peribulbar block on the quality of the block.

Methods: The study included ninety adult patients presented for vitreoretinal surgeries. Patients were randomly allocated into three groups. All patients received peribulbar block with a local anesthetic mixture composed of 4 ml lidocaine 2% containing hyaluronidase, and 5 ml of plain bupivacaine 0.5% with an addition of either 1 ml of normal saline, 30 μg fentanyl, or 25 mg ketamine in Control group, Fentanyl group, and Ketamine group respectively. The measurements included the onset and duration of both anesthesia and akinesia with evaluation of intraocular pressure, postoperative pain score and need of analgesics.

Results: As compared to control group, the use of either fentanyl or ketamine as local anesthetic adjuvant significantly fastened the onset of anesthesia (1.67 ± 1.21 min) (1.93 ± 1.36 min), prolonged the duration of lid akinesia (127.50 ± 22.20 min) (127.00 ± 22.19 min), increased the duration of globe akinesia (156.00 ± 28.02 min) (158.00 ± 31.18 min), minimized the time required to start surgery (6.57 ± 1.99 min) (6.57 ± 1.85 min), and increased the time for first request of postoperative analgesia (189.50 ± 34.92 min) (184.67 ± 35.37 min) ($P < .05$). However, neither fentanyl nor ketamine had a significant effect on the onset of lid or globe akinesia or the intraocular pressure ($P > .05$).

Conclusion: Fentanyl or ketamine can be used as a local anesthetic adjuvant in the peribulbar block in patients presented for vitreoretinal surgeries as both of them improved the quality of the block without increasing intraocular pressure.

1. Introduction

Regional anesthesia of the eye had gained greater popularity over general anesthesia in the ophthalmic surgeries as it becomes easier [1], associated with a lesser incidence of respiratory and hemodynamic depression, and associated with better postoperative analgesia [2]. Peribulbar block seems to be the best choice for ophthalmic surgeries [3]. The single injection peribulbar percutaneous block with the use of short needles was proved to be easy, simple, and less painful technique providing adequate analgesia and akinesia [4].

The use of regional anesthesia techniques for vitreoretinal surgeries seems to be difficult as they are longer surgeries with increased postoperative pain. Thus, prolongation of the duration of the peribulbar block through adding adjuvant to local anesthetics allows performing of vitreoretinal surgeries under regional anesthesia [5].

There are many available studies evaluating the addition of opioids especially fentanyl to the local anesthetics in many regional anesthetic techniques with an improvement of the quality of the block which may be due to binding to opioid receptors in the nerve ending [6]. Moreover, certain studies found that the use of dissociative intravenous anesthetic agent, Ketamine, as an adjuvant to local anesthetic drugs in certain regional anesthesia techniques improves the quality of block which was attributed to the abolishment of afferent noxious stimuli [7].

The main concern with the use of ketamine in ophthalmic anesthesia is its effect on the intraocular pressure [8]. Certain animal and human studies reported that ketamine use was associated with significant increase in the intraocular tension [9,10]. However, other studies suggested that ketamine has no or little effect on the intraocular pressure [11,12].

The aim of our study was to evaluate the effect of the use of fentanyl

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(30 μg) or ketamine (25 mg) as an adjuvant to a local anesthetic mixture in single injection peribulbar block for patients presented for vitreoretinal surgeries. Our primary outcome was the onset of globe akinesia, while, the secondary outcome was the duration of lid and globe akinesia.

2. Patients and methods

Firstly, The study was approved by the local ethics committee (Tanta Faculty of Medicine Research Ethics Committee 30472/08/2015) and registered on the Pan African Clinical Trial Registry with an identification number of PACTR201602001406377. This prospective, controlled, randomized, double-blinded study was carried out in The Ophthalmology Department of Tanta University Hospital on adult patients of both gender, aged from 45 up to 65 years, ASA class I or II, admitted for vitreoretinal surgeries. The study lasted for a duration of one year starting immediately after ethical committee approval (October 2015-October 2016). Patients were assessed preoperatively in the anesthesia clinic with an explanation of the purpose and the technique of the research, then an informed written consent was obtained from all patients. All the given data was kept in a secret manner and used for current medical research only. All the studied patients and participating investigators were blinded to the used mixture of local anesthetics through the whole duration of the study.

Patients were excluded from the study if they refused to participate in the study, were unconscious or uncooperative, had glaucoma or ocular infection, suffered from coagulopathy, or had a recent history of myocardial infarction or uncontrolled blood pressure. Patients were distributed randomly into three equal groups (30 patients each; Fig. 1) using Computer generated randomization in opaque sealed envelopes to allow every patient to select the envelope of his group.

Local anesthetic solutions were prepared by an anesthesiologist resident who wasn't participating in the research in similar syringes for the three studied groups, each syringe contain 10 ml solution composed of 4 ml of lidocaine 2% containing 75 IU of hyaluronidase, and 5 ml of plain bupivacaine 0.5%, and 1 ml of normal saline in ***Control group (C)***, and the solution composed of 30 ug fentanyl (1 ml), 4 ml of lidocaine 2% containing 75 IU of hyaluronidase, and 5 ml of plain bupivacaine 0.5% in ***Fentanyl group (F)***, While, the solution was composed of 25 mg ketamine (1 ml), 4 ml of lidocaine 2% containing 75 IU of hyaluronidase, and 5 ml of plain bupivacaine 0.5% in ***Ketamine group (K)***.

Once, the patients were admitted to the operating room, an intravenous access was established using 20 gauge venous cannula, then, patients were attached to monitor of three leads ECG, noninvasive blood pressure, and pulse oximetry. The peribulbar block was performed with the use of 25 gauge 16 mm bevel disposable needles for all blocks with a limitation of injection site by inferior lacrimal canaliculus superiorly, inferior orbital margin inferiorly, lateral nasal margin medially, an imaginary line from the inferior orbital margin and inferior lacrimal papilla laterally [13]. Injection of 10 ml of previously prepared solution over a period of 30 s was done which was followed by a transient fullness of the upper and lower eye lids. Careful closure of the eye, padding and intermittent compression with the use of Honan

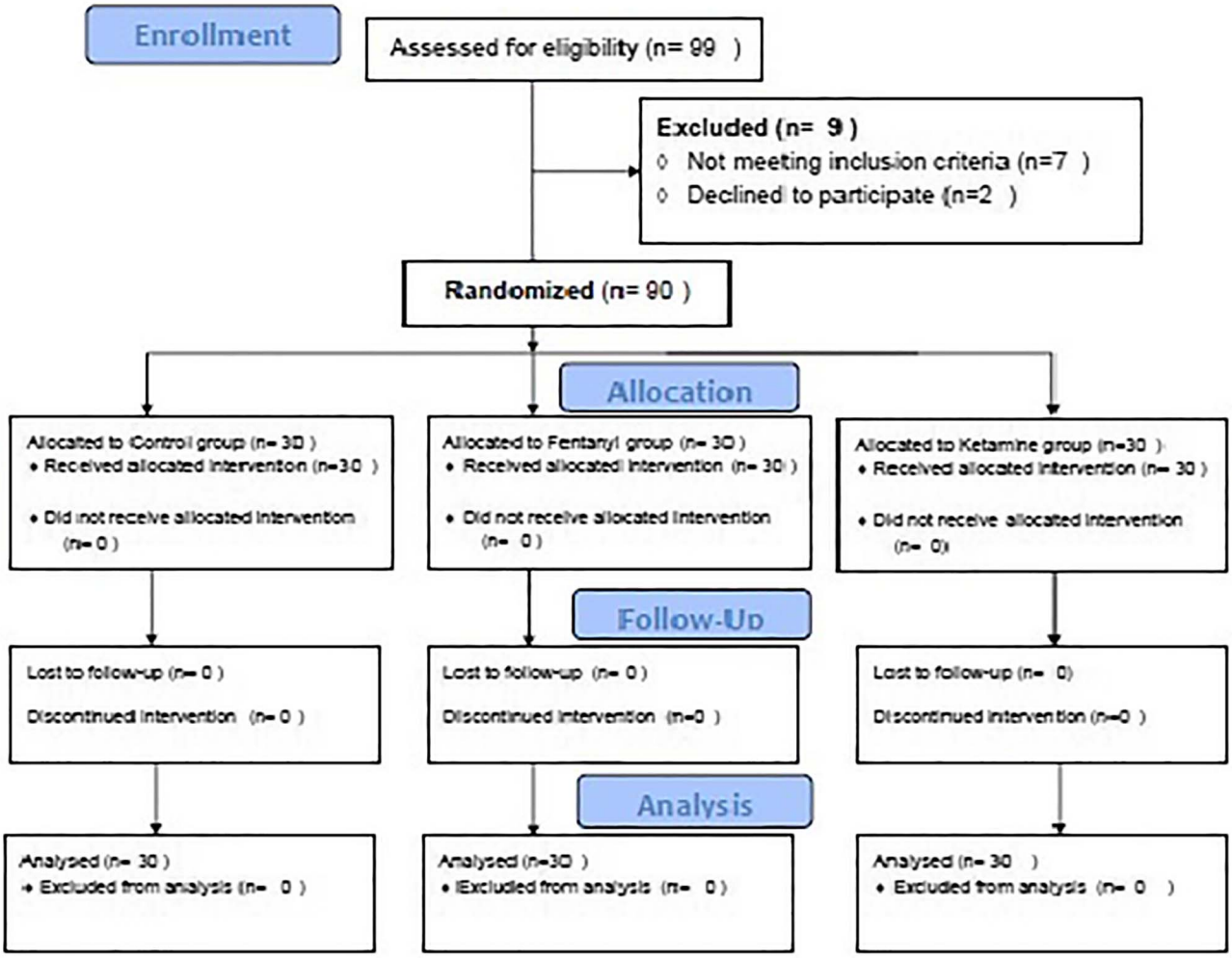

Fig. 1. CONSORT flow chart of the distribution of participating patients throughout each stage of the trial.

ball for 10 min to exert a pressure of 20 mmHg. The intermittent compression was relieved after 1 min, 3 min, 5 min, 7 min, 9 min, and 10 min from injection to assess the corneal anesthesia, lid and globe akinesia. Corneal anesthesia was assessed with evaluation of corneal reflex to the application of a piece of cotton. While the lid akinesia was evaluated by asking the patient to open and squeeze his eye. Moreover, globe akinesia was evaluated by detecting the ability of the patients move his eye globe in the four cardinal directions superior, inferior, nasal, and temporal. The onset of anesthesia was defined as time interval between performing the block and loss of corneal sensation, while, onset of lid akinesia was the elapsed time between the peribulbar injection and partial loss of lid movement, also, onset of globe akinesia was the time interval from initiating the injection and partial loss of globe movement (loss of globe movement into at least two directions).

A special akinesia score [14] was used to evaluate lid and globe akinesia composed of 3 point score, (where, 0 = inability to move, 1 = partial ability to move, 2 = complete ability to move) applied to lid akinesia and globe movement superiorly, inferiorly, nasally, and temporally with overall score of 10. The akinesia score was evaluated before the block, 1 min, 3 min, 5 min, 7 min, 9 min, and 10 min after the injection. The surgery was started when patients had anesthesia together with akinesia score less than 5. Time to start surgery was measured to be the elapsed time between the peribulbar injection and satisfying goals of the start of surgery. If the patient didn't fulfill the criteria to start surgery after 10 min of initiating the block, additional 4 ml of lidocaine 2% were injected while the patient was excluded from the study. Duration of lid akinesia and globe akinesia were calculated by the time interval between the peribulbar injection and the first regain of full lid and globe movements respectively. The intraocular pressure was measured before peribulbar injection, 1 min, 5 min and 10 min after peribulbar injection.

After completing the surgery, the Visual Analogue Scale (VAS) was assessed immediately, then after 1 h, 2 h, 4 h, 6, and 8 h. Any patient who had VAS ≥ 4 received rescue analgesia in the form of paracetamol 1000 mg intravenous infusion with recording the time for the first request for rescue analgesia. Patients who developed certain complications as pain on injection, nausea, vomiting or sedation were recorded. All the received measurements were obtained by an assistant nurse who wasn't participating in the study.

3. Statistical analysis of data

Calculation of sample size based on results of a previous similar study [15] revealed that at least 26 patients in each group were required to detect a significant difference of the onset of globe akinesia of one minute at α value of 0.05 and 90% power of the study. The statistical analysis was done by the use of SPSS. Parametric data was presented as mean, and standard deviation after analysis with One-way ANOVA test and post-hoc Turkey's HSD Test, while, categorical data was analyzed by Chi-square test and described as number and frequencies (%). The results were considered to be statistically significant when P value is less than 0.05.

4. Results

Ninety patients were enrolled into the three studied groups with a statistically insignificant difference as regards patient's characteristics that included age, gender, body weight, ASA class, the duration of surgery, or the side of surgery ($P > .05$) Table 1.

The onset of anesthesia was significantly faster in Fentanyl and Ketamine group compared to Control group ($P < .05$) with insignificant difference in the onset of anesthesia between Fentanyl and Ketamine group ($P > .05$) Despite that, the onset of lid or globe akinesia was comparable between the three studied groups ($P > .05$). The required time to start surgery was significantly shortened with the use of either fentanyl or ketamine as compared to Control group ($P < .05$), with indifference between Fentanyl group and Ketamin group ($P > .05$) Table 2.

Duration of lid and globe akinesia was significantly prolonged in the both Fentanyl and Ketamine groups compared to Control group ($P < .05$) with an insignificant difference between Fentanyl group and Ketamine group ($P > .05$) Table 2.

As regarding the degree of akinesia, which was evaluated by special akinesia score, there was a statistically insignificant difference between three groups before injection and one minute after performing peribulbar injection ($P > .05$). However, at the time intervals of 3 min, 5 min, 7 min, 9 min, and 10 min after the injection of local anesthetic mixture, there was statistically significant difference of values of akinesia score between Fentanyl and Ketamine groups as compared to Control group ($P < .05$), with an insignificant difference between Fentanyl group and Ketamine group ($P > .05$) Fig. 2.

The mean value of intraocular pressure was comparable in the three studied groups at baseline, 1 min, 5 min, and 10 min after injection ($P > .05$). The intraocular pressure was significantly increased in the three groups 1 min after injection as compared to baseline values ($P < .05$) Fig. 3.

The values of Visual Analogue Scale was comparable in the three groups immediately postoperative, and 1 h, 2 h, 4 h, and 8 h of the postoperative period ($P > .05$). But, 6 h postoperatively, there was a statistically significant decrease in VAS in Fentanyl and Ketamine groups in comparison to Control group ($P < .05$) with an insignificant difference between Fentanyl group and Ketamine group Fig. 4.

The time required for the first request of postoperative analgesia was significantly prolonged in both Fentanyl and Ketamine groups in comparison to control group ($P < .05$), with indifference between Fentanyl group and Ketamine group ($P > .05$) Table 2.

The incidence of sedation, nausea, vomiting or pain on injection was comparable in the three groups ($P > .05$). No severe or major complication was faced in all groups Table 1.

5. Discussion

Our results demonstrated that, adding either 30 μg fentanyl (3ug/ml), or 25 mg ketamine (2.5 mg/ml) to local anesthetic mixture in single injection peribulbar block for patients presented for surgeries in the posterior segment of the eye was associated with an improvement in the block quality as compared to control group. Both of them increased the onset of anesthesia and duration of lid and globe akinesia, decreased the time required to start surgery and the need for postoperative analgesics, and weren't associated with increased intraocular pressure.

The retrobulbar block is nowadays largely replaced by peribulbar block as they have the same anesthetic effect with a lower incidence of complication with the peribulbar block [16]. Vitreoretinal surgeries are more time-consuming surgeries that require adequate motor and sensory blockade, so, added drugs to the usually used local anesthetics may be needed in such conditions [17].

The mechanism of analgesic effect of fentanyl administrated through peripheral nerve block may be due to binding to the peripheral opioid receptors at the afferent fibers [18], or it may be due to binding to opiate receptors at dorsal root ganglion [19]. Another possible mechanism is the centrally mediated opioids, through the stimulation of central opioid receptors [20]. Certain opinions suggest that fentanyl exerts its local anesthetic effect through its direct action on peripheral nerves [21].

Ketamine, N-Methyl-D-Aspartate receptor antagonist have peripheral analgesic properties if used with regional anesthesia [22]. The exact mechanism of this analgesic effect isn't clear [23]. Ketamine may have sodium channel blocking effect that prevents initiation and propagation of action potential [24,25]. According to our best knowledge, few studies evaluating the addition of fentanyl or ketamine to a local anesthetic mixture in the peribulbar block are available.

Table 1
Patient's characteristics in the studied groups.

		Control group	Fentanyl group	Ketamine group	P value
Age (years)		55.03 ± 6.03	55.27 ± 6.06	55.17 ± 5.89	0.988
Gender	Male	17 (56.67%)	18 (60%)	16 (53.33%)	0.873
	Female	13 (43.33%)	12 (40%)	14 (46.67%)	
Body weight (kg)		82.43 ± 6.62	82.03 ± 5.98	82.13 ± 6.38	0.968
ASA Class	Class I	10 (33.33%)	11(36.67%)	10 (33.33%)	0.952
	Class II	20(66.67%)	19 (63.33%)	20 (66.67%)	
Duration of surgery (min)		57.83 ± 9.44	57.83 ± 8.88	56.33 ± 9.46	0.769
Site of surgery	Right	15 (50%)	16 (53.33%)	17 (56.67%)	0.874
	Left	15 (50%)	14 (46.67%)	13 (43.33)	
Complications	Sedation	0 (0%)	2 (6.67%)	4 (13.33)	0.117
	Pain on injection	4 (13.33%)	3 (10%)	5 (16.67%)	0.749
	Nausea&Vomiting	4 (13.33%)	5 (16.67%)	6(20%)	0.786

Data were presented as mean ± SD or patients number (%).

Table 2
Characteristic features of the peribulbar block in the studied groups.

	Control group	Fentanyl group	Ketamine group	P	P1	P2	P3
Onset of Anesthesia (min)	3.20 ± 1.91	1.67 ± 1.21	1.93 ± 1.36	< 0.001*	0.001*	0.005*	0.426
Onset of lid akinesia (min)	3.93 ± 1.94	3.20 ± 2.31	3.40 ± 2.25	0.40	0.188	0.33	0.735
Onset of globe akinesia (min)	4.866 ± 2.10	4.33 ± 2.31	5.00 ± 2.35	0.4826	0.352	0.817	0.272
Duration of lid akinesia (min)	109.50 ± 14.29	127.50 ± 22.20	127.00 ± 22.19	0.001*	< 0.001*	0.001*	0.93
Duration of globe akinesia (min)	140.00 ± 15.92	156.00 ± 28.02	158.00 ± 31.18	0.013*	0.009*	0.008*	0.821
Time required to start surgery (min)	7.77 ± 1.695	6.57 ± 1.99	6.57 ± 1.85	0.018*	0.014*	0.011*	0.99
Time for the first request for analgesia (min)	155.33 ± 18.93	189.50 ± 34.92	184.67 ± 35.37	< 0.001*	< 0.001*	< 0.001*	0.596

Data were presented as mean ± SD. P represented comparison between three groups. P1 represented comparison between C group and F group, while, P2 represented comparison between C group and K group, and, P3 represented comparison between F group and K group.

* The value was considered significant if P value is less than 0.05.

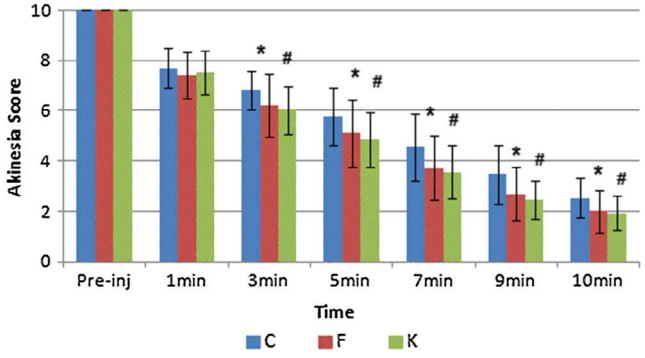

Fig. 2. Akinesia score in the studied groups. Pre-inj, before injection. * indicates statistically significant difference between control group and fentanyl group. # indicates statistically significant difference between control group and ketamine group.

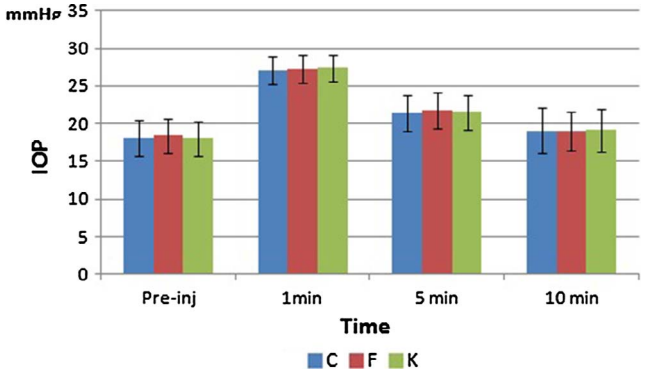

Fig. 3. Mean value of intraocular pressure in the three groups. Pre-inj, Before peribulbar injection.

In concordance with our results, Kamel et al. who evaluated the effect of addition of different doses of fentanyl to lidocaine in peribulbar block for cataract surgery and found that use of fentanyl as a local anesthetic additive in a concentration more than 2 μg/ml improve onset and duration of both sensory and motor block with improved patients satisfaction and postoperative analgesia without increasing incidence of side effects [15]. Also, Moustafa et al., who concluded that use of fentanyl 20 μg as an adjuvant to a mixture of mepivacaine and bupivacaine significantly prolong the duration of motor block and improve postoperative analgesia. But, their results detected that fentanyl addition was associated with a more rapid onset of akinesia than the control group which was against our results [26]. Moreover, Noyan who studied the use of ketamine in a dose of 2 mg/kg as an additive to articaine in axillary brachial plexus and concluded that ketamine shortened the onset and prolonged the duration of the block [7]. However, these effects may be due to systemic absorption of ketamine as the used dose was high.

In addition, Schnabel in a meta-analysis that involved thirteen randomized controlled studies (584 patients) reported that adding ketamine to a local anesthetic mixture in caudal block improved the quality of the block and postoperative analgesia without a significant increase in complications [27]. Moreover, Kulkarni suggested that adding ketamine to a mixture of lidocaine and bupivacaine in stellate ganglion block was safe and effective [28].

In contrast to our study, Lee et al. who concluded that adding 30 mg of ketamine to ropivacaine 0.5% in interscalene block didn't have any effect on the onset and duration of sensory and motor block [29].

For many years, ketamine was considered to be relatively contraindicated in ophthalmic anesthesia due to the potential hazard of increasing the intraocular pressure [8,10]. Certain studies suggested that,

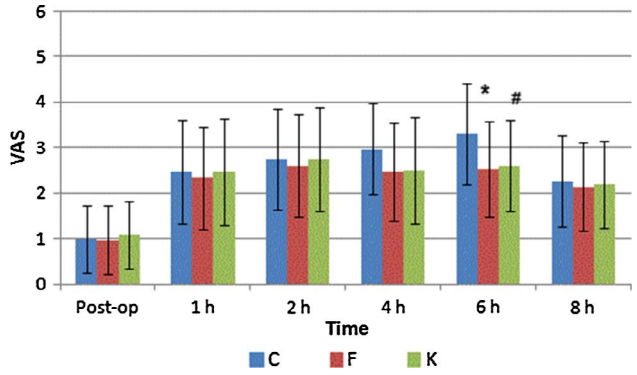

Fig. 4. Visual Analogue Score in the studied groups. Post-op, immediate postoperative. * indicates statistically significant difference between control group and fentanyl group. # indicates statistically significant difference between control group and ketamine group.

the use of a low dose of ketamine wasn't accompanied with increased intraocular pressure such as, Sarah et al. who evaluated the effect use of the use of ketamine as sedative on the intraocular tension in pediatric population and concluded that ketamine wasn't associated with increase in intraocular pressure [30]. Moreover, Nagdeve et al. who revealed that the use of low dose of ketamine for anesthetizing pediatric patients had no effect on the intraocular pressure [12]. Also, Frey et al. found that the use of ketamine as a sedative agent in patients receiving retrobulbar anesthesia didn't increase or decrease intraocular pressure [31].

6. Limitation of study

The available controlled randomized studies evaluating the effect of adding fentanyl or ketamine to local anesthetic mixtures are few studies especially studies evaluating ketamine as an adjuvant to local anesthetics in peripheral nerve block. Moreover, the study was carried on a limited number of patients.

7. Conclusion

Use of either fentanyl (3 μg/ml) or ketamine (2.5 mg/ml) as an additive to a local anesthetic mixture containing hyaluronidase in single injection peribulbar block in patients presented for vitreoretinal surgeries is beneficial in improving onset, duration, and quality of the block with decreased postoperative requirements of analgesics. Also, their use wasn't associated with significant increase in certain complication as increased intraocular tension.

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Conflict of interest

No conflict of interest.

Authors contribution

(1) Sameh Abdelkhalik Ahmed make substantial contributions to the study design, collection of the data, analysis and interpretation of the data, and final revision and submission.
(2) Mohamad Gamal Elmawy participated in collection of the data, drafting, and revising the article. Also, he gave final approval to the final format of the article.
(3) Mohammed Awd participated in design of the study, analysis of the data, and final revision of the article.

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