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Intravenous magnesium-fentanyl sedation versus midazolam-fentanyl sedation before local anesthesia for eye surgery: a comparative study

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Abstract

Background: Phacoemulsification operation is a common practice nowadays, and it is usually done under local anesthesia in elderly patients who have multiple comorbidities. Sedation is important in these patients to eliminate intraoperative anxiety and stress response. The aim of this study is to compare the effect of single dose of intravenous magnesium sulfate to a single dose of 2 mg midazolam in patients receiving local anesthesia to the eye for phacoemulsification operation as regards the sedative effect, cardiovascular and respiratory stability.

Method: In this study, 100 patients (American physical status II-III, 50–75 years) were randomized to receive either intravenous magnesium sulfate 20 mg/kg IV bolus together with 25 μg fentanyl (M group) or 2 mg midazolam together with 25 μg fentanyl IV bolus (D group) during cataract surgery performed under peribulbar block. The study groups were compared with respect to hemodynamic variables, perception of pain during local anesthetic injection by using a numeric rating scale, intraoperative Ramsay Sedation Score, incidence of intraoperative complications, and patient and surgeon satisfaction by using a numeric rating scale.

Results: Intraoperative mean heart rate, systolic and diastolic blood pressures, and respiratory rate were found to be lower in the M group, while arterial oxygen saturation was significantly higher. The level of sedation was also better in the M group. The midazolam group showed also adequate sedation; however, three patients were agitated. Patients in the M group were more satisfied with the procedure and did not experience pain during application of local anesthetic to the eye, whereas surgeons were equally satisfied with both types of sedation given.

Conclusions: This study demonstrates that both combinations of drugs were effective in providing adequate level of sedation. However, intravenous magnesium sulfate 20 mg/kg IV bolus, together with 25 μg fentanyl, decreased pain on injection and provided effective sedation without causing respiratory depression.

Keywords: Magnesium, Sedation, Midazolam, Fentanyl, Local anesthesia, Eye surgery

Background

Regional anesthesia is a routine procedure that is commonly used nowadays for ophthalmic surgical procedures having the advantage of providing an immobile eye as well as a clear operative field and a low-normal intraocular pressure, and that's what makes it favorable to surgeons. But for the anesthetist, providing cardiovascular and respiratory stability; allowing patient to communicate during the procedure, rapid postoperative recovery, and preservation of protective airway reflexes; and avoiding general anesthesia complications in elderly and high-risk patients are the most important advantages of regional anesthesia (Murphy 1985).

However, pain at the puncture site, fear of needles, and recall of the procedure are considered major drawbacks of regional anesthesia. These factors stress the importance of sedation that offers analgesia, anxiolysis, and amnesia, thus preventing the hypertensive response to anxiety and providing patient comfort (Asehnoune et al. 2000;

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Table 1 Patients' characteristics in both study groups

Variable	Magnesium-fentanyl group ($n = 50$)	Dormicum-fentanyl group ($n = 50$)	p value
Age (year)	60.1 (8.2)	58.9 (7.4)	0.446
Male/female	23/27	24/26	0.841

Data are presented as mean (SD) or as ratio

American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists 2002).

Actually, many agents were used to provide sedation and anxiolysis during operations under local anesthesia such as midazolam, α_2 agonists (clonidine or dexmedetomidine), ketamine, sevoflurane, and remifentanil.

Magnesium (Mg) is the fourth commonest cation in the body and the second intracellular cation after potassium and activates approximately about 300 enzymatic pathways, including many that are involved in energy metabolism and nucleic acid synthesis (Fawcet et al. 1999).

Magnesium acts as a calcium channel blocker, plays an important role in catecholamine release in response to sympathetic stimulation, and is a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, hence its antinociceptive effects. Mg, which is a physiological calcium antagonist, also modulates and controls cell calcium entry and calcium release from sarcoplasmic and endoplasmic reticular membranes. This calcium transportation control is responsible for its numerous physiological roles among which are control of neuronal activity, cardiac excitability, neuromuscular transmission, muscular contraction, vasomotor tone, blood pressure, and peripheral blood flow (Fawcet et al. 1999), whereas the analgesic properties are due to NMDA receptor blocking actions.

Magnesium sulfate ($MgSO_4$) has been investigated as a possible adjuvant for intra- and postoperative analgesia in different kinds of surgeries including gynecological, orthopedic, and thoracic. The majority of these studies suggest that perioperative magnesium sulfate reduces anesthetic requirements and improves postoperative analgesia (Kara et al. 2002). Yet, its function as a sedative during regional anesthesia, to our knowledge, has not been discussed before.

Midazolam is the drug preferred and widely used for sedation due to its reasonably rapid on- and off-set time. It produces good sedation and excellent amnesia but depresses respiration and arterial blood pressure and has no specific analgesic properties. Cases of paradoxical reaction have been reported, with advanced age proposed as a predisposing factor. However, the availability of flumazenil as specific antagonist is an additional safety factor, although its elimination is faster than that of midazolam (de Andres and Bolinches 1993; Wilson et al. 2003; Martinez-Telleria et al. 1992; Höhener et al. 2008).

The aim of this study is to investigate the potential sedative and hemodynamic stability effect of a single IV dose of magnesium sulfate for sedation before local anesthesia of the eye during eye surgery, as we compared the use of either $MgSO_4$ or midazolam to patients undergoing eye surgery under local anesthesia, as regards their efficacy to provide hemodynamic stability (primary outcome) and adequate sedation, respiratory stability, and patient and surgeon satisfaction (secondary outcomes).

Methods

After ethics committee approval (R40 2016), 100 patients (ASA II–III, 50–75 years) of both sexes, with a body mass index (BMI) between 22 and 30 undergoing day-case phacoemulsification operation (phacoemulsification for cataract surgery), under local (peribulbar) anesthesia of the eye, were included in this study in the period between January 2013 and December 2013. The details regarding the study objectives and risks were fully explained to the patients and those who agreed to participate in the study gave a written consent.

Patient's refusal or those with a history of cardiovascular, hepatic, or renal dysfunction, neuromuscular diseases, opioid or analgesic abuse, allergy to local anesthetics, coagulation disorders, and preoperative treatment with calcium channel blockers were excluded from this study. Patients were excluded also if the expected surgery time exceeds an hour, or if they developed severe pain intraoperatively that mandated rescue analgesia and sedation or required the conversion to general anesthesia.

We conducted a prospective double-blind randomized study, and patients were randomly assigned into two

Table 2 Heart rate changes in both study groups

	Magnesium-fentanyl group ($n = 50$)		Midazolam-fentanyl group ($n = 50$)		
Heart rate (bpm)	Mean	SD	Mean	SD	p value
Pre-induction heart rate	68.4	12.2	73.0	13.7	0.076
1–10 min after sedation	68.0	11.6	73.4	14.2	0.041*
2–20 min after sedation	68.2	12.3	72.2	13.1	0.117
3–30 min after sedation	70.7	9.9	71.7	13.5	0.667
Postoperative heart rate	73.2	11.3	76.3	13.7	0.220

bpm beat per minute
*indicates a statistically significant result

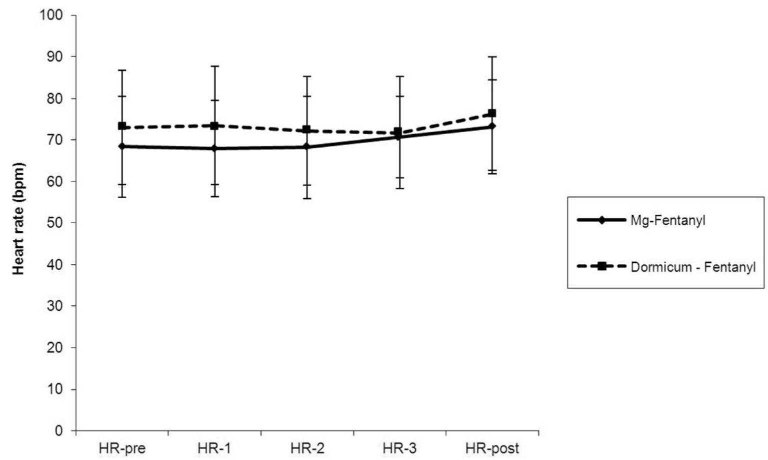

Fig. 1 Heart rate changes in both study groups. Markers represent means and error bars represent 95% C I

groups using a computer-generated random number table and sealed opaque envelops into two groups: The magnesium group (M group) received intravenous magnesium sulfate 10% (Magnisol Memphis For Pharmaceuticals & Chemical Industries, Cairo, Egypt) 20 mg/kg IV bolus together with 25 μg fentanyl (Sunny Pharmaceutical under license of Hameln pharmaceuticals, Germany) diluted in normal saline (NSS) to a volume of 10 ml given slowly over 5 min before peribulbar block of the eye is performed. The midazolam group (D group) received 2 mg midazolam (Dormicum 5 mg/5 ml Roche F. Hoffmann-La Roche Ltd., Basel, Switzerland) 0.01–0.03 mg/kg together with 25 μg fentanyl diluted in NSS to a volume of 10 ml given slowly over 5 min before peribulbar block. The study groups were compared with respect to hemodynamic variables; perception of pain during local anesthetic injection by using a numeric rating scale (NRS) (McCaffery and Pasero 1999) (1 = satisfied, 10 = unsatisfied); intraoperative Ramsay Sedation Score (RSS) (Ramsay et al. 1974), adequate sedation is considered at RSS 2 or 3; incidence of intraoperative complications; and patient and surgeon satisfaction by using the NRS from 1 to 10 (1 = satisfied and the procedure is well tolerated to 10 = unsatisfied).

In the induction room, all patients were connected to basic monitors (pulse-oximetry, non-invasive arterial blood pressure, and electrocardiogram). Heart rate (HR), ECG changes, arterial blood pressure, and arterial oxygen saturation (SpO_2) were recorded once before the start of intravenous sedation and every 10 min throughout the study period. Respiratory rate (RR) was recorded once before the start of intravenous sedation and every 10 min throughout the study period, and a mean was taken. A 20-G intravenous cannula was inserted and secured, and IV sedation was given slowly over 5 min to all patients.

In both groups, IV sedation either magnesium sulfate 20 mg/kg IV bolus, together with 25 μg fentanyl, or 2 mg

Table 3 Changes in systolic and diastolic blood pressures in both study groups

	Magnesium-fentanyl group ($n = 50$)		Midazolam-fentanyl group ($n = 50$)		
Blood pressure (mmHg)	Mean	SD	Mean	SD	*p* value
Pre-induction SBP	136.8	17.5	132.8	19.1	0.282
SBP-1	135.6	18.6	144.9	23.0	0.029*
SBP-2	132.1	19.8	140.3	23.0	0.061
SBP-3	133.0	15.9	134.9	20.8	0.612
Postoperative SBP	139.8	20.3	152.3	25.9	0.008*
Pre-induction DBP	79.0	7.4	81.6	8.7	0.111
DBP-1	80.8	9.3	85.1	11.4	0.044*
DBP-2	79.0	9.6	77.5	6.9	0.377
DBP-3	73.3	8.4	79.7	9.2	< 0.005*
Postoperative DBP	68.7	12.5	82.8	9.1	< 0.005*

SBP systolic blood pressure, *DBP* diastolic blood pressure
*Significant

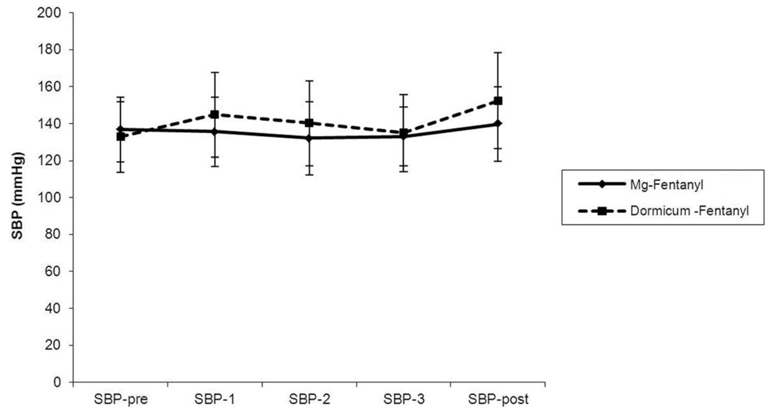

Fig. 2 Changes in systolic blood pressure (SBP) in both study groups. Markers represent means and error bars represent 95% CI

midazolam together with 25 μg fentanyl was given 5 min before performing peribulbar block to both study groups.

With the patient in the supine position, the eye upon which the surgery should be assigned and sterilized, topical anesthesia was applied to the eye and the block was performed under complete aseptic technique by injecting 5 ml of local anesthetic in the inferolateral region and additional 5 ml in the medial canthal region. The surgeon, patient, and the anesthetist were totally blinded to the randomization. After ensuring complete akinesia of the blocked eye, nasal prongs were applied to the patient's nostrils and oxygen flow of 4 L/min was delivered. The patient was monitored throughout the surgery.

Level of sedation was assessed using the RSS (where 1: patient is anxious and/or agitated, 2: patient is cooperative, oriented, and tranquil, 3: patient responds to commands only, 4: patient shows a brisk response to a light glabellar tap, 5: patient shows a sluggish response to a light glabellar tap, and 6: no response occurs). Adequate sedation was considered at RSS 2 or 3. Bradycardia was considered when HR is less than 60 bpm and was treated by IV atropine at 0.5-mg increments. Hypotension is defined as a 20% decrease from the baseline and was treated by IV ephedrine.

After the procedure, patients were monitored in the recovery room. The participants were asked to determine their satisfaction and tolerance to the procedure based on a NRS from 1 to 10 (1 = satisfied and the procedure is well tolerated to 10 = unsatisfied). Patients were also asked about experiencing pain during injection of local anesthesia using the NRS from 1 to 10 (1 = no pain during injection to 10 = sever pain) and about their willingness to repeat the procedure using the same technique.

Finally, the surgeon was asked to determine his satisfaction based on a NRS from 1 to 10 (1 = satisfied to 10 = not satisfied).

The study groups were compared with respect to hemodynamic variables, perception of pain during local anesthetic injection by using the NRS, intraoperative RSS, incidence of intraoperative complications, and patient and surgeon satisfaction by using the NRS.

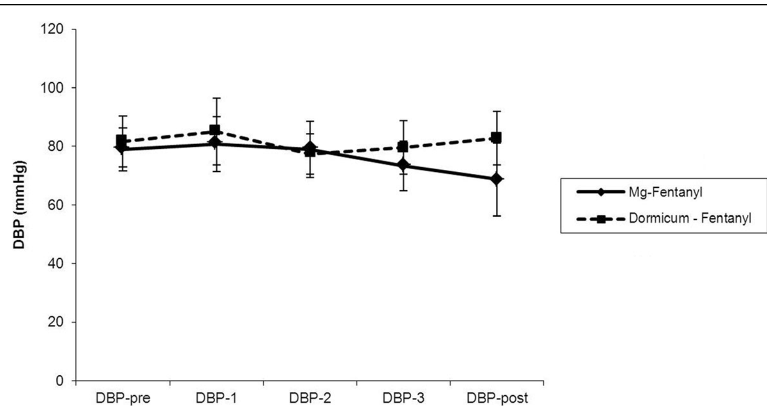

Fig. 3 Changes in diastolic blood pressure (DBP) in both study groups. Markers represent means and error bars represent 95% CI

Table 4 Changes in arterial oxygen saturation and respiratory rate in both study groups

	Magnesium-fentanyl group (*n* = 50)		Dormicum-fentanyl group (*n* = 50)		
Variable	Mean	SD	Mean	SD	*p* value
Pre-induction SpO_2 (%)	97.3	2.1	97.5	1.4	0.760
SpO_2–1 (%) 10 min	97.3	1.8	97.3	1.6	0.860
SpO_2–2 (%) 20 min	98.4	1.8	97.2	1.3	< 0.005*
SpO_2–3 (%) 30 min	98.6	1.4	96.8	0.9	< 0.005*
Postoperative SpO_2 (%)	98.2	2.0	97.5	1.2	0.034*
Respiratory rate (bpm)	11.4	0.6	11.8	0.7	0.003*

bpm breath per minute, *SpO_2* arterial oxygen saturation
*Significant

Statistical methods

The required sample size was calculated using G*Power software (Heinrich Heine Universität, Düsseldorf, Germany). It was estimated that a sample of 50 patients in either study group would achieve a power of 84% to detect an effect size (Cohen's *d*) of 0.6 as regards the difference in hemodynamic variables, and satisfaction scores between the two study groups.

Data were analyzed using IBM© SPSS© Statistics version 21 (IBM© Corp., Armonk, NY, USA).

Continuous numerical data were presented as mean and SD, and between group differences were compared using the unpaired *t* test. Discrete numerical data were presented as median and interquartile range, and inter-group differences were compared using the Mann-Whitney *U* test. Qualitative data were presented as number and percentage and the chi-square test or Fisher's exact test, when appropriate, was applied for comparison of between-group differences.

$P < 0.05$ was considered statistically significant.

Results

Our study included 100 patients scheduled for cataract surgery performed under peribulbar block. They included 47 males and 53 females with a mean age 60.1 ± 8.2 years in the M group and 58.9 ± 7.4 years in the D group. Baseline patients' characteristics were similar in both study groups (Table 1). The mean duration of the operation was about 30 min.

HR before intravenous sedation, 20 min, 30 min, and postoperative showed no significant difference in both study groups, whereas HR 10 min after IV sedation was significantly less in the M group which is 68.0 ± 11.6 beats/min compared to the D group which is 73.4 ± 14.2 beats/min (Table 2) (Fig. 1).

Regarding both systolic and diastolic blood pressure, they were significantly less in the M group 10 min after IV anesthesia compared to those in the D group. Post-operatively, there was a significant difference between the two groups regarding both systolic and diastolic blood pressures (Table 3, Figs. 2 and 3).

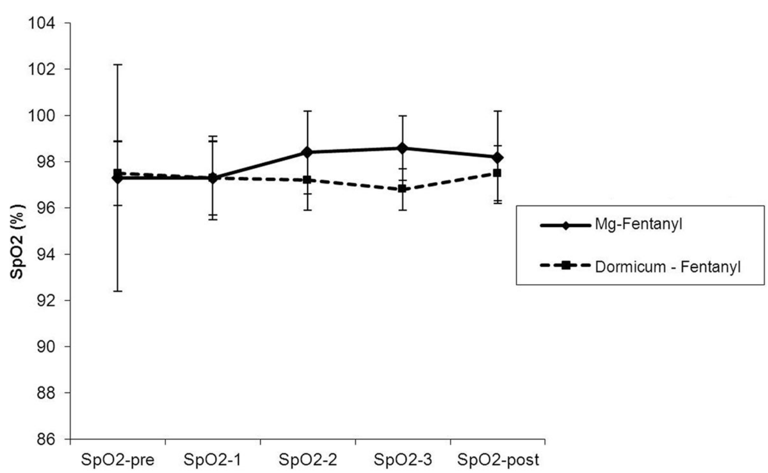

Fig. 4 Changes in arterial oxygen saturation (SpO_2) in both study groups. Markers represent means and error bars represent 95% CI

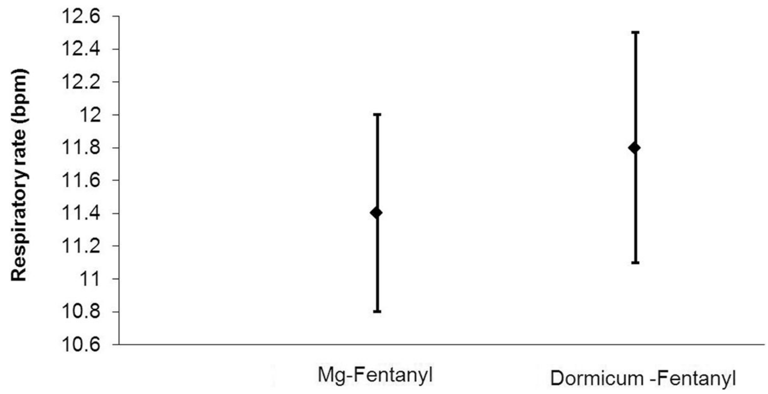

Fig. 5 Average respiratory rates in both study groups. Markers represent means and error bars represent 95% CI

Arterial oxygen saturation was significantly higher in the M group specially 20 min and 30 min; respiratory rate (RR) was also lower in the M group in comparison to the D group (Table 4, Figs. 4 and 5).

The level of sedation evaluated by the Ramsay Sedation Scores was better in the M group where most patients were quite oriented and cooperative throughout the procedure; only few were deeply sedated responding to commands. The midazolam group showed also adequate sedation; however, three patients were agitated (Table 5, Fig. 6).

Patients in the M group were more satisfied with the procedure and did not experience pain during application of local anesthetic to the eye. It is worth mentioning that patients in the midazolam group could not recall pain of injection because of anterograde amnesia caused by midazolam, so there was no significant difference between the two groups regarding pain on injection, whereas surgeons were equally satisfied with both types of sedation given (Table 5, Fig. 7).

No major adverse effects were observed in this study including ECG changes and pain during application of local anesthetic to the eye (Table 6).

Discussion

$MgSO_4$ has been reported to enhance the activity of local anesthetic agents as well as producing general anesthesia (James 1992). This may be due to its Ca-antagonizing effect which causes reduction of catecholamine release from the sympathetic nervous system and this may decrease peripheral sensitization of nociceptor as well as surgery-induced stress response. In addition to its being a NMDA receptor antagonist (Woolf and Thompson 1991), depressant effects of $MgSO_4$ on the central nervous system (CNS) of animals have also been reported (Feria et al. 1993).

IV Mg sulfate had been used as an adjuvant to general anesthesia in multiple studies with good results regarding hemodynamic stability and reduction in opioid dose, but to our knowledge, Mg sulfate has never been used for sedation during local anesthesia (Alhashemi 2006).

Many regimens and doses had been proposed and used for supplementing general anesthesia with commonly used dose of 30–40 mg/kg followed by infusion of 10–20 mg/kg/h (Feria et al. 1993; Alhashemi 2006). In our study, we used a smaller single bolus dose of $MgSO_4$ of 20 mg and no intraoperative infusion as the procedure was a short one (less than an hour).

In this randomized, double-blind study, we compared the effects of a single bolus dose of midazolam-fentanyl, which is the commonly used regimen for sedation during monitored anesthesia care during cataract surgery under local anesthesia, to a single bolus dose of magnesium sulfate-fentanyl and demonstrated that magnesium sulfate together with fentanyl can be used for sedation and may be even superior to a bolus dose of midazolam-fentanyl adjuvants of local anesthesia of the eye.

This was evident from the hemodynamic parameters, where HR, systolic and diastolic blood pressure, and RR

Table 5 Ramsay Sedation Score and patient and surgeon satisfaction scores in both study groups

	Magnesium-fentanyl group ($n = 50$)		Midazolam-fentanyl group ($n = 50$)		
Variable	Median	Interquartile range	Median	Interquartile range	*p* value
Ramsay Sedation Score	2	2–3	2	1–2	< 0.005*
Patient satisfaction score	3	2–3	3	3–4	< 0.005*
Surgeon satisfaction score	2	2–3	3	2–4	0.004*

*Significant

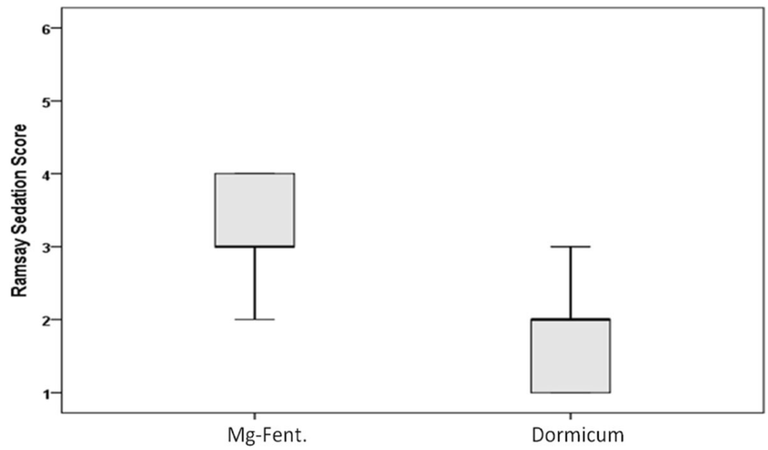

Fig. 6 Box plot showing Ramsay Sedation Scores in both study groups. Box represents interquartile range. Median is overlapped by 1st quartile in the magnesium-fentanyl group and by 3rd quartile in the midazolam-fentanyl group. Error bars represent minimum and maximum values

changes in M group patients were significantly more stable than those in D group patients. Moreover, patients in the M group were more satisfied with the type of sedation they received.

The lower HR and systolic and diastolic blood pressure observed in the M group could be because Mg is a physiological calcium antagonist that decreases sympathetic outflow and circulating levels of catecholamines; moreover, it controls calcium cell entry and release from the sarcoplasmic reticulum thus controlling the membrane's neuromuscular transmission, muscular contraction, vasomotor tone, blood pressure, and peripheral blood flow (Alhashemi 2006).

The dose of $MgSO_4$ we used in this study resulted in a more or less steady HR and systolic and diastolic blood pressure, with no episodes of severe bradycardia and hypotension. Our finding matched well with study done by Altan et al. (2005) and Telci et al. (2002) although they used a higher dose of $MgSO_4$ alone than ours.

Patients in the midazolam-fentanyl group showed a higher RR than those who were sedated with Mg-fentanyl and that may be because many patients in the D group were more anxious as proved by a RSS (Ramsay et al. 1974) of 1; this explanation may be supported by a higher HR in the same group.

This finding was also observed by Alhashemi, who used an IV bolus dose of midazolam of 20 μg/kg, and he attributed it to midazolam-induced decrease in tidal volume which in turn was compensated by increased RR to maintain minute ventilation (Alhashemi 2006); he also supported his hypothesis by the lower SpO_2 trend he also observed in patients who received midazolam which may be due to the shallow breathing with consequent atelectasis and ventilation-perfusion mismatch.

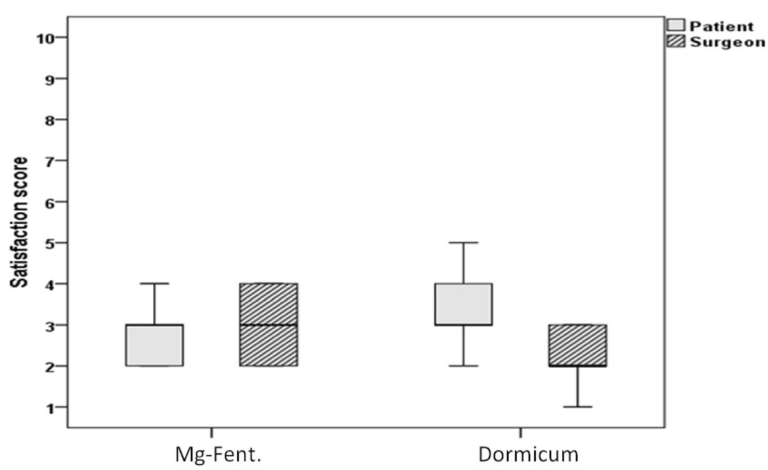

Fig. 7 Box plot showing patient and surgeon satisfaction scores in both study groups. Box represents interquartile range. Line across box represents median. Error bars represent minimum and maximum values

Table 6 Incidence of undesired side effects in both study groups

Side effect	Magnesium-fentanyl group ($n = 50$)	Midazolam-fentanyl group ($n = 50$)	p value
ECG changes	0 (0%)	(0%)	NA
Pain on injection	22 (44%)	22 (44%)	1.0

NA test not applicable

In this study, SpO_2 levels were lower in the D group when compared to those in the M group, which can be attributed to the decreased tidal volume (hypoventilation) caused by midazolam; yet, decrease in SpO_2 in the D group was not clinically significant. Moreover, hypoventilation cannot be proved as end tidal CO_2 was not monitored in our study, as oxygen was supplied through nasal prongs which cannot be connected to a capnogram.

Other investigators have also observed low SpO_2 readings among patients, who received midazolam sedation, and this has been attributed to hypoventilation or lack of supplemental oxygen administration (Inan et al. 2003), which is not the case in this study.

An interesting observation in this study was that although patients in the M group were more satisfied with the type of anesthesia they received, had less anxiety, and experienced no pain at local injection, patients of the D group had amnesia and did not remember injection during application of the local anesthesia.

Limitations of this study are that level of sedation was assessed by a Ramsay Sedation Score which is a well-established widely used score in monitored anesthesia care of cataract surgery; however, it requires clinician-patient interaction. Another method which is bispectral index is not a standard monitor during monitored anesthesia care. Another potential point of criticism is the lack of monitoring recovery time and time of discharge from the post-operative anesthesia care unit (PACU).

Midazolam sedation in our study was associated with lower patient satisfaction; Benedik and Manohin reported similar results when they compared midazolam during sedation in local eye surgery to propofol, the latter provided significantly better patient and surgeon satisfaction scores and earlier recovery times (Benedik and Manohin 2008). In another study by Lee and Lee, the addition of remifentanil to midazolam was associated with less intraoperative anxiety and greater patient satisfaction than midazolam alone (Lee and Lee 2011).

It is worth mentioning that significant adverse effects were observed in neither study group, including pain on injecting local anesthesia, nor postoperative nausea and vomiting which can be attributed to the small dose of fentanyl used.

Conclusions

In conclusion, both combinations of drugs were effective in providing an adequate level of sedation, and this was evident by equal surgeon satisfaction; however, patients in the M group were more satisfied with the type of sedation they received compared to those in the D group. This may be attributed to the additional analgesic property of $MgSO_4$ which is its NMDA receptor blocker activity. Moreover, $MgSO_4$ showed more hemodynamic stability which makes it preferred in elderly and high-risk patients.

However, the combination of this small dose of $MgSO_4$ and fentanyl needs more to be investigated in a wider variety of short procedures to validate its efficiency as a sedative.

Abbreviations

BMI: Body mass index; CNS: Central nervous system; HR: Heart rate; Mg: Magnesium; $MgSO_4$: Magnesium sulfate; NMDA: *N*-Methyl-D-aspartate; NRS: Numeric rating scale; PACU: Post-operative anesthesia care unit; RR: Respiratory rate; RSS: Ramsay Sedation Score; SpO_2: Arterial oxygen saturation

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Idea conception, data collection, data analysis, and editing of the manuscript were done by the two authors. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was done after institutional ethical committee approval with the committee's reference number (R40 2016). A consent to participate was signed by participants.

Consent for publication

A consent to publish has been obtained from the participants to report individual patient data.

Competing interests

The authors declare that they have no competing interests.

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