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Research Article

Clonidine versus fentanyl as adjuvants to bupivacaine in peribulbar anesthesia

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KEYWORDS

Clonidine;
Fentanyl;
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Abstract *Background:* Peribulbar anesthesia is widely practiced as a safe local block for cataract eye surgeries. Fentanyl has been used as an adjuvant to local anesthetics, prolonging their duration of action. Clonidine has been shown to increase the duration of analgesia and anesthesia produced by local anesthetics.

Aim of the study: The aim of this study was to compare the effect of fentanyl versus that of clonidine when used as adjuvants to bupivacaine in peribulbar block.

Methodology: Ninety patients, ASA physical status I–III, scheduled for cataract operations, under peribulbar block, were enrolled in the study and randomly assigned into 3 equal groups. Group F ($n = 30$) received a mixture of bupivacaine, hyaluronidase, and fentanyl; Group C ($n = 30$) received a mixture of bupivacaine, hyaluronidase, and clonidine; and in the control Group B ($n = 30$), a mixture of bupivacaine, hyaluronidase, and saline was used for peribulbar block. The onset, duration of globe anesthesia, akinesia, and lid akinesia were recorded. Intraoperative and postoperative patient comfort, first time to analgesic request, and any recorded complications due to drugs used were all assessed.

Results: Groups C and F showed significantly faster onset and longer duration of globe anesthesia, akinesia, lid akinesia, and the time to first analgesic request when compared to Group B ($p < 0.001$). The onset, of lid akinesia was significantly faster in Group C compared to Group B ($p < 0.01$). Group C showed a significantly longer duration of lid akinesia and globe akinesia compared to Group F ($p < 0.01$).

Conclusion: The addition of either clonidine or fentanyl to the local anesthetic during peribulbar block results in a faster onset and longer duration of the block with a longer period of postoperative analgesia. The addition of clonidine was found to prolong the duration of the block more than fentanyl.

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1. Introduction

Regional anesthesia has gained wider popularity over general anesthesia, especially in different ophthalmic surgeries [1,2]. The majority of patients undergoing ophthalmic surgeries are elderly, with multiple chronic diseases, which makes them at increased risk of morbidity and mortality under general anesthesia [3]. Different eye blocks have been practiced with great success. Peribulbar anesthesia is widely practiced now as a safe local block for cataract eye surgeries. However, the limited duration of these blocks was shown to be the main problem encountered intraoperatively. Therefore, additional top-up doses are usually needed to continue the operation. Many researches tried to introduce solutions in order to prolong the duration of the local anesthetics used. Several drugs were added as adjuvants to local anesthetics, and their effects have been studied [4–7]. Fentanyl is a narcotic that has been successfully used as an adjuvant to local anesthetics, prolonging its action with better analgesia and anesthesia [8]. Likewise, clonidine, an alpha 2 agonist was shown to increase the duration of analgesia and anesthesia when used as an adjuvant to local anesthetics [9–11]. Several studies found that the best dose for clonidine as an adjuvant to local anesthetics was 1 μg/kg. This concentration was shown to produce desirable effects without systemic complications [12]. Adding hyaluronidase to the local anesthetic proved to be of help in spreading the injected mixtures, thus accelerating the onset time as well as improving the quality of the block [13].

We hypothesized that the addition of either fentanyl or clonidine will affect the quality of the peribulbar block, prolonging its anesthetic and analgesic duration. This will later help in providing adequate anesthesia, analgesia, and comfort during lengthy ophthalmic operations. The aim of this study was to compare the effect of the addition of fentanyl versus the addition of clonidine to bupivacaine, when used as adjuvants to local anesthetics in peribulbar block.

2. Methods

The study was conducted in Kasr Al-Ainy teaching hospital, Cairo University from December 2012 to May 2013. After getting approval from the local ethical committee and taking patients' written consents, 90 patients, scheduled for elective cataract operations under peribulbar block, were enrolled in the study. Patients aged 40–60 years, ASA physical status I–III, with no history of anticoagulant therapy or allergy to local anesthetics, and with axial length <28 mm were included in the study. Exclusion criteria were as follows: patient refusal, cardiac patients on anticoagulants, international normalized ratio (INR) >1.5, recent myocardial infarction, uncontrolled hypertension, disturbed conscious level, mentally retarded patients, active respiratory disease, morbidly obese patients, chronic clonidine or analgesic therapy, failure of proper communication in deafness diseases, patients with excessive tremors or agitations, impaired orbital/periorbital sensations, and patients with glaucoma. The patients were randomly assigned into 3 equal groups; Group B, Group F, and Group C by computer generated lists and then concealed in closed envelopes. In the control Group B ($n = 30$) the peribulbar block was performed using a mixture of 8 ml bupivacaine 0.5%, 1 ml hyaluronidase (75 IU), and 1 ml of normal saline. Group F ($n = 30$) received a mixture of 8 ml bupivacaine 0.5%, 1 ml hyaluronidase (75 IU), and 20 μg fentanyl diluted in 1 ml normal saline. Group C ($n = 30$) received a mixture of 8 ml bupivacaine 0.5%, 1 ml hyaluronidase (75 IU), and 1 μg/kg clonidine diluted in 1 ml normal saline. The total volume of the mixture was amounting to 10 ml in each group. Both the patient and the anesthetist were blind to the drug mixture used. Preoperative assessments and details of the anesthetic technique were explained to the patients at the preoperative visit.

At the operating room, the patient was fully monitored, by electrocardiogram (ECG), pulse oximetry, and intermittent non-invasive blood pressure. Preoperative hemodynamic data were recorded. Midazolam 0.02 mg/kg was injected intravenously to the patient to provide conscious sedation while performing the block. The specified eye was sterilized with antiseptic solution. The patient was asked to fix his eyes looking straight forward toward the ceiling while lying in a supine position. A 10 ml syringe with a 25G needle was used for the local anesthetic injection. The Peribulbar block was performed by inserting the needle at the junction between lateral third and medial two thirds of the inferior eyelid (inferior orbital notch). With the sharp bevel facing the globe, the needle was inserted along the inferior orbital wall 20 mm deep, in a perpendicular direction to the frontal plane. After negative aspiration, 4–6 ml of local anesthetic solution was injected slowly until the appearance of proptosis and lid fullness. This was followed by gentle digital massage to the eyeball to facilitate diffusion of the local anesthetic mixture.

The onset of the sensory and motor block was assessed using the following measurements: **The ocular sensations** (globe anesthesia, was recorded from the time of injection of the local anesthetic solution until complete disappearance of sensation) were assessed by gentle sensory touch to the conjunctiva with a cotton swab. The onset of the sensory block was confirmed by the disappearance of sensation. ***The onset of motor block*** was confirmed by testing the ability to move the ocular muscles (*globe akinesia*) and lid muscles (*lid akinesia*). ***Globe akinesia*** was assessed by scoring the ocular movements in each direction of gaze (superior, inferior, medial, and lateral), using a 3 point scale [14,15]. Scores ranged from (0 to 2) in each direction, where 0 = total akinesia (no movement), 1 = partial akinesia (reduced movement), and 2 = no akinesia (normal movement) with total score of the four directions ranging from (0 to 8). The onset of globe akinesia was recorded from the time of injection of local anesthetic solution until complete globe akinesia (score 0). ***Lid akinesia*** was assessed by informing the patient to open both eye lids widely followed by squeezing them maximally. The onset of lid akinesia was defined as the time elapsing from injection of local anesthetic solution until complete lid akinesia (complete lid paralysis). If the total ocular movement score was $\geqslant 6$ or there was full movement in any direction, reflecting incomplete block after 10 min from injection, extra 2–3 ml from the same mixture was reinjected via the same approach. The maximum allowed volume of local anesthetic solution injected was 8 ml. However, if more than 8 ml was required the patient was excluded from the study. After satisfactory sensory and motor block, oxygen 4 L/min was delivered through a nasal cannula to the patient. Surgery was then allowed to proceed. The duration of the lid akinesia was recorded, from the time of injection of the anesthetic mixture till full recurrence of lid movement when was tested as before. The duration of globe akinesia was recorded, measuring

it from the time of injection of the anesthetic mixture till recurrence of muscle movements (score 8). The return of sensation to the globe was assessed by cotton swab test as mentioned previously. Intraoperative and postoperative patient comfort were assessed using 2 scale simple questionnaire (1 = comfortable, 0 = uncomfortable). Pain was assessed at 30 min intervals by verbal rating scale (VRS) on a scale of 0–10 (where 0 no pain, and 10 worst imaginable pain) for a period of 6 h postoperatively or until first analgesic request. An analgesic (Panadol Extra oral tablet, paracetamol ph.Eur. 500 mg and caffeine ph.Eur. 65 mg, GalaxoSmithKline, Dungarvan Ltd., Ireland) was given if the VRS $\geqslant 5$ [16–18]. The time to first analgesic request, which was defined as the time interval measured from injection of local anesthetic to first analgesic intake, was recorded. Lastly, any local or systemic complications, namely hematoma, diplopia, blindness, nausea, vomiting, dry mouth, dizziness, and hypotension, were recorded.

3. Statistical analysis

The primary outcome variable was total anesthesia duration. Previous study indicated that mean (SD) of peribulbar analgesia using Bupivacaine was 188 (35) min [19]. At alpha 0.05, we calculated that 20 patients per group would provide 90% power to detect a 20% increase in the treatment groups. However to allow for the comparisons between the control group and each treatment group, an adjusted p (Bonferroni correction) of 0.025 was considered significant for the primary outcome and the required sample size increased to 24 per group. To compensate for possible drop out 30 patients per group were included. Data were collected and analyzed using SPSS [19]. Ordinal data are expressed as Mean ± SD. Intergroup comparison of ordinal data was made by one-way analysis of variance (ANOVA) followed by Duke Test. Categorical data were compared together using Chi square Test, and expressed as frequencies (%). $p < 0.05$ was considered statistically significant.

4. Results

Ninety patients were enrolled in the study. They were divided randomly by closed envelopes into 3 equal groups, Group B, Group F, and Group C. The demographic characteristics, axial length, duration of surgery, and volumes injected are shown in Table 1. There were no statistical significant differences between the 3 groups in any of the recorded demographic data.

The onset of globe anesthesia showed high statistically significant difference between groups when Group F and Group C were compared to Group B ($p < 0.001$) (Table 2).

The mean onset of lid akinesia showed a statistically significant difference between Group B and Group C ($p = 0.002$) (Table 2).

Regarding the onset, duration of globe akinesia and duration of lid akinesia, there was highly statistical significant difference between studied groups ($p < 0.001$) (Table 2). Group C showed the longer duration of lid akinesia than Group F, with a statistically significant difference between both groups ($p < 0.01$).

As to the duration of globe akinesia, there was highly statistically significant difference between studied groups ($p < 0.001$), when Group F and Group C were compared to the control Group B. Furthermore, there was statistical significant difference between Group C and Group F ($p < 0.01$).

Referring to the time to first analgesic request, there was high statistical significant difference between studied groups when Group C and Group F were compared to the control Group B ($p < 0.001$). The time to first analgesic request was also significantly longer in Group C than Group F ($p < 0.01$). Nineteen (63%) patients in Group B, 22(73%) patients in Group F, and 24(80%) patients in Group C were comfortable during operation. Postoperatively, 17(56%) patients in Group B, 21(70%) patients in Group F, and 23(76.7%) patients in Group C were comfortable; with no statistical significant difference between groups. None of the cases had any local or systemic complications. The onset, duration of lid akinesia, globe anesthesia and akinesia, time to first analgesic request, and comfort sensation studied results are presented in Table 2.

5. Discussion

The use of different drugs as adjuvants to local anesthetics is widely practiced nowadays aiming to prolong their duration of action. Fentanyl, a synthetic opioid which proved its efficacy when added to bupivacaine, was also shown to have a local anesthetic action [20–22]. The effect of fentanyl could be mediated through a direct action on the peripheral opioid receptors, in the primary afferent tissues (dorsal roots), [20] or through centrally mediated opioid receptor analgesia after being uptake into the systemic circulation [21]. The addition of opioids to local anesthetics showed a synergistic interaction in many previous studies [23,24]. Clonidine, an alpha 2 agonist with analgesic, and sedative properties was used as an adjuvant to prolong the analgesic duration of local anesthetics in different regional blocks [25–28]. This action was produced by blocking conduction of C fibers and increasing potassium conductance in specific neurons [29–32].

In the present study, although Group F showed high statistical significant difference regarding the onset of globe anesthesia and akinesia, Group C results were more accelerated with 1.8 ± 0.57, 3.3 ± 0.69 min respectively showing high statistical significant difference between groups. The onset of lid akinesia was accelerated in Group C more than Group F. However, that difference was minimal and non-significant. In consistence with our results, Kasaba et al. [33] found that the addition of fentanyl to mepivacaine accelerates the onset of analgesia and improves the analgesic effect of the epidural block. In contrast, other studies regarding several regional blocks, showed different results in the onset time, quality of block, and incidence of side effects [25,27]. On the contrary to our findings, the study done by Connelly et al. [32] had shown no significant effect between studied groups on the onset of akinesia and sedation. Studying the duration of anesthesia within the three groups revealed that the longest duration of action in globe anesthesia, akinesia, and lid akinesia was also seen in Group C (79.5 ± 5.46 min; 269.7 ± 7.06 min; 200.2 ± 4.63 min respectively) showing high statistical significant difference between groups. However, there was no significant difference between Group C and Group F regarding the duration of globe anesthesia. Group F also showed better results than Group B regarding duration of the block (lid akinesia, globe akinesia, and anesthesia), and these results were highly statistically significant as well. In consistence with our findings, the study presented by Karakaya et al. [34] showed

Table 1 Demographic Characteristics.

	Group B (n = 30)	Group F (n = 30)	Group C (n = 30)
Age_{years}	55.1 ± 5.75	54.8 ± 6.47	54.1 ± 6.21
Sex			
M(%)	13(43.3%)	19 (63.3%)	12 (40%)
F(%)	17(57.7%)	11(36.7%)	18 (60%)
$Weight_{kg}$	74.8 ± 8.41	77.5 ± 7.65	79.4 ± 7.81
Axial $length_{mm}$	23.9 ± 1.35	24.6 ± 1.37	24.8 ± 1.11
Duration of $surg_{min}$	56.2 ± 9.83	59.1 ± 10.6	56.2 ± 9.64
Volume of LA_{ml}	5.3 ± 0.80	5.1 ± 0.86	5.5 ± 0.94

Ordinal data are expressed as Mean ± SD, nominal data are expressed as frequencies (%), $p < 0.05$ is considered significant. All shown data were not significant.

Table 2 Studied Data Between Different Groups.

	Group B (n = 30)	Group F (n = 30)	Group C (n = 30)
Onset (min)			
Globe anesthesia	2.6 ± 0.92**	1.9 ± 0.76**	1.8 ± 0.57**
Lid akinesia	3.2 ± 0.85*	2.8 ± 0.76	2.5 ± 0.82*
Globe akinesia	5.2 ± 0.92**	3.5 ± 0.81**	3.3 ± 0.69**
Duration (min)			
Globe anesthesia	66.2 ± 5.97**	78.8 ± 4.85**	79.5 ± 5.46**
Lid akinesia	114.7 ± 7.76**	179.6 ± 5.71** ***	200.2 ± 4.63** ***
Globe akinesia	144.7 ± 7.76**	244.7 ± 13.83** ***	269.7 ± 7.06** ***
Time to first analg			
Min	168.6 ± 16.34**	262.6 ± 9.71** ***	298.3 ± 11.16** ***
Comfort *n*(%)			
Intraoperative	19(63%)	22(73%)	24(80%)
Postoperative	17(56%)	21(70%)	23(76.7%)

Ordinal data are expressed as Mean ± SD, nominal data are expressed as frequencies (%), p is considered significant if $p < 0.05$.
* $p < 0.01$ when Group F and Group C were compared to Group B.
** $p < 0.001$ when Group F and Group C were compared to Group B.
*** $p < 0.01$ when Group C and Group F were compared together.

that the addition of fentanyl to bupivacaine in axillary block prolongs the duration of both anesthesia and analgesia.

Several published studies concluded that the addition of fentanyl in a dose response concentration prolongs the anesthetic and analgesic effects of the local anesthetic [35–37]. In our study, the time to first analgesic request was also prolonged in Group C more than Group F and Group B. The time to first analgesic request was also increased significantly in Group F. These results are similar to the results of Constant et al. [38], Varkel et al. [39], Abo EL Enin et al. [40], and Abd El-Hamid [41]. In accordance with our study, Gupta and Gurunadh [42] found that the duration of lid akinesia, globe akinesia and anesthesia were considerably increased with peribulbar anesthesia when using a mixture of clonidine and local anesthetics. In a dose-response study, many authors found that the addition of clonidine with local anesthetic results in prolongation of anesthesia and analgesia relative to the dose of the drug given. Sedation was recorded in patients receiving higher doses of clonidine [12,26,43]. Mjahed et al. [25] reported a significant increase in duration of analgesia and akinesia when clonidine was mixed with 2% lidocaine for retro bulbar block. The decrease in onset time was seen due to local and central direct action of Clonidine on the nerves. Madan et al. [12] found that, in the clonidine group, the duration of akinesia and magnitude of globe anesthesia were significantly increased, with the decrease in pain scores and analgesic requirements. These findings support our work. None of the patient showed any systemic or local complications related to the use of the adjuvant drugs. Similarly, studies by Bharti et al. [44], and Förster and Rosenberg [45] also showed no significant hemodynamic, respiratory, or sedative side effects between the studied groups. A limitation to our study was the limited sample size in each group. Further investigations are needed on a wider population sample in order to concur our results, to confirm their safety, and to support the absence of systemic complications. More researches may be suggested using different local anesthetics and different doses of clonidine and fentanyl to confirm our data.

6. Conclusion

Clonidine and fentanyl, when used as adjuvants to bupivacaine in peribulbar block, were shown to significantly accelerate the onset and prolong the duration of lid akinesia, globe anesthesia and akinesia, which leads to a prolonged time till first postoperative analgesic request and better patient comfort. The effect of clonidine on prolonging the duration of the block was significantly more than the effect of fentanyl.

Conflict of interest

No conflict of interest.

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