Dexmedetomidine vs. Magnesium Sulphate as an Adjuvant to Rocuronium Bromide, and Local Anaesthetic Mixture in Peribulbar Anaesthesia for Viteroretinal Surgery

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Abstract

Background: A wide variety of additives have been used in a mixture with local anesthetics in PBA to fasten the onset, increase the potency and prolong the duration of the block to cover the long viteroretinal surgeries. Dexmedetomidine, magnesium sulphate and rocuronium bromide have been added to local anesthetics to achieve such goal.

Patients and methods: This randomized double-blind prospective study was carried out on 96 ASA I and II patients aged 40 to 65 years who were scheduled for elective vitreoretinal surgery in Tanta university. Patients were divided randomly allocated into three groups, 32 patients in each group. Group C received the combination of 3.5 ml bupivacaine 0.5%, 3.5 ml lidocaine 2%, 0.5 ml rocuronium bromide (5 mg) plus 0.5 ml Normal saline (0.9% NaCl), group D received the same local anesthetic rocuronium mixture supplemented plus 0.5 ml Dexmedetomidine (5 Group M) group received the same local anesthetic rocuronium mixture plus 0.5 ml MgSO4 5% (50 mg), the onset of corneal anesthesia, time to adequate condition to begin surgery, the score and duration of akinesia, number of patients requiring supplementary injection, IOP, sedation scores, intraoperative pain, patients and surgeon satisfaction and incidence of complication were assessed.

Results: There was no statistical significance in the onset of corneal anesthesia between all groups with p value > 0.05 (Group M 2.00 ± 0.70, Group M, 2.04 ± 0.77 and Group C 2.26 ± 0.62 min). However, the time adequate to start the surgery was significantly shorter (p<0.0001) in group M than in group D and group C (7.05 ± 1.54, 7.86 ± 1.61 and 8.63 ± 1.65 min respectively); also, it was significantly shorter in group D than group C. The duration of akinesia was significantly longer (p<0.0001) in group M compared with other groups (200.55 ± 7.55, 180.11 ± 1.61 and 140.44 ± 13.04 min in group M, D and C respectively). IOP comparison was statistically insignificant between all groups with p value>0.05. No significant difference was noticed between the 3 groups regarding sedation score HR and MAP at all-time measures. As regards the akinesia score Mg group had the least akinesia score (p<0.0001) compared with the other groups in all measurement times. The VAS score and the need of supplemental dose were much higher in the control group. Patient satisfaction (p<0.0001) was best achieved in the D Group while surgeon satisfaction (p=0.01) was the best in M Group.

Conclusion: Adding Mg to local anesthetic mixture in peribulbar anaesthesia resulted in a fast onset, long duration and better akinesia score while Dexmedetomidine supplementation offered more patient satisfaction.

Keywords: Peribulbar anaesthesia; Rocuronium; Dexmedetomedine; Magnesium

Introduction

Vitreoretinal surgery is a surgery involving the vitreous and retina, they are lengthy procedures and associated with significant pain [1], it has traditionally been performed under general anesthesia but local anesthesia has increased in popularity in recent years [2]. The retro bulbar can provide adequate anesthesia, akinesia and control of intraocular pressure as well as postoperative analgesia [3]. However, many complications are associated with this technique such as globe perforation, brain stem anesthesia and retro bulbar hemorrhage, which is the most frequent complication [4].

Many believe that the peribulbar block is a safer technique however, it has the disadvantage of a slow onset of orbital akinesia and to produce it a larger volume or repeated injections of anesthetic solution is required due to limited diffusion of local anesthetics (LA) [5]. This also increases the frequency of complications such as globe perforation and hemorrhage [4]. To prevent this and to increase tissue diffusion, hyaluronidase and other adjutants such as clonidine, epinephrine and alkalinization were used to improve peribulbar block [6-8]. Neuromuscular blocking drugs, such as vecuronium [9] and atracurium [10], and rocuronium have also been added to the local anaesthetic mixture and have been shown to accelerate onset and improve the quality of peribulbar block [11]. Magnesium (Mg) has antinociceptive effects due to its antagonistic effect of NMDA receptors, and its analgesic effect is based on its
inhibitory properties for calcium channels [12]. At the motor nerve terminal, MgSO4 inhibits acetylcholine release, thus it enhances the effect, speeds the onset and increases the clinical duration of neuromuscular blocking agents [13].

Dexmedetomidine is a highly selective a2-adrenoreceptor agonist that has an a2 to a1 selectivity ratio of 1620:1 [14]. It enhances central and peripheral neural blockades when added to LAs as an adjuvant. It has been used as additives to local anaesthetics in peripheral nerve block, brachial plexus block [15] and peribulbar block. Dexmedetomidine may be used to improve the reliability and efficacy of regional anesthesia [16]. It is also a potent and effective drug for decreasing IOP in rabbits [17].

In several studies, systemic magnesium sulphate [13] was proved to speed the onset and prolong the duration of neuromuscular blockade while the effects of dexmedetomidine on neuromuscular blockade is still unclear.

Using dexmedetomidine, and magnesium sulphate as adjuvants to peribulbar anesthesia has been investigated in several studies [18-20], comparing their effects versus rocuronium in peribulbar anesthesia [19,21] has been studied as well. To our knowledge little was done to investigate the local effects of dexmedetomidine or magnesium on the muscle relaxant potentiated block.

Patient and Methods

The study was carried out on 96 patients, aging (40-65 y), (ASA I&II) of both sex presented for vitreoretinal surgery under local anesthesia in Tanta University Hospital Ophthalmology department. The duration of the study was 3 months. After approval from institutional ethics committee an informed consent was taken from each patient. All data of the patients was confidential with secret codes and private file for each patient, all given data were used for the current medical research only.

Exclusion criteria

Patient with renal and liver diseases, Cardiovascular instability, orthopnea, History of allergy to local anesthetics, Patient with coagulopathies and impaired platelet functions, Parkinsonism, claustrophobia, difficulty in communication, patients with high myopia, staphylomas. Local infection at the site of the block and extraocular muscles or eyelid abnormalities were excluded

This study was conducted in a randomized, double blind and prospective manner. Any unexpected risks appeared during the course of the research were cleared to the participants and ethical committee on time.

All physicians, patients, nursing staff, and data collector were blinded to the patient group assignment. For all patients, full clinical examination and laboratory investigations as regards renal and hepatic functions as well as cardiovascular status were done.

Using a computer-generated randomization schedule and serially numbered, opaque, sealed envelopes, patients were randomly allocated to one of three study groups; 32 patients in each group.

Patients were randomly allocated to one of three study groups; 32 patients in each group:

**Group 1 (C group) (n=32):** Each patient received the combination of 3.5 ml bupivacaine 0.5%, 3.5 ml lidocaine 2%, 0.5 ml rocuronium bromide (5 mg) plus 0.5 ml Normal saline (0.9% NaCl).

**Group 2 (D group) (n=32):** Each patient received the combination of 3.5 ml bupivacaine 0.5%, 3.5 ml lidocaine 2%, 0.5 ml rocuronium bromide (5 mg) plus 0.5 ml MgSO4 (5% (50 mg).

**Group 3 (M group): (n=32):** Each patient received the combination of 3.5 ml bupivacaine 0.5%, 3.5 ml lidocaine 2%, 0.5 ml rocuronium bromide (5 mg) plus 0.5 ml MgSO4 5% (50 mg).

Prior to performance of the block, a blinded observer evaluated the patient’s eyelid and ocular movement at the site of surgery. On arrival in the anesthetic room, Standard monitors were attached and oxygen was administered at 21/min via nasal prongs and a peripheral IV cannula was inserted

Peribulbar anesthesia was performed, by the same anesthesiologist who was blinded to the local anesthetic drug used. An infratemporal transconjunctival injection of the study drug (4 ml) using a 25gauge, 25 mm needle was performed followed by gentle massage for 30 seconds to facilitate the spread of the local anesthetic mixture. A second transconjunctival injection of the study drug (4 ml) was performed medial to the lacrimal caruncle.

Injection of the intended volume of the study drug was stopped when there was fullness of the orbit and/or drooping of the upper eyelid during injection. Gentle ocular massage was done, the eye pad was removed every 2 min to assess ocular movements and the orbicular muscle. Corneal anesthesia was also evaluated using a small cotton wool at the same time intervals. To assess ocular akinesia, patients were asked to look in four directions: Lateral, medial, superior, and inferior. Ocular movement in each direction was scored as 2 if it was normal, 1 if it was limited, and 0 if there was no directional movement (total score 0-8). The patient was then asked to forcefully close his/her eyes to assess the orbicularis muscle on a scale of 0-2 (0=complete akinesia, 1=partial movement, 2=pronounced movement).

Time to adequate condition to begin surgery (defined as the presence of corneal anesthesia together with ocular movement score ≤ 1 and eyelid squeezing score of 0) was recorded using a stopwatch. If adequate condition to begin surgery was not obtained 10 min after performing the block, supplemental injection with 2 ml of lidocaine 2% either inferotemporally or medially was administered based on the anesthesiologist’s assessment. At the end of surgery, all patients were asked to rate their intraoperative pain using a visual analogue scale (VAS) 0 being no pain and 10 being the worst imaginable pain. All adverse events including the presence of diplopia and/or ptosis were recorded.

The following were recorded in the three groups

Patients characteristics including age, sex, and weight, and ASA status, axial length of the globe measured by echocardiography, type and duration of surgery.

1. Baseline HR and MAP.
2. Onset time of corneal anesthesia every 30 sec.
3. Time to adequate condition to begin surgery defined as the presence of corneal anesthesia together with ocular movement score ≤ 1 and eyelid squeezing score.
4. The score of akinesia in the 1, 3, 5 and 10 minutes after injection (score 0 total, score 1 relative, score 2 no akinesia).

5. Number of patients requiring supplementary injection.

6. The offset time of akinesia in the recovery unit.

7. HR and MAP every 5 min in the first 20 min then every 10 min till the end of the surgery.

8. Sedation levels were assessed with modified Ramsay sedation scale (1-Anxious and agitated or restless or both, 2-Cooperative, oriented, and tranquil, 3-Responds to commands only, 4-Brisk response to light glabellar tap or loud auditory stimulus, 5-No response to light glabellar tap or loud auditory stimulus) at every 10 min during surgery and every 30 min in first 2 h.

9. Intraocular pressure measured using a Schiotz tonometer 5 min before the injection of LA as a baseline 10 min after the injection of LA.

10. Intraoperative pain at the end of the surgery using a visual analogue scale (VAS).

11. The surgeon’s and patient’s satisfaction (both blinded to group assignment) were assessed using a satisfaction verbal rating scale from 0 (total dissatisfaction) to 10 (total satisfaction).

12. Incidence of complications: Complications during or after the block: Such as episodes of nausea or vomiting, occulocardiac reflex arrhythmia, convulsions, allergy, weakness, diplopia, ptosis and subconjunctival haemorrhage were recorded.

Statistical methods

Based on the previous study of Nicholson et al. [18], which resulted in mean ocular movement score of 5 in group 1 and 7 in group 2, Initial sample size estimation showed that 41 patients should be included for detecting a clinically meaningful in ocular movement score of 2 (at least), with (α=0.05, two side, power of 90%). However, to enable detection of potential variations and avoid potential errors, 45 patients will be included in each group. All analyses were performed on an intention to treat basis. Data were analyzed using Statistical Program for Social Science (SPSS) version 18.0. Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done

1. (X²) test of significance was used in order to compare proportions between qualitative parameters.

2. One-way analysis of variance was used for intergroup comparisons as regards normally distributed.

3. Variables Probability (P-value).
   a). P-value<0.05 was considered significant.
   b). P-value<0.001 was considered as highly significant.
   c). P-value>0.05 was considered insignificant.

Results

A total of 96 patients were randomly included in this study, all of them had performed viteroretinal surgeries under peribulbar anesthesia, all cases complete the surgeries under local anesthesia, none of them required general anesthesia (Table 1 and Figures 1-3).

|                  | Group D (n=45) | Group M (n=45) | Group C (n=45) | F test of X² of P value |
|------------------|---------------|----------------|----------------|-------------------------|
| Time for adequate conditions to start the surgery (min) | 7.05 ± 1.54   | 7.86 ± 1.61    | 8.63 ± 1.65    | <0.0001                 |
| Onset time of corneal anesthesia (min)                | 2.00 ± 0.70   | 2.04 ± 0.77    | 2.26 ± 0.62    | 5.39*                   |
| Offset time: (min)                                    | 200.55 ± 7.55 | 180.11 ± 1.61  | 140.44 ± 13.04 | <0.0001                 |
| IOP pre: (mmHg)                                      | 11.00 ± 1.85  | 11.30 ± 2.15   | 11.00 ± 2.18   | 0.13                    |
| IOP at 10 min (mmHg)                                  | 12.98 ± 2.78  | 12.41 ± 2.68   | 13.35 ± 3.12   | 1.23                    |

Table 1: Demographic data and duration of surgery.

Table 1 showed that both the demographic data regarding (age, sex) and duration of surgeries were statistically comparable in three groups.
Table 2: comparison between the 3 groups regarding time for adequate conditions to start the surgery, Onset time of corneal anesthesia, Offset time, preoperative IOP and IOP at 10 min post-injection.

As shown in Table 2 the time of onset time of corneal anesthesia, showed no significant difference between the 3 groups. while the time for adequate conditions to start the surgery in Magnesium group was significantly the shortest among both dexmedetomidine and control groups, also, dexmedetomidine had significantly shorter time than control group. The Offset time of akinesia was significantly the longest in magnesium group than in dexmedetomidine and control groups with dexmedetomidine group had also a significantly longer offset than the control. As regards the IOP it was found that dexmedetomidine had the lowest values in 10 min IOP measurements but without statistical significance.

Table 3: comparison between the 3 groups regarding sedation score at different time measures.

Table 3 shows No significant difference between the 3 groups regarding sedation score at all-time measures.
Table 4: Comparison between the 3 groups regarding Akinesia score at different time measure.

Table 4 shows that Magnesium group significantly had the least akinesia score at 1 min than both dexmedetomidine and control group (p<0.0001). The akinesia score between magnesium and dexmedetomidine group at 3, 5 and 10 min showed that magnesium had insignificantly lesser values than dexmedetomidine.

![Figure 3: Mean VAS score among the 3 groups.](image)

Intraoperative pain assessed by VAS score showed that control group has the highest score if compared with both Magnesium and dexemede group with a mean of (2.77 ± 0.87).

Table 5: Comparison between the 3 groups regarding the need of supplementary injection.

Table 5 shows that control group had significantly (p<0.001) more need for supplementary injection than both Magnesium and dexmedetomidine group while it was insignificantly lesser in Magnesium group when compared with dexmedetomidine group.

Table 6: Comparison between the 3 groups regarding patient and surgeon satisfaction.

Table 6 showed that Patient and surgeon satisfaction were significantly (<0.05) p lower in control group than both Magnesium and dexmedetomidine groups. To be noticed that patient satisfaction was best achieved in dexmedetomidine group while surgeon satisfaction had highest scores in magnesium group but this remark was of no significance between both groups.

Discussion

Using nondepolarizing muscle relaxants such as atracurium [10], vecuronium [9] and rocuronium [11], as adjuvants to local anesthetics in peribulbar anesthesia has been proved in several studies to improve the quality and the duration of the block.

In our study, we compared the effects of adding Dexmedetomidine or magnesium sulphate as an adjuvant to rocuronium bromide and local anesthetic mixture in peribulbar anesthesia for viteroretinal surgery.

Although performing viteroretinal surgeries under topical anesthesia has been tried in several studies [22-24]. Many ophthalmic
surgeons prefer to operate on completely akinetic eyes. Iatrogenic complications, such as retinal tearing [25] or hemorrhage may occur due to sudden movement of the eye during the surgery.

The addition of neuromuscular blockers as adjuvants to the local anesthetic does not influence analgesia; however, they induce akinesia in extraocular muscles, but the mechanisms are still unclear. It may be due to local action in the motor neurons extraocular muscles or by interfering the muscle spindle activity resulting in lower muscle tone and spasm [26].

Our study investigated the effects of adding MgSO\textsubscript{4} or Dexmedetomidine to NDMRs in peribulbar blocks. Our study showed that the time taken to achieve suitable akinesia (score 0 or 1) to start surgery was significantly shorter in magnesium than dexmedetomidine and control groups, also it was significantly shorter in dexmedetomidine than in control group.

Similarly the akinesia score, MgSO\textsubscript{4} and DEX groups showed significantly more akinesia when compared with the control group in all measurement times.

Also, MgSO\textsubscript{4} group had significantly more akinesia (lesser akinesia score) than DEX group in min 1 and insignificantly lesser score in 3, 5, 10 min. This could be explained by the local effects of MgSO\textsubscript{4} on the motor end plate. While the duration of akinesia in magnesium group was statistically prolonged when compared with the other groups, and in the same manner Dexmedetomidine group akinesia lasted statistically longer time than in the control group.

Several studies were made on the effects of magnesium on nondepolarizing muscle relaxant. SinghS et al. [13] found pre-treatment with MgSO\textsubscript{4} before non-depolarizing muscle relaxant, resulted in faster onset of neuromuscular block, needed for intubation of trachea. Also, it resulted in an intensified and prolonged neuromuscular blockade and delayed recovery. Similar results were obtained by Ghodraty MR et al. [27] who studied the effects of different doses of MgSO\textsubscript{4} on the properties of neuromuscular blockade by cisatracurium during induction of anesthesia and found that the speed of onset and the intensity of muscle relaxation increased as higher doses of magnesium were used.

MgSO\textsubscript{4} by acting as a calcium channel blocker at presynaptic level reduces acetylcholine release at the motor endplate, which lowers the excitability of the muscle and the amplitude of endplate potential, resulting in the augmentation of a neuromuscular blockade by NDMRs [13]. However, A study done by Wang H et al. [28] found that this potentiation of NDMRs by magnesium can be in part due to a combined effect on adult muscle-type acetylcholine receptors.

According to our results, regarding the onset of corneal anesthesia, there were no statistically significant differences between all groups although it was insignificantly delayed in the control group. Meanwhile, regarding the duration of anesthesia, we found it was more prolonged in magnesium group than the other two groups and in Dexmedetomidine group than the control group.

This was quite similar to the results of the study done by Hamawy TY et al. [21] who studied the effects of Rocuronium versus magnesium as an adjuvant to local anesthetics in peribulbar block and found that magnesium sulfate did not show any benefit as regards the onset of the block.

A meta-analysis done by Morrison AP et al. [29] found that the addition of intrathecal magnesium to local anesthetic did not result in a significant delay on the onset nor prolonged duration of sensory blockade.

In contrary, Haghighi M et al. [30] who studied the effect of Magnesium Sulfate Axillary Plexus Blockade he found a delayed onset and prolonged duration of sensory block in magnesium group.

A metanalysis done by Zhang et al. [31] studying the effect of different doses of intrathecal Dexmedetomidine on spinal anesthesia showed that Dexmedetomidine had a dose dependent effect on fastening the onset and prolonging the duration of sensory and motor blockade.

Abd El-Hamid AM et al. [32], addition of MgSO\textsubscript{4} to local anesthetic in peribulbar eye block produces predictable rapid onset of anesthesia without any side-effects, Dogru et al. [33] also found statistically decreased motor and sensory block onset times by the addition of magnesium to levobupivacaine for axillary brachial plexus block in chronic renal failure patients scheduled for arteriovenous fistula surgery.

Narang et al. [34] observed that the addition of magnesium sulfate as adjunct to lignocaine for total intravenous anesthesia for upper limb surgery hastened the onset of sensory and motor block and decreased tourniquet pain.

When magnesium was compared with clonidine as an adjunct for epidural bupivacaine, the onset of anesthesia was rapid, but the duration of analgesia was shorter in magnesium group in comparison to clonidine group [35]. Sedation was seen in the clonidine group. The author established that magnesium is predictable and safe adjunct to epidural bupivacaine. Abd El-Hamid [32] also found the longer duration of peribulbar block in the patients receiving clonidine with local anesthetic in comparison to the patients receiving magnesium.

Dexmedetomidine was used in several studies as an additive to local anesthetics producing variable effects on the onset and duration of sensory and motor blocks.

Eskandr AM et al. [36] studied the effects of adding Dexmedetomidine in subtenon block and found that it significantly fastened the onset of sensory and motor block, prolonged the duration of analgesia with little effects on duration of akinesia.

Similarly El-Ozairy et al. [37] studying the effects of adding different doses of Dexmedetomidine in peribulbar block in vitreoretinal surgeries found that higher dose (50 µgm DEX group) was combined with significantly faster onset and prolonged duration of both sensory and motor blocks than all other groups while the smaller dose (50 µgm DEX group) was combined with significantly prolonged duration of both sensory and motor blocks than the control group with no significant effects on the onset of corneal anesthesia nor the akinesia of the globe.

Hafez M et al. [38] studying the effect of adding different doses of Dexmedetomidine to peribulbar block in 160 patients undergoing vitreoretinal surgeries found a shorter onset time of corneal anesthesia in all groups which was statically significant in higher doses (D20, D25) when compared with the control group , as regards the onset of akinesia none of the groups had a statistically significant effects when compared with control group while the duration of analgesia and akinesia were statistically prolonged only in the D25 Group when compared with the control group.

A metaanalysis done by Abdullah FW et al. [39] showed that using dexmedetomine in as an additive different (either in brachial plexus
Dexmedetomidine has been used as an adjuvant to local anaesthetic drugs in peripheral nerve block and eye block [41]. This action is mainly due to blocking the hyperpolarization-activated cation current [42].

Menis D et al. [40] studying the effects of intravenous dexmedetomidine on rocuronium requirements in sevoflurane anaesthesia showed marked reduction in rocuronium doses and explained this by the hemodynamic effects of dexmedetomidine which could affect the pharmacokinetics of rocuronium.

Dexmedetomidine is a selective alpha 2 adrenoreceptor agonist. It produces a dose dependent sedation and analgesia, recently, Dexmedetomidine has been used as an adjuvant to LA drugs in peripheral nerve block and eye block [41]. This action is mainly due to blocking the hyperpolarization-activated cation current [42].

A study done by Talke PO et al. [43] on the effects of Dexmedetomidine on the neuromuscular blockade showed that dexmedetomidine resulted in a more decrease in the muscle force using mechanomyography. Although these changes were statistically significant, the investigators concluded that they were not clinically relevant. The mechanism by which α2-adrenergic receptor agonist produces analgesia and sedation is not fully understood but likely to be multifactorial. Peripherally, α2-agonist produces analgesia by reducing the release of norepinephrine and causing α2-receptor-independent inhibitor effect on nerve fiber action potential. Centrally, α2-agonists produce analgesia and sedation by inhibition of substance P release in the nociceptiive pathway at the level of the dorsal root neuron and by activation of α2-adrenoreceptor in the locus coeruleus [44].

As regards, hemodynamics our results showed no statically significant changes in HR nor in MAP in different measurement times. This was quite different from significant decrease in HR and MAP noticed in many studies, when dexmedetomidine was added to local anaesthetics [45,46]. This could be explained by that dexmedetomidine in these studies was given either parenterally or neuroaxially resulting in a central action by decreasing the sympathetic outflow and norepinephrine release.

While our results were similar to Hafez M et al. [38] study who failed to find any statically significant effects of peribulbar dexmedetomidine on haemodynamics.

As regards IOP, our results showed non-significant reduction in IOP in DEX and when compared with the control group and magnesium group.

Also, Hafez M et al. [38] study found a significant reduction in IOP at 5 and 10 min after injection in higher dose (D25) group compared to the baseline in the same group and also with the control group, while he found nonsignificant reduction in IOP in the smaller dose group.

In Eskander AM et al. [35] study, a significant reduction in IOP in DEX group was found at the end of surgery when compared to preoperative values and also when compared with the control group.

In Abdelhamid et al. [32] study more significant reduction was noticed in the IOP when Dexmedetomidine is injected intravenously.

The effects of dexmedetomidine on IOP could be explained by its vasoconstrictive effects on ciliary body blood vessels resulting in a decrease in aqueous humour formation [47]. The combined effects of dexmedetomidine on improving aqueous humour drainage thereby decreasing sympathetic vasoconstriction of aqueous drainage system [48] could be another explanation.

Regarding the assessment of Pain, theVAS during surgery showed significant lower scores in DEX and MgSO4 groups when compared with the control group with non-significant difference between DEX and MgSO4 groups.

This is in contrary to Hafez et al. [38] who found no significant effect to Dexmedetomidine addition in different doses on VAS score when compared to the control group.

The need of supplementary injections was significantly higher in the control group.

The sedation score was significantly higher in dexmedetomidine group when compared with other groups this could be explained by the systemic absorption of dexmedetomidine exerting central sedation effects by α2 agonistic effects which is similar to other studies [33].

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