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Research Article

Ultra-low-dose naloxone added to fentanyl and lidocaine for peribulbar anesthesia: A randomized controlled trial

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KEYWORDS

Ultra-low-dose naloxone;
Fentanyl;
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Abstract *Purpose:* Purpose was to evaluate the quality of the block and the duration of postoperative analgesia when ultra-low-dose of naloxone added to fentanyl and lidocaine for peribulbar anesthesia.

Methods: Sixty adult patients of both sexes, ASA I and II scheduled for open globe cataract surgery in the Ophthalmology Department Tanta University Hospital were included in this randomized prospective clinical trial.

The patients were randomized into 2 groups (30 patients each). Group I: patients received 50 μg fentanyl and lidocaine 2% with hyaluronidase 15 IU/ml. Group II: patients received 100 ηg naloxone, 50 μg fentanyl and lidocaine 2% with hyaluronidase 15 IU/ml.

Total akinesia was scored every 2 min till the best akinesia score. Onset, best akinesia score, total injected volume, number of patients needed supplemental injection, time of first request for analgesia and, any complication were recorded. Pain was assessed during and after surgery at 30, 60, 90 min, 2, 3, 4, 6 and 8 h postoperatively, using Visual Analogue Score; 0 = no pain, to 10 = maximum pain.

Results: The time to first rescue analgesic was significantly longer in group II (7.73 ± 0.98) than group I (4.30 ± 0.47). The IOP was increased significantly at 2 min post-injection then, it became insignificant at 10 min postinjection compared to the preinjection values in both groups. There were few minor complications with no significant difference between groups.

Conclusion: Addition of ultra-low-dose naloxone to fentanyl and lidocaine for peribulbar anesthesia prolongs the duration of postoperative analgesia without increasing the adverse effects.

1. Introduction

When fentanyl was used as adjuvant to local anesthetic, it improved the quality of block and prolonged the duration of postoperative analgesia, without increasing the side effects. It

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was used through intrathecal [1], and epidural [2] routes. It was also used as adjuvant to local anesthetic for peripheral nerve blocks; e.g. axillary brachial plexus block [3,4], cervical plexus block [5], Intravenous regional anesthesia [6], infra-orbital nerve block [7], and in intra-articular injection after knee arthroplasty [8]. It has been reported that opioid receptors are expressed by central and peripheral neurons especially within injured tissues and can attenuate the excitability of primary afferent neurons and lead to anti-nociceptive effects [9].

Peribulbar block is easier, safer, and less painful but, has a higher failure rate, and a longer onset time compared with retrobulbar block, unless the onset is accelerated with the use of adjuvants [10,11]. Fentanyl as adjuvant to lidocaine is safe and effective in improving postoperative analgesia of peribulbar anesthesia [12–14]. However, its analgesia is of short duration.

Ultra-low-dose (pg–ηg/kg) of naloxone combined with opioid agonists can improve their analgesic efficacy [15] via blocking the excitatory opioid receptor pathway and enhancing opioid analgesia [3,16,17] but not used before with fentanyl as adjuvants to the local anesthetic in peribulbar anesthesia. So, the aim of the present study was to evaluate the effect of addition of ultra-low-dose of naloxone to fentanyl and lidocaine for peribulbar anesthesia on the quality of the block and the duration of postoperative analgesia.

2. Patients and methods

After obtaining an institutional board approval and written informed consent from the patient or his closest relative 60 adult patients of both sexes, ASA I and II scheduled for open globe cataract surgery in the Ophthalmology Department Tanta University Hospital were included in this randomized double blind prospective clinical trial.

Exclusion criteria included clotting abnormalities and patients on anticoagulant therapy, impaired mental status, patients with communication difficulties, uncontrolled movements or tremors e.g. Parkinsonism, inability to lie flat, one eyed patients, uncontrolled glaucoma, recent surgical procedure on the same eye, high myopia, with axial length $\geqslant$26 mm as detected by ultrasonography, and allergy to hyaluronidase or local anesthetics.

The trial is registered in the Australian New Zealand Clinical Trials Registry: ACTRN12614000545662.

The primary end point was the duration of analgesia as indicated by the first time for rescue analgesic (measured from the time of onset to the first time of feeling of moderate or severe pain). For each group 26 patients were required for naloxone to increase the mean value of the first time for rescue analgesic by 20% [30 min (0.5 h)] based on a previous pilot study in our institute with 90% power (α = 0.05%) and standard deviation (SD) of 0.55. We used 30 patients in each group for more accurate statistical analysis. The patients were randomized using a computer generated random numbers and closed envelops into 2 groups (30 patients each) to undergo peribulbar anesthesia. Group I (fentanyl group): each patient received 50 μg fentanyl and lidocaine 2% with hyaluronidase 15 IU/ml. Group II (fentanyl-naloxone group): each patient received 100 ηg naloxone, 50 μg fentanyl and lidocaine 2% with hyaluronidase 15 IU/ml.

Preoperatively, no premedication was given and, intravenous cannula was inserted. The patients were monitored continuously for ECG, heart rate, pulse oximetry. Arterial blood pressure (ABP) was measured non-invasively every 5 min. Topical local anesthetic (benoxinate hydrochloride) was applied to the eye then, with the eye in the primary gaze position, a 25-gauge short bevel needle was inserted trans-conjunctivally at the junction between the medial two thirds and lateral third of the inferior orbital rim in a strictly posterior direction. Depth of needle insertion was limited to 25 mm. The anesthetic mixture was injected after aspiration test and, the injection was continued until subconjunctival edema and lid fullness appeared. Intermittent digital compression was applied to lower the intraocular pressure until sufficient motor block occurred.

Akinesia (immobility) of the globe and eye lids was scored every 2 min till the best akinesia score. We used an 18-point scale, which was the sum of six sub-scores for the four rectus muscles, levator palpebrae and orbicularis oculi from 0 to 3 (0 = no block, 1 = partial akinesia not sufficient for surgery, 2 = partial akinesia sufficient for surgery, 3 = complete akinesia) [18].

The best akinesia score: was the highest akinesia score obtained for each block without or before supplemental injection. The total volume of local anesthetic injected, number of patients who needed supplemental injection, time of onset, time of first request for rescue analgesic (time from the onset of block to first time of moderate or severe pain) and, occurrence of any complication (e.g. pain on injection, chemosis, diplopia, bradycardia, hypotension, nausea, vomiting, etc) were recorded. If after 10 min akinesia was insufficient 4 ml of the same solution was re-injected.

Pain was assessed during and after surgery at 30, 60, 90 min, 2, 3, 4, 6 and 8 h postoperatively, using Visual Analogue Score (VAS). 0 = no pain, to 10 = maximum pain, 1–3 = mild pain, 4–6 = moderate pain, >6 = severe pain. Patients with moderate or severe pain received diclofenac sodium 75 mg intramuscular injection. The intraocular pressure (mmHg) was measured before, 2 and 10 min after injection of local anesthetic mixture.

The data were analyzed using SPSS (version 20), quantitative data were expressed as mean ± SD (for age, weight, duration of surgery, onset, IOP, total akinesia score, best akinesia score, total injected volume and first time for rescue analgesic) and analyzed using independent-*t*-test for comparison between the two groups. F test was used for comparison of IOP within the same group and Tukey's test is used as post hoc test. The VAS (did not follow the normal distribution was expressed as median (range) and Mann–Whitney *U* test was used for comparison between the two groups. While, the sex, number of patients who needed supplemental injection, and complica-

Table 1 Patient characteristics and duration of surgery in the studied groups.

	Group I (n = 30)	Group II (n = 30)	P value
Age (years)	57.8 ± 5.72	59.30 ± 4.81	0.276
Sex (male:female)	16:14	15:15	
Weight (kg)	74.27 ± 6.88	72.20 ± 6.21	0.227
Duration of surgery (min)	51.93 ± 3.81	53.80 ± 3.89	0.065

Data expressed as mean ± SD.

Table 2 Quality of block in the studied groups.

Group	Group I (n = 30)	Group II (n = 30)	P value
Total injected volume (ml)	8.47 ± 1.33	9.00 ± 1.95	0.221
Onset (min)	8.40 ± 2.84	8.13 ± 2.47	0.699
Best akinesia score	15.83 ± 3.04	16.67 ± 2.60	0.259
Patients needed supplemental injection (n%)	5 (16.6%)	4 (13.3%)	
Time to first rescue analgesic (h)	4.30 ± 0.47	7.73 ± 0.98*	<0.001

Data expressed as mean ± standard deviation (SD).
* Significant at $P < 0.05$.

tions were expressed as (number %). $P < 0.05$ was considered statistically significant.

3. Results

The two groups were comparable for the patient characteristics; age, sex, weight, and duration of surgery ($p > 0.05$) Table 1. As regards the quality of block; there was no significant difference between the two groups regarding the total injected volume (ml) ($p = 0.221$), onset (minutes) ($p = 0.699$), best akinesia score ($p = 0.259$), and number of patients needed supplemental injection (n%). No patient experienced pain during surgery. The time to first rescue analgesic (hours) was significantly longer in group II (7.73 ± 0.98) than group I (4.30 ± 0.47) ($P < 0.001$); Table 2. No significant difference was found between the two groups regarding the total akinesia score at 2, 4, 6, 8 and 10 min postinjection (the p value was 0.102, 0.515, 0.468, 0.455 and 0.259, respectively) Table 3. The IOP was increased significantly at 2 min postinjection compared to the preinjection values in both groups. While, there was a significant decrease in the IOP 10 min compared to 2 min postinjection in the two groups Table 4. The VAS was significantly lower at 60, 90 min, 2 and 3 h, then increased significantly at 6 h postoperatively in group II compared to group I ($P = 0.003$, 0.002, <0.001, <0.001 and <0.001, respectively; Fig. 1. As regards the complications; 1 patient (3.33%) in group I, and 2 patients (6.67%) in group II had chemosis, while 3 patients (10%) in group I, and 2 (6.67%) patients in group II had pain on injection. No diplopia, post-operative squint, globe perforation, or penetration occurred in any patient of the studied groups.

Table 3 Total akinesia score in the studied groups.

	Group I (n = 30)	Group II (n = 30)	P value
Total akinesia at 2 min	4.13 ± 0.94	4.60 ± 1.22	0.102
Total akinesia at 4 min	8.80 ± 2.17	9.17 ± 2.17	0.515
Total akinesia at 6 min	13.73 ± 3.03	13.17 ± 2.98	0.468
Total akinesia at 8 min	15.70 ± 3.16	16.30 ± 3.01	0.455
Total akinesia at 10 min	15.83 ± 3.04	16.67 ± 2.60	0.259

Data expressed as mean ± standard deviation (SD).

4. Discussion

In the present study there was a significant prolongation of the time to first request for analgesic in the naloxone group. This can be explained by the study of Crain and Shen, who demonstrated that naloxone (NLX) and naltroxone (NTX) have selective antagonistic effects on the excitatory opioid receptor functions in nociceptive dorsal root ganglion (DRG), thus unmasking the inhibitory effects of morphine and other opioids acting on μ, δ and κ receptors and provided a cellular mechanism for such effect, as they elicited prolongation of the Ca^{2+} dependent component of the action potential by ultra-low-dose naloxone and naltroxone [19]. Naloxone prevents the transient switch in G-protein coupling by μ-opioid receptor from Gi/o to Gs and attenuates the opioid tolerance and dependence via high-affinity interaction of naloxone to a penta-peptide region in c-terminal filamin A (FLNA) interacting with μ-opioid receptors [20].

This is in agreement with the study of Movafegh et al. [3] who studied the effect of addition of ultra-low-dose of naloxone to lidocaine 1.5% with or without fentanyl in axillary brachial plexus block and they found that the ultra-low-dose of naloxone prolongs the time to first post-operative pain. Also, Hamann and Sloan [9] in their case report used low dose (20 ηg) intrathecal naloxone added to intrathecal morphine (2 mg) bolus and infusion of 5 mg morphine and 50 ηg naloxone intrathecal daily throughout 3 years follow up period in a patient with severe chronic low back pain (post-lamenectomy), they reported that; the patient maintained pain reduction of 60–80% with a return to daily activities and no further hospitalization.

Table 4 Intraocular pressure in the studied groups.

	Pre-injection	2 min post-injection	10 min post-injection	P value
Group I (n = 30)	10.40 ± 1.40	15.77 ± 1.10*	11.23 ± 1.25•	<0.001
Group II (n = 30)	10.87 ± 1.38	15.20 ± 1.03*	11.57 ± 1.17•	<0.001
P value	0.27	0.07	0.29	

Data expressed as mean ± standard deviation (SD).
* Significant difference between pre-injection and 2 min post-injection within the same group.
• Significant difference between 2 and 10 min post-injection within the same group.

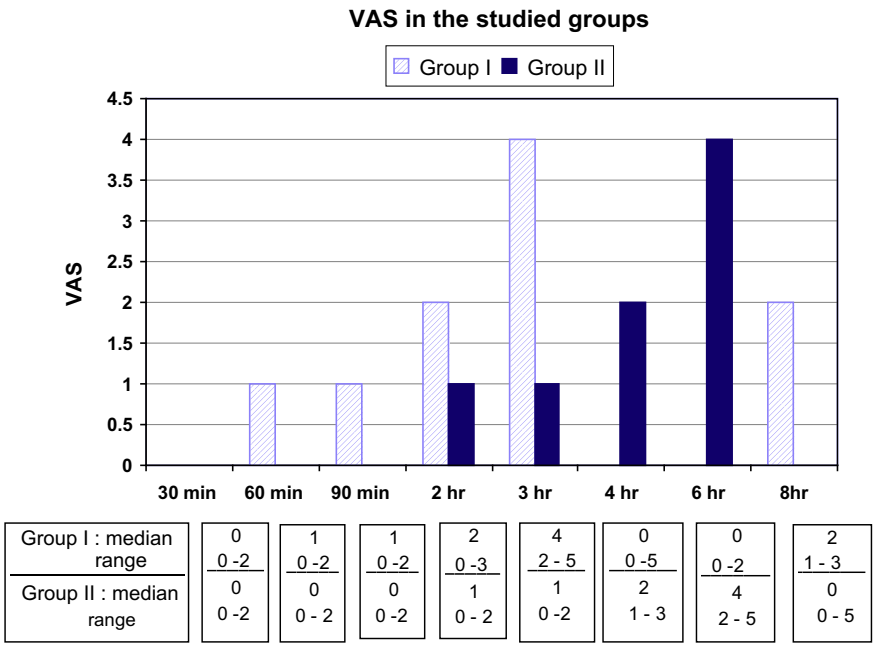

Figure 1 Pain intensity in the studied groups.

As regards the onset time and the akinesia score in the present study, there was no significant difference between the two studied groups. In contrary to our results is the study of Movafegh et al. [3] who found prolongation of the onset time in the naloxone group. This difference may be due to the addition of hyaluronidase to the local anesthetic in our study, which was proved to decrease the onset time and improve the akinesia [21].

Concerning the IOP in the present study; in each group there was a significant increase in the IOP 2 min after injection of the local anesthetic then, it became insignificant after 10 min compared to the preinjection value while there was a significant decrease in the IOP 10 min compared to 2 min post-injection. This indicates that, the intermittent digital compression was effective in reversing the increase in IOP after local anesthetic injection. The transient increase in IOP was due to injection of local anesthetic in the limited orbital space, and then it decreased due to decrease of the external pressure on the globe as a result of relaxation of the extra-ocular muscles [22]. In agreement with our results is the study of Bowman et al. [21].

In the present study, there were few complications and adverse effects which were chemosis and pain on injection with no significant difference between the two groups.

We conclude that, addition of ultra-low-dose naloxone to fentanyl and lidocaine for peribulbar anesthesia prolongs the duration of post-operative analgesia and decreases the analgesic requirement without increasing the adverse effects.

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Presentation

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