Original Article

Effects of dexmedetomidine for retrobulbar anesthesia in orbital ball implants after enucleation surgery

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Background: Dexmedetomidine (DEX) can prolong the duration of local anesthetics, but the use of retrobulbar DEX has not been fully elucidated. This study was designed to determine the effects of adding DEX to lidocaine-bupivacaine for retrobulbar block in orbital ball implants after enucleation surgery. **Materials and Methods:** A total of 200 patients of both sexes aged 30–60 years of American Society of Anesthesiologists I and II, scheduled for orbital ball implants after enucleation surgery, were enrolled for the study. Patients were randomly assigned into one of the two groups: Control (n = 100) received lidocaine-bupivacaine retrobulbar block, DEX (n = 100) received lidocaine-bupivacaine plus 1 ug/kg DEX retrobulbar block. Hemodynamic data, duration of motor and sensory blocks, pain by visual analog scale, bispectral index (BIS), side effects, consumption of dezocine as a rescue analgesic, patient and surgeon satisfaction were recorded. **Results:** Duration of analgesia was prolonged in the DEX, compared with the control group ([258.35 ± 66.82 min] as [130.75 ± 29.52 min], [P < 0.05]). The median number of postoperative analgesic requests per patient during the first 24 h was decreased in the DEX group (P < 0.05). In the first 24 postoperative hours, DEX group consumed significantly less dezocine (P < 0.05). BIS values and mean arterial pressure remained lower in the DEX group, but within the safe range (P < 0.05). The side effect profile was similar between the two groups. Patients and surgeon satisfaction were higher in the DEX group (P < 0.05). Demographic characteristics were comparable in both groups (P > 0.05). **Conclusion:** Retrobulbar DEX reduces consumption of rescue analgesic, prolonged the duration of retrobulbar block, improved postoperative pain, provided better sedation effects, and increased patient and surgeon satisfaction after orbital ball implants after enucleation surgery.

Key words: Dexmedetomidine, orbital ball implants after enucleation surgery, retrobulbar block

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Retrobulbar anesthesia is one of the most popular, reliable, and safe anesthetic techniques for orbital ball implants after enucleation surgery because it is associated with fewer respiratory and hemodynamic untoward events, less nausea and vomiting than general anesthesia.[1] The main disadvantage of retrobulbar anesthesia is the short duration of action. Orbital ball implants after enucleation surgery is a lengthy procedure that frequently experience moderate or severe pain.[2] Patients are often concerned about the eye injection and operative pain, various agents including midazolam, opioids, and clonidine[3,4] have been used as an adjuvant to local anesthetics to try and reduce patients' anxiety and to improve intraoperative and postoperative pain.

Dexmedetomidine (DEX) is a potent α-2 adrenoceptor agonist that is 8 times more selective for the α-2 adrenoceptor than clonidine.[5] DEX has been shown to produce analgesic properties, prolonging the duration of local anesthetics in intrathecal,[6] caudal,[7,8] intravenous (IV) regional anesthesia,[5] and brachial plexus block.[9] Animal[10-12] and human studies[13,14] have demonstrated that it has an effective adjunct to local anesthetics without causing nerve damage.

The effects of DEX as an adjunct to retrobulbar anesthesia has not been examined. We conducted a randomized controlled trial to establish whether adding DEX to lidocaine-bupivacaine in retrobulbar anesthesia influenced the duration of block and the degree of pain after orbital ball implants after enucleation surgery. Secondary endpoints were patient and surgeon satisfaction, bispectral index (BIS), and rescue analgesia requirements.

Materials and Methods

This clinical trial was reviewed and approved by the Ethics Committee of The Second Affiliated Hospital of Zhejiang University School of Medicine. A written informed consent was obtained from all patients. A total of 200 American Society of Anesthesiologists (ASA) physical status I and II patients between the ages of 30 and 60 years scheduled to undergo enucleation surgery with orbital ball implants under

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mon anesthesia care were enrolled in our study. A thorough preanesthetic evaluation was carried out. The patients included sympathetic ophthalmia after eye trauma, blind painful eye, blind disfigured eye, ocular tumors, corneal (corneal-sclera) staphyloma, and endophthalmitis. Hydroxyapatite and MEDPOR orbital implants were included for surgery. All the patients fasted for 4 h before surgery, but not premedicated. Patients with a history of allergy to local anesthetics, severe systemic disease, active ocular infection, single eye, who were pregnant, or those taking anti-coagulants, anti-epileptic drugs, anti-psychotic medication, anti-glaucoma drugs, atrioventricular block, and obstructive apnea were excluded from the study.

On arrival in the operating room, an IV line was placed and the electrocardiogram, pulse oximetry, noninvasive blood pressure, and BIS monitors were applied in all patients. Patients were randomized into one of the two groups using the sealed envelope technique: Control received a retrobulbar anesthesia with lidocaine-bupivacaine (n = 100) and DEX received lidocaine-bupivacaine plus 1 ug/kg DEX (n = 100). According to our past research result, retrobulbar 1 ug/kg DEX is found to be safe and effective.[15] The study solutions were prepared by an ophthalmic technician who was given a written set of instructions and was unaware of the study design. The results of the randomization were concealed in opaque envelopes and opened sequentially.

The retrobulbar anesthesia was performed by a senior anesthesiologist resident of the Ophthalmology Department. Both the anesthesiologist performing the anesthesia and the patient were masked the composition of the anesthetic mixture. Topical anesthesia to the conjunctiva with 0.4% oxybuprocaine drops was given before performing the retrobulbar block. The globe was maintained in a neutral gaze position; then a 25-gauge, 30 mm ophthalmic cannula needle (Steriseal; Unomedical, Ltd., Redditch, UK) was inserted in the inferotemporal quadrant at the junction of the lateral one-third and the medial two-third of the inferior orbital rim. The initial direction of the needle was tangential to the globe; the needle was then passed below the globe. Once passed the equator, as gauged by the axial length of the globe, the needle was allowed to go upward and inward. The study drug preparation was slowly injected after aspiration. To promote spread of the local anesthetic solution and decrease bleeding, gentle digital massage was done. Visual analog scale (VAS) for pain (on a scale from 0 to 10) and BIS for sedation (on a scale from 0 to 100) were recorded at baseline (T0), 1 min (T1), 5 min (T2), 10 min (T3), and 15 min after retrobulbar block (T4), the beginning of surgery (T5), enucleation of eyeball (T6), the end of surgery (T7), 2 h postoperation (T8), and 5 h postoperation (T9). Vital signs including heart rate, mean arterial pressure (MAP), SpO_2, and sedation level (BIS) were monitored until 24 h postoperation. Demographic data, heart rate, MAP, pulse oximetry, episodes of bradycardia (heart rate <20% of baseline), hypotension (MAP < 20% of baseline), postoperative nausea and vomiting (PONV), dezocine consumption, patient and surgeon satisfaction were recorded. The time to the first analgesic request (VAS > 4) was recorded. Dezocine, an opioid drug with agonist-antagonist effect, was used to treat intraoperative or postoperative pain. Dezocine 5 mg was used intravenously as rescue analgesic when VAS scores were 4 or more. The maximum dose administered in the first 24 postoperative hours was 20 mg. The number of postoperation analgesic requests during the first 24 h were recorded. Azasetron 10 mg was administered intravenously for PONV, if necessary. Intravenously, midazolam 2 mg was administered for restlessness. Atropine 0.01 mg/kg or etilefrine 2 mg was given in cases of bradycardia or hypotension, respectively. Patient and surgeon satisfaction was evaluated 24 h after surgery using a five-point Likert scale (completely satisfied: Patient with painless, quiet, and ideal surgical conditions; satisfied: Patient with some painful expression, slight anxiety, and good surgical conditions; slightly dissatisfied: Patient with moderate pain, anxiety, and adequate surgical conditions; dissatisfied: Patient with severe pain, anxiety, and suboptimal surgical conditions; very dissatisfied: Patient with severe pain, restless, and inadequate surgical conditions).

At the end of the study, the data were compiled systematically and were subjected to statistical analysis using SPSS version 15.0 for windows (Chicago, IL, USA). Numerical variables are reported as means, standard deviation, and medians, while qualitative variables are reported as percentages. Difference of measurement data was compared with analysis of variance. Heart rate and MAP were evaluated using repeated measures variance analysis. The rank test was used to evaluate the difference in the distribution of variables. The Chi-square test was used to evaluate the difference in qualitative variables. Statistical significance was set at $P = 0.05$.

Results

- All the demographic characteristics including age, sex, weight, ASA grade, side of the eye operated, PONV, and duration of surgery were comparable in both groups and were found to be statistically nonsignificant ($P > 0.05$) [Table 1]
- The median number of postoperative analgesic requests per patient during the first 24 h was higher in the control than DEX ($P < 0.05$); most of the patients in DEX group made 0 or one analgesic request, while most of patients in control group made two or three analgesic requests [Fig. 1]
- Patients requiring rescue analgesia in DEX group were significantly less than the control group. In the first 24 postoperative hours, the patients in the DEX group consumed significantly less dezocine than those of in control group (3.1 ± 3.6 mg and 10.3 ± 4.7 mg, respectively). The time

Table 1: Demographic data

Demographic characteristics	Control (n=100)	DEX (n=100)
Age (years) (mean±SD)	49.8±5.8	41.2±8.1
Gender male/female	64/36	68±32
Weight (kg) (mean±SD)	72.8±12.4	79.8±11.8
Side of eye right/left	54/46	35/65
ASA Grade I/II	77/23	68/32
Duration of surgery (min)	58.2±8.2	63.4±10.1
Nausea (%)	22	14
Vomit (%)	18	16
Block onset time (min)	3.3±1.6	2.9±1.4

Values are mean±SD numbers for nausea and vomiting, which are the number of patients who complained of nausea and vomiting. P values were not significant. ASA: American Society of Anesthesiologist, Control: Control group, DEX: Dexmedetomidine group, SD: Standard deviation

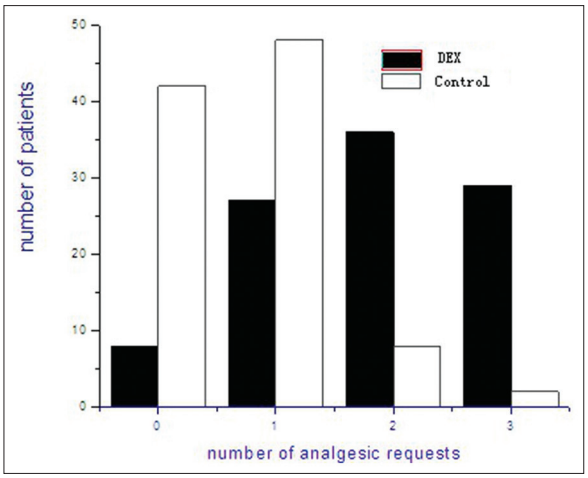

Figure 1: Distribution of patients by number of postoperation analgesic requests during the first 24 h

to first rescue analgesic was also significantly prolonged in DEX group (258.35 ± 66.82) ($P < 0.05$) [Table 2]

- Patient and surgeon satisfaction was higher in the DEX group than control group ($P < 0.05$) [Table 3]
- BIS was significantly lower in DEX group than that in control group at T4～T7, whereas there was no significant difference in T1 and T8 BIS values [Table 4]
- In the analysis of the hemodynamics between the two groups, the MAP in DEX group was lower at T3～T4 compared with control group and reached the lowest value at T4 ($P < 0.05$). Heart rates in DEX group were lower at T2～T3 compared with control group and reached the lowest value at T3 ($P < 0.05$), Heart rate in the control group was lower significantly at T6 compared to at T0 [Table 5].

Discussion

The purpose of this study was to determine the value of DEX in prolonging the duration of the local anesthetic, lidocaine-bupivacaine, for retrobulbar anesthesia. Although adding a small amount of drug acquisition costs, we found that adding DEX to the local anesthetic mixture used for retrobulbar anesthesia improved intraoperative sedation and postoperative analgesia, reduced rescue analgesic requirements, and increased patient and surgeon satisfaction after orbital ball implants after enucleation surgery.

Orbital ball implants after enucleation surgery are associated with severe tissue damage, especially optic nerve and extraocular muscle manipulation, patients often complain of severe pain afterward. Regional anesthesia techniques provide important advantages compared with general anesthesia and systemic analgesia, including excellent pain control, reduced side-effects, and shortened stay in the postanesthesia care unit. A single retrobulbar nerve block or a peribulbar block is administered with local anesthetics to counteract pain.[16] This direct injection of anesthesia provides rapid and effective pain relief, but the effect is short-lived. DEX is a highly selective α-2-adrenoreceptor agonist with α-2:α-1 binding ratio of 1620:1 compared to 220:1 for clonidine. It potentiates the anesthetic duration of lidocaine-bupivacaine analgesia.[5,17] DEX used for analgesia and sedation by IV administration, is in a preservative-free solution, containing no additives or chemical

Table 2: Comparison of retrobulbar block characteristics

Variables	Control	DEX	*P*
Patients requesting postoperative analgesics	92 (92)	40 (40)	<0.05*
Total rescue analgesic consumption (mg)	10.3±4.7	3.1±3.6	<0.05*
Time to first analgesic request (min)	130.75±29.52	258.35±66.82	<0.05*

Values are numbers (%), mean±SD, or medians (ranges). *P*<0.05 was considered statistically significant between the two groups. Control received retrobulbar block lidocaine-bupivacaine. DEX received lidocaine-bupivacaine plus 1 ug/kg of DEX. SD: Standard deviation, Control: Control group, DEX: Dexmedetomidine group

Table 3: Percentage of patients and surgeons satisfaction for anesthesia (*n* %)

Variables	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)
Patient's satisfaction					
Control (*n*=100)	23 (23)	21 (21)	56 (56)	0 (0)	9 (9)
DEX (*n*=100)	92 (92)*	8 (8)*	0 (0)	0 (0)	0 (0)
Surgeon's satisfaction					
Control (*n*=100)	42 (42)	58 (58)	0 (0)	0 (0)	0 (0)
DEX (*n*=100)	100 (100)*	0 (0)*	0 (0)	0 (0)	0 (0)

Comparison of patient's and surgeon's satisfaction *n* (%). 1: Completely satisfied, 2: Satisfied, 3: Slightly dissatisfied, 4: Dissatisfied, 5: Very dissatisfied. **P*<0.05 was considered statistically significant between the two groups. Control: Control group, DEX: Dexmedetomidine group

Table 4: Results on BIS comparing the two studied groups

Variables	DEX	Control	*P*
BIS (T1)	96.95±2.26	97.35±2.06	>0.05
BIS (T4)	76.35±4.90	98.45±2.25	<0.05*
BIS (T5)	73.20±1.87	97.35±1.37	<0.05*
BIS (T6)	79.42±6.21	98.12±4.53	<0.05*
BIS (T7)	83.25±8.32	98.65±6.80	<0.05*
BIS (T8)	97.05±3.00	96.79±4.31	>0.05

Results on BIS comparing the two groups. **P*<0.05 was considered statistically significant between the two groups. Control: Control group, DEX: Dexmedetomidine group, BIS: Bispectral index

stabilizers. However, it has recently been used as intrathecal, epidural, caudal for peripheral nerve blocks in the range of 1～2 ug/kg without any incidence of neurological deficits.[6-8,18] Keplinger *et al*.[19] assessed the dose-dependency of DEX when injected with ropivacaine for peripheral nerve blockade. It produced a dose-dependent prolongation of sensory block and clinically relevant dose-dependent sedation. DEX 100 μg may represent a balance between efficacy and sedation. Similar to our past research[15] in children, we carried out a prospective and randomized control clinical trials in our hospital to compare the anesthetic effects of lidocaine-bupivacaine with and without 1 ug/kg DEX in administration of retrobulbar block for orbital ball implants after enucleation surgery in adults. DEX exerts its analgesic effects by inhibiting norepinephrine release mediated by α-2 receptors located at nerve endings. Kanazi *et al*.[6] showed

Table 5: The analysis of hemodynamics between the two groups

	Heart rate (*n*=100)		MAP (*n*=100)	
	DEX	Control	DEX	Control
T0	76.5±12.4	73.9±12.8	103.2±12.7	100.1±16.4
T1	77.5±11.4	75.4±11.5	98.7±16.8	101.3±15.2
T2	68.9±10.7*,#	75.9±10.2	91.8±13.8	103.0±12.8
T3	65.0±11.7*,#	73.2±10.9	85.1±13.9*,#	104.7±12.7
T4	67.1±10.5	72.9±8.7	81.3±12.1*,#	101.4±11.8
T5	74.5±10.1	75.5±11.3	91.2±12.6	99.8±13.2
T6	79.2±9.8	61.2±11.8#	97.2±14.1	95.0±16.2
T7	73.1±11.0	74.0±8.5	100.8±9.7	97.5±15.0
T8	69.8±10.3	67.5±11.0	102.4±16.0	100.9±16.0
T9	69.6±6.8	68.2±7.6	104.3±12.5	101.4±13.6

*P<0.05 compared to control; #P<0.05 compared to T0 value.
DEX: Dexmedetomidine group, MAP: Mean arterial pressure

that DEX produced analgesia by depressing the release of C-fiber transmitters and by hyperpolarization of postsynaptic dorsal horn neurons. Funai *et al*.[20] found a novel anti-nociceptive mechanism for systemic a-2-adrenoceptor agonists at low doses via the facilitation of inhibitory synaptic transmission in the spinal dorsal horn. This is mediated by an activation of the descending noradrenergic inhibitory system originating from locus coeruleus in the pons, which is acting to modulate inhibitory tone in the superficial dorsal horn of the spinal cord. Brummet *et al*.[10] reported that a short period of analgesia is observed following local injection of DEX, implying that it has a peripheral effect. The same investigators also reported that DEX is more effective in a rat sciatic nerve model when injected perineurally rather than systemically, although they state that the underlying mechanism is unclear.[21] We aimed to increase the quality and duration of retrobulbar block while avoiding the adverse effects associated with systemic use, such as hypotension and bradycardia. A variety of doses of DEX have been used in peripheral nerve blocks as an adjunct to local anesthetics. She *et al*.[8] showed that the addition of 1 and 2 ug/kg of caudal DEX reduced the MLAC of levobupivacaine and improved postoperative analgesia in children undergoing surgery for inguinal hernia repair or hydrocele, without any permanent neurological deficit. Bengisun *et al*.[9] showed that when DEX is used to augment the action of levobupivacaine in a single-shot interscalene block followed by IV patient-controlled analgesia for 24 h after arthroscopic shoulder surgery, analgesia and patient satisfaction appear to be improved without increasing the incidence of side effects. Better pain relief was reflected in reduced pain VAS scores and reduced local anesthetic and rescue analgesia requirements. Epidural DEX 0.5 ug/kg appears to intensify thoracic epidural anesthesia with levobupivacaine including better blockade duration, increasing the quality of analgesia, and lowering the need for rescue analgesic for nephrectomy.[22]

In our study, 1 ug/kg DEX was added to lidocaine-bupivacaine for retrobulbar anesthesia. We found no statistically significant difference in the onset time compared with those who received only lidocaine-bupivacaine, which can be explained by the relatively low dose of DEX used. This result is found to be in line with a meta-analysis by Abdallah and Brull.[23] The duration of analgesia was prolonged, and rescue analgesic requirements were lower. This may be due to the vasoconstrictive effect and slower absorption of local anesthetic. We had better patient and surgeon satisfaction similar to the findings of previous studies. This may be due to improved hemostasis and better prolonged perioperative pain relief.

Besides the observed improvement in analgesic effects, DEX has other physiological properties including sedation, anxiety, decreasing the convulsive potency of local anesthetics, reducing plasma catecholamine concentration, and preventing shivering.[24-26] Intranasal DEX in pediatric patients in a dose of 2 ug/kg achieved satisfactory preoperative sedation, allowed calm separation of the patient from their parent, resulted in acceptance of IV cannulation, and did not cause excessive PONV or psychological disturbance.[27] DEX uniquely provides analgesia and sedation without respiratory depression.[28] The mechanism by which α-2-adrenergic receptor agonists produce analgesia and sedation is not fully understood, but is likely to be multifactorial. Peripherally, α-2-adrenergic agonists produce analgesia by reducing the release of norepinephrine and causing α-2 receptor-independent inhibitory effects on nerve fiber action potentials. Centrally, α-2 agonists cause analgesia and sedation by inhibition of substance *P* release in the nociceptive pathway at the level of the dorsal root neuron and by the activation of α-2 adrenoceptors in the locus coeruleus.[29] In our study, retrobulbar block lidocaine-bupivacaine combined with DEX showed a mild depth of sedation compared to retrobulbar block lidocaine-bupivacaine alone from 15 min after retrobulbar block to the end of surgery including while cutting the optic nerve and extraocular muscle manipulation. There was no occurrence of SaO_2 decreasing to 90% or less. However, the sedative effect of DEX allows patients to respond to verbal or physical stimuli during surgery, and easy conversion from sleeping to awakening is possible. High-dose DEX causes peripheral vasoconstriction, increased systolic arterial pressure, and bradycardia in adults.[30] Other investigators have found bradycardia in an 11-year-old girl following administration of intranasal DEX for sedation for a voiding cystourethrogram.[31] It is commonly observed due to increased vagal tone, decreased sympathetic tone, and peripheral vasoconstriction.[32] In our study, 1 ug/kg DEX caused lower blood pressure and heart rate before the beginning of surgery, but severe hypotension and bradycardia did not occur, which may be a reflection of the lower dose of DEX that we used and may be a slow-release of the retrobulbar DEX. This is consistent with the results of study by Marhofer *et al*.[33] on the effects of DEX as an adjuvant to ropivacaine on peripheral nerve block.

The observed bradycardia was transient, successfully reversed by IV atropine administration when necessary and did not recur later during the postoperative period. None of the patients in these trials experienced respiratory depression or significant sedation. The incidence of PONV showed no difference between the two groups. There were no adverse events such as bradycardia, respiratory depression, or hypotension in our study.

Conclusion

Our randomized trial showed that the addition of 1 ug/kg DEX to the retrobulbar improved analgesia block, sedation, and patient and surgeon satisfaction after enucleation surgery

without increasing the incidence of side effects. Better pain relief was reflected in reduced pain VAS scores and rescue analgesia requirements. Future studies should focus on establishing the optimal dosage of DEX in this setting and the best combination of local anesthetics.

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Conflicts of interest

There are no conflicts of interest.

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