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Effect of *N*-methyl-D-aspartate (NMDA) receptor antagonist combination as adjuvant to general anesthesia in functional endoscopic sinus surgery

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Abstract

Background: This randomized, placebo-controlled, double-blind study was designed to assess controlled hypotension using *N*-methyl-D-aspartate (NMDA) receptor antagonists in patients undergoing functional endoscopic sinus surgery under general anesthesia.

Methods: In this randomized, double blind, prospective study, 40 patients undergoing functional endoscopic sinus surgery under general anesthesia were divided into two groups of 20 patients each. Group 1: Patients received after the induction of anesthesia an intravenous (IV) ketamine (racemic) bolus 0.2 mg/kg followed by continuous infusion 0. 15 mg/kg/h in addition to IV bolus of magnesium sulfate 50 mg/kg in 15 min, followed by a continuous infusion 8 mg/kg/h until extubation. Group 2: Patients received after the induction of anesthesia a bolus and a continuous infusion of normal saline (placebo) until extubation.
In both groups, nitroglycerin infusion was titrated to maintain mean arterial pressure (MAP) in the range of 50–60 mmHg. Intraoperative bleeding, the intraoperative nitroglycerin requirements, MAP, heart rate (HR), surgeon's satisfaction, VAS for pain, Aldrete score, and the incidence of adverse events were recorded.

Results: Group 1 patients had significantly lower (p value < 0.001) infusion rates of nitroglycerin than the placebo group 2 patients at all measured intervals. Intraoperative bleeding measured by bleeding scale was significantly less in group 1 than in group 2. The MAP was significantly lower in group 1 after starting infusion, after extubation, and at postanesthesia care unit (PACU) admission. The HR was significantly higher in group 2 during hypotensive period, after extubation, and at PACU admission. Surgeon satisfaction by using the Likert scale showed that group 1 was significantly higher than scores in group 2. As regards the use of postoperative rescue analgesic drug if VAS ˃ 3, the number of patients who needed pethidine as a postoperative rescue analgesic was significantly less in group 1 compared with group 2. There is no statistically significant difference between the two groups as regards the Aldrete score.

Conclusion: Continuous infusion of NMDA receptor antagonists magnesium and ketamine had led to optimal surgical field and reduction in MAP, heart rate, blood loss, and nitroglycerin consumption.

Keywords: Magnesium, Ketamine, NMDA antagonists, FESS

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Background

Functional endoscopic sinus surgery is a form of surgical intervention used for treatment of patients with nasal and paranasal sinus pathology and done under endoscopic magnification in a narrow area where surgical manipulation is difficult (Stammberger 1986). Intraoperative bleeding is one of the major problems during surgery which may diminish surgical visualization with only a small amount of bleeding (Boezaart et al. 1995). This may prolong the surgical duration and increase the chances of complications like orbital cellulitis, optic nerve injuries, and meningitis (Stankiewicz 1989). Patients' head elevation, topical vasoconstrictors together with local anesthetics, and controlled hypotension can be used to minimize bleeding and improve surgical field (Ankichetty et al. 2011).

Controlled hypotension involves reducing the patient's baseline mean arterial pressure (MAP) to 60–70 mmHg (Van Aken 2000) or 50–65 mmHg (Gokçe et al. 2009). A variety of medications can be used to induce intraoperative hypotension including calcium channel blockers, β-blockers, vasodilators, inhalational agents, propofol, and opioids (Degoute 2007).

IV magnesium sulfate may be a good agent for hypotensive anesthesia because magnesium interferes in the activation of membrane Ca ATPase and Na–K ATPase involved in transmembrane ion exchanges during depolarization and repolarization process and thus stabilizes cell membrane and the sarcoplasmic reticulum (Koinig et al. 1998). In addition, magnesium sulfate acts as a vasodilator by increasing the synthesis of prostacyclin, as well as inhibiting angiotensin converting enzyme activity (Sanders and Sim 1998). The effect of magnesium as *N*-methyl-D-aspartate (NMDA) receptor antagonist has led to studies of its adjuvant effect in perioperative analgesia (Dube´ and Granry 2003).

Ketamine is an antagonist at NMDA receptors, which are considered important in the mechanism of central hypersensitivity (Woolf and Thompson 1991). Low-dose ketamine given before surgical incision reduced the postoperative morphine requirement following abdominal and orthopedic surgery (Engelhardt et al. 2008).

This prospective, randomized, placebo-controlled, double-blind study was designed to assess controlled hypotension using the combination of two NMDA receptor antagonists in patients undergoing functional endoscopic sinus surgery under general anesthesia.

Patients and methods

The study was conducted in Ain Shams University hospitals at the E.N.T surgical department. After the institutional ethics committee approval, informed written consent was taken from each patient in the period from December 2015 till November 2016. This study was designed as a prospective, randomized, double blind clinical trial.

Forty ASA physical status I–II patients were studied. All were scheduled to undergo elective functional endoscopic sinus surgery under general anesthesia. Patients were chosen to participate in the study if they were at least 18 years old, willing to comply with the postoperative follow-up evaluations, within 50% of the ideal body weight, and had no clinically significant cardiovascular or central nervous system disease.

Exclusion criteria were age younger than 18 years or older than 50 years, history of chronic pain, regular medications with analgesics, analgesic use within 24 h of surgery, drug or alcohol abuse, psychiatric disorders, known allergy or contraindications to anesthetics or any drug used, asthma, renal insufficiency, hepatic disorder, history of a peptic ulcer or bleeding diathesis and pregnancy.

Baseline mean arterial blood pressure, heart rate, and peripheral oxygen saturation values were obtained using standard monitors. Twenty-two-gauge intravenous line was inserted and lactated Ringer's solution IV infusion was started at a rate of 40 ml/h in all patients. An intra-arterial catheter was inserted under local anesthesia in the radial artery for direct measurement of arterial blood pressure. Anesthesia was induced with propofol (2 mg/kg) and atracurium (0.5 mg/kg) and fentanyl (2 μg/kg) intravenously. Endotracheal intubation was done followed by mechanical ventilation in order to maintain the end expiratory CO_2 values between 34 and 36 mmHg.

After the induction of anesthesia, patients were randomly assigned to one of two groups using a computer-generated table.

Group 1: Patients received after the induction of anesthesia an intravenous (IV) ketamine (racemic) bolus (0.2 mg/kg) followed by continuous infusion (0.15 mg/kg/h) in addition to IV bolus of magnesium sulfate 50 mg/kg in 15 min, followed by a continuous infusion (8 mg/kg/h) until extubation.

Group 2: Patients received after induction of anesthesia a bolus and a continuous infusion of normal saline (placebo) until extubation.

Anesthesia was maintained with isoflurane (1.5%) at a fresh gas flow rate of 2 l/min and intermittent IV bolus of atracurium (0.1 mg/kg). Intraoperative mean arterial blood pressure was recorded at 5 min interval. After successful induction, nitroglycerin infusion was started at a rate of 0.5 μg/kg/min; this rate was subjected to change (increased or decreased) in order to maintain a mean arterial blood pressure (50–60 mmHg). The rate of infusion of nitroglycerin was recorded every 5 min and then at the end of the procedure.

Bradycardia (HR < 50 bpm) was treated with IV atropine (0.5 mg), and hypotension (MAP < 50 mmHg) was

treated with decrease infusion rate of nitroglycerin, IV 10 ml/kg 0.9% saline and ephedrine 5 mg.

Morphine of 2 mg IV was administered immediately before discontinuing isoflurane. At the end of surgery, residual neuromuscular blockade was antagonized with neostigmine of 50 μg/kg and atropine of 0.01 mg/kg IV.

To follow the double-blind nature of the study, drugs were prepared by an independent anesthesia technician and diluted to a fixed volume for every single drug used. The anesthesiologist who attended the surgery and recorded the data was also blind to both groups assigned.

Intraoperative bleeding was assessed by a bleeding scale (0–4), acceptable bleeding score being 0–2 Jacobi et al, 2000. Bleeding in the operative field was objectively evaluated by the same surgeon every 15 min.

After the completion of the surgery, patients were transferred to the recovery room where the following were done:

- Assessment of postoperative pain using the visual analogue scale (0–10 cm); if visual analogue scale (VAS) was > 3, analgesia was provided with intravenous pethidine 0.5–1 mg/kg.
- Assessment of the Aldrete score (Thomas and Macario 2005) in the recovery room every 5 min, till score of 10 was achieved. The time to achieve the Aldrete score of 10 was recorded, which was the time to shift the patient to the ward.
- Surgeons were also asked to rate their satisfaction with operative conditions, using the 7-point Likert verbal rating scale at the end of surgery, acceptable satisfaction score being 5 to 7 (Norman 2010).
- Serum magnesium was assessed 1 h postoperatively.
- Any complication related to the study drug or techniques were recorded.

Various scores used in the study are as follows:

A. Intraoperative bleeding scale
   0—no bleeding
   1—slight bleeding; no suctioning of blood required
   2—slight bleeding; occasional suctioning required. Surgical field not threatened.
   3—slight bleeding; frequent suctioning required. Bleeding threatened surgical field a few seconds after suction was removed.
   4—moderate bleeding; frequent suctioning required. Bleeding threatened surgical field directly after suction was removed.
B. Likert scale
   1. Extremely dissatisfied
   2. Dissatisfied
   3. Somewhat dissatisfied
   4. Undecided
   5. Somewhat satisfied
   6. Satisfied
   7. Extremely satisfied
C. Postanesthesia Recovery Score (modified Aldrete score)

Parameter	Score		
	2	1	0
Activity	Moves all extremities voluntarily or on command	Moves two extremities voluntarily or on command	Unable to move extremities
Respiration	Breathes deeply and coughs freely	Dyspnea, shallow or limited breathing	Apneic
Circulation	BP ± 20 mm of preanesthetic level	BP ± 20–50 mm of preanesthetic level	BP ± 50 mm of preanesthetic level
Consciousness	Fully awake	Arousable on calling	Not responding
Oxygen saturation	SpO_2 > 92% on room air	Supplemental O_2 required to maintain SpO_2 > 90%	SpO_2 < 90% with O_2 supplementation

Total score = 10; a score of ≥ 9 required for discharge

D. Visual analogue scale ranging from 0 cm (no pain) to 10 cm (worst pain)

Statistical analysis

The mean and standard deviation of the surgical field score from a previous study was 2.665 ± 0.410 (Chauhan et al. 2016). Taking power of 0.9 and alpha error of 0.05, a minimum sample size of 16 patients per group was needed to detect the difference of 0.465 in the surgical field score. Twenty patients were included for each group to compensate for possible 20% dropouts.

The statistical analysis was performed using a standard SPSS software package version 17 (Chicago, IL). Normally distributed numerical data were presented as mean ± SD and were compared using Student's t test. Non-normally distributed numerical data were presented as median (IQR) and were compared using Mann-Whitney U test. ANOVA was used to analyze the MAP and HR. Categorical variables were analyzed using the χ^2 test, with p values < 0.05 considered statistically significant.

Results

The demographic data of the two study groups are summarized in Table 1. Statistical analysis revealed non-significant differences between the two study groups as regards age, weight, sex distribution, ASA physical status, and the duration of surgery.

Table 1 Demographic data

	Group 1 $n = 20$	Group 2 $n = 20$	P value
Age (years)	32.55 ± 8.43	30.95 ± 8.87	0.562
Weight (kg)	71.45 ± 8.6	76.733±	0.593
Gender (male/female)	11/ 9	12 /8	1
ASA status I/II	16/4	17 /3	1
Surgical time (min)	76.45 ± 6.75	79. 1 ± 7.03	0. 231
Intraoperative IV fluid intake (ml)	600 (40)	630 (60)	0.07

Data are expressed as mean (SD) or number of patients
ASA American Society of Anesthesiologists

Group 1 patients had significantly lower (p value < 0.001) infusion rates of nitroglycerin than the placebo group 2 patients at all measured intervals (Table 2).

Intraoperative bleeding measured by the bleeding scale was statistically significantly less in group 1 than in group 2. The bleeding scale was 1 (0.25–1.75) in group 1, while in group 2, it was 2 (2–3) (p ˂ 0.001) Table 2.

The MAP (Fig. 1) was significantly lower in group 1 after starting infusion, after extubation, and at PACU admission. The HR (Fig. 2) was significantly higher in group 2 during hypotensive period, after extubation, and at PACU admission.

As regards the use of postoperative rescue analgesic drug if VAS ˃3, there was statistically significant difference between the two studied groups where 5 patients in group 1 (25%) and 12 patients in group 2 (60%) needed pethidine injection (p ˂ 0.05) (Table 2).

No statistically significant difference between the two groups as regards the recovery time. Time to achieve score 10 in Alderate score was 28.1 ± 3.46 min in group 1 in comparison to 26.85 ± 2.56 min in group 2 (p value > 0.05) (Table 2).

Surgeon satisfaction by using the Likert scale showed that group 1 score of 5 (5–6) was significantly higher than scores in group 2 which is 3.5 (3–4) (p value < 0.001) (Table 2).

Table 2 Operative and postoperative data

	Group 1 $n = 20$	Group 2 $n = 20$	p value
Average rate of nitroglycerin infusion (μg/kg/min)	0.75 ± 0.2115	1.32 ± 0.35	< 0.001
Bleeding score	1 (0.25–1.75)	2 (2–3)	< 0.001
Rescue analgesic needed (*n*, %)	5 (25%)	12 (60%)	0.04
Recovery time (min)	28.1 ± 3.46	26.85 ± 2.56	0.208
Surgeon satisfaction	5(5–6)	3.5 (3–4)	< 0.001
Postoperative serum Mg (mmol l^{-1})	1.10 (0.09)	0.82 (0.20)	< 0.001

Data are presented as mean (SD), median (1st–3rd quartile), or numbers of patients (percentage)

Patients in group 1 had significantly higher serum Mg concentrations 1 h postoperative than those in group 2, but there was no signs of hypermagnesemia (delayed recovery, delayed ankle jerk reflex, bradycardia, or respiratory depression).

No other complication related to the study drug or techniques such as signs of hallucinations, nausea, vomiting, rebound hypertension, or postoperative bleeding.

Discussion

This study evaluated NMDA receptor antagonists as a hypotensive anesthesia adjuvant to general anesthesia in functional endoscopic sinus surgery; there was a objectively better operative field, reduced intraoperative nitroglycerin consumption, less postoperative pain, and more surgeon satisfaction. In our study, the NMDA group received after the induction of anesthesia an intravenous (IV) ketamine (racemic) bolus (0.2 mg/kg) followed by continuous infusion (0.15 mg/kg/h) in addition to IV bolus of magnesium sulfate (50 mg/kg) in 30 min, followed by a continuous infusion (8 mg/kg/h) until extubation. This resulted in a steady reduction in heart rate and MAP, with no episodes of severe hypotension.

The possible mechanism for the reduction of the intraoperative nitroglycerin requirements is vasodilator action of magnesium sulfate by increasing the synthesis of prostacyclin, as well as inhibiting angiotensin-converting enzyme activity (Engelhardt et al. 2008). Also, using magnesium sulfate had analgesic effect due to antagonism of NMDA receptors in the CNS, and reduction of catecholamine release by sympathetic stimulation, thus decreasing peripheral nociceptor sensitization or the stress response to surgery (Dube´ and Granry 2003). Magnesium sulfate was chosen as a vasodilator with minimal myocardial depression. It produces a dose-dependent depressant effect on cardiac contractility, and it has been shown that the negative inotropic effect of magnesium on heart ceased by lowering of the peripheral vascular resistance, thus maintaining cardiac output (Nakaigawa et al. 1997). Magnesium was given before the operation to control intraoperative hypertension which has been studied in hypertensive patients undergoing cataract surgery with local anesthesia (Nastou et al. 1995) and was shown to reduce the intraoperative variability in arterial pressure.

The ketamine dose used in this study (0.2 mg/kg followed by continuous infusion 0.15 mg/kg/h) proved its safety and effectiveness (Tsui et al. 2007). Using ketamine as recommended for analgesia (< 1 mg/kg), adverse effects seem to be absent (Engelhardt et al. 2008).

The dual effect of ketamine of being a good analgesic at sub-anesthetic doses and NMDA receptors antagonist makes this drug somewhat an unusual analgesic

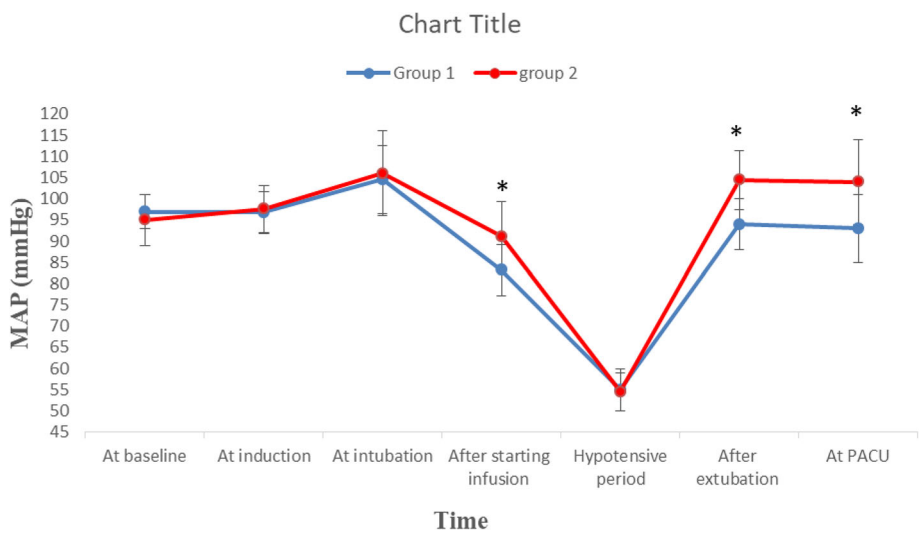

Fig. 1 MAP (mmHg) at various times of measurements of the studied groups. Asterisk indicates significant difference between the studied groups. MAP mean arterial pressure

(Hadi et al. 2009). However, this unusual analgesic action is well documented as is its ability at low doses to induce a morphine-sparing effect, which can be a very useful effect to utilize postoperatively (Himmelseher and Durieux 2005), and for this reason, we had chosen low-dose ketamine in this study. Furthermore, the low dose of ketamine would lead to less tachycardia, hypertension, and a shorter duration of action, which potentially would result in lower incidence side effects such as postoperative hallucinations and emergence delirium (Stubhaug et al. 1997).

Hypotension is tolerated in all patients without any untoward adverse effect during surgery and in the postoperative period. In none of the patients, rebound hypertension or postoperative bleeding was noted.

Conclusion

We concluded that continuous infusion of the two NMDA receptor antagonists magnesium and ketamine had led to optimal surgical field and reduction in MAP, heart rate, blood loss, and nitroglycerin consumption.

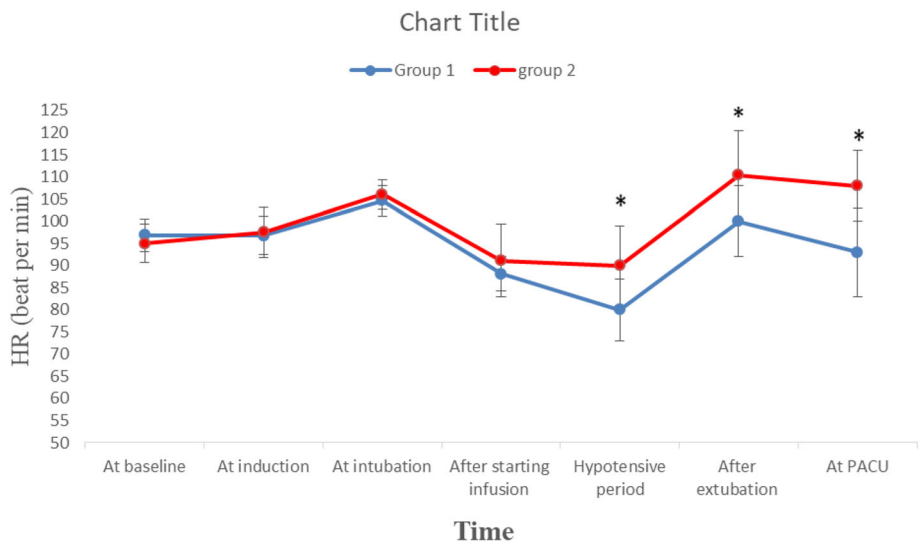

Fig. 2 HR at various times of measurements of the studied groups. Asterisk indicates significant difference between the studied groups. HR heart rate

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
MA analyzed and interpreted the patient data. KYH was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study protocol was approved by Ain Shams University ethics committee. Informed written consent was taken from each patient.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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