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SCIENTIFIC ARTICLE

Comparison between magnesium sulfate and dexmedetomidine in controlled hypotension during functional endoscopic sinus surgery

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Controlled hypotension;
Dexmedetomidine;
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Magnesium sulfate

Abstract
Background and objectives: It is crucial to decrease bleeding during functional endoscopic sinus surgery. Our primary goal was to investigate the effects of magnesium sulfate and dexmedetomidine used for controlled hypotension on the visibility of the surgical site.
Methods: 60 patients aged between 18 and 65 years were enrolled. In the magnesium sulfate group (Group M), patients were administered 40 mg/kg magnesium sulfate in 100 mL saline solution over 10 min as the intravenous loading dose 10 min before induction, with a subsequent 10–15 μg/kg/h infusion during surgery. In the dexmedetomidine group (Group D), patients were administered 1 μg/kg dexmedetomidine in 100 mL saline solution as the loading dose 10 min before surgery and 0.5–1 μg/kg/h dexmedetomidine during surgery. Deliberate hypotension was defined as a mean arterial pressure of 60–70 mmHg.
Results: Bleeding score was significantly decreased in Group D ($p = 0.002$). Mean arterial pressure values were significantly decreased in Group D compared to that in Group M, except for the initial stage, after induction and 5 min after intubation ($p < 0.05$). The number of patients who required nitroglycerine was significantly lower in Group D ($p = 0.01$) and surgeon satisfaction was significantly increased in the same group ($p = 0.001$). Aldrete recovery score ≥ 9 duration was significantly shorter in Group D ($p = 0.001$). There was no difference between the two groups in terms of recovery room verbal numerical rating scale.
Conclusions: Dexmedetomidine can provide more effective controlled hypotension and thus contribute to improved visibility of the surgical site.

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PALAVRAS-CHAVE
Hipotensão controlada;
Dexmedetomidina;
Cirugia funcional endoscópica dos seios paranasais;
Sulfato de magnésio

Comparação entre dexmedetomidina e sulfato de magnésio em hipotensão controlada durante cirurgia funcional endoscópica dos seios paranasais

Resumo
Justificativa e objetivos: Diminuir o sangramento durante a cirurgia funcional endoscópica dos seios paranasais é essencial. Nosso objetivo primário foi investigar os efeitos de dexmedetomidina e sulfato de magnésio, usados para o controle da hipotensão, sobre a visibilidade do sítio cirúrgico.
Métodos: Foram incluídos no estudo 60 pacientes entre 18 e 65 anos. No grupo sulfato de magnésio (Grupo M), receberam 40 mg de sulfato de magnésio em 100 mL kg^{-1} de solução salina durante 10 minutos como dose de carga intravenosa 10 minutos antes da indução e infusão subsequente de 10-15 $\mu g\,kg^{-1}\,h^{-1}$ durante a cirurgia. No grupo dexmedetomidina (Grupo D), receberam 1 $\mu g\,kg^{-1}$ de dexmedetomidina em 100 mL de solução salina durante 10 minutos como dose de carga 10 minutos antes da cirurgia e 0,5-1 $\mu g\,kg^{-1}\,h^{-1}$ de dexmedetomidina durante a cirurgia. Hipotensão controlada foi definida como pressão arterial média de 60-70 mmHg.
Resultados: O volume de sangramento diminuiu significativamente no grupo D ($p = 0{,}002$). Os valores da pressão arterial média foram significativamente menores no Grupo D, em comparação com o Grupo M, exceto no estágio inicial, pós-indução e cinco minutos pós-intubação ($p < 0{,}05$). No Grupo D, o número de pacientes que necessitou de nitroglicerina foi significativamente menor ($p = 0{,}01$) e o grau de satisfação do cirurgião foi significativamente maior ($p = 0{,}001$). O tempo de recuperação para atingir o escore de Aldrete ≥ 9 foi significativamente menor no grupo D ($p = 0{,}001$). Não houve diferença entre os dois grupos em relação aos escores da escala numérica de classificação verbal na sala de recuperação.
Conclusões: Dexmedetomidina pode proporcionar um controle mais eficaz da hipotensão e contribuir, assim, para uma melhor visibilidade do sítio cirúrgico.

Introduction

Controlled hypotension is performed in order to reduce blood loss and the need for transfusion during the surgery and to improve visibility of the surgical site by decreasing the arterial pressure until hypotension is reached.[1] The primary surgical treatment for chronic rhinosinusitis is functional endoscopic sinus surgery (FESS). Intraoperative bleeding can diminish the visibility of the surgical site, leading to an increased rate of complications. Therefore, improving the visibility of the surgical site by reducing bleeding during FESS is an important issue for anesthesiologists.[2] In controlled hypotension, several agents have been used, either alone or in combination with each other; however, an ideal agent for inducing controlled hypotension cannot be asserted. The ideal agent used for controlled hypotension must have certain characteristics, such as ease of administration, a short onset time, an effect that disappears quickly when administration is discontinued, rapid elimination without toxic metabolites, negligible effects on vital organs, and predictable and dose-dependent effects.[1,3–5]

Dexmedetomidine is a highly selective α_2-adrenoceptor agonist with sedative, anxiolytic, and analgesic characteristics. Dexmedetomidine mediates central α_{2A} and imidazoline type 1 receptors. The activation of these central receptors results in a decrease in norepinephrine release and leads to a decrease in blood pressure and heart rate.[6]

It has been reported that magnesium sulfate is a good agent for controlled hypotension, and that it stabilizes the cell membrane and intracytoplasmic organelles by mediating the activation of Na^+-K^+ ATPase and Ca^{++} ATPase enzymes, which play a role in transmembrane ion exchange during the depolarization and repolarization phases.[5,7,8] In addition, Mg^{++} inhibits the release of norepinephrine by blocking the N-type Ca^{++} channels at nerve endings and thus decrease the blood pressure.[9]

There are several studies which have assessed the effectiveness of dexmedetomidine and magnesium sulfate in controlled hypotension. These two agents have been compared with other hypotensive agents in terms of their role in hypotensive anesthesia, but to the best of our knowledge, no study comparing these two agents with each other has been cited in the scientific literature.[2,5,7,10]

Our primary goal in this study was to compare the effects of dexmedetomidine and magnesium sulfate agents on the visibility of the surgical site; our secondary goal was to compare these two agents in terms of satisfaction of the surgeon, recovery period, adverse effects and postoperative analgesia.

Materials and methods

This study is a randomized, prospective study and was conducted on 60 ASA I–II patients aged between 18 and 65 years

who were selected for FESS, between January 2012 and July 2013. This study was approved by the local ethics committee (No: 2011-221), and informed consent was obtained from the patients. The study was conducted according to the Declaration of Helsinki. Patients with kidney, liver, hematological and neuromuscular diseases, diabetic neuropathy or any known allergy history to studied agents were excluded from the study. Those with a body weight exceeding the ideal body weight by more than 30% and those receiving calcium channel blockers, non-steroidal anti-inflammatory drugs, agents affecting neuromuscular blockage, and agents contraindicated for controlled hypotension were also excluded from the study. Patients and their relatives were informed for verbal numerical rating scale (NRS) (0: no pain, 10: severe pain) at the preoperative patient examination. All patients were administered a 5 mL/kg/hour intravenous (i.v.) isotonic solution(Lactated Ringer) infusion 2 h before the induction, which was continued during the surgery.

After the patients were taken into the operating room, mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation (SpO_2) and end tidal carbon dioxide were monitored (Datex Ohmeda S/5, Helsinki, Finland); hemodynamic data were measured every 5 min. Hemodynamic data were recorded at the initial phase, after the induction, 5, 10, 15, 30 and 45 min after intubation, and 1 and 5 min after extubation.

Patients were divided into two groups by choosing randomly from sealed envelopes. The study participants, operation nurse and the otorhinolaryngologist constituted the 'blind' study group. An anesthetist who did not take part in the intra-operative follow-up prepared the medicine used. For topical vasoconstriction and local anesthesia, 1/1000 epinephrine soaked cotton was placed in the nasal cavity for 5 min. A solution containing 40 mg/2 mL lidocaine hydrochloride + 0.025 mg/2 mL epinephrine (Jetocaine, Adeka, Istanbul, Turkey) was applied to the nasal side of both the medial and lateral conchae at the same dose. To the patients in Group M, 40 mg/kg i.v. magnesium sulfate (OSEL, İstanbul, Turkey) in 100 mL saline solution was applied as a loading dose 10 min before the induction and then titrated at an infusion rate of 10–15 mg/kg/hour to maintain MAP within the target range during surgery. To the patients in group D, 1 μg/kg i.v. dexmedetomidine (Precedex; Hospira, Rocky Mount, NC, USA) in 100 mL saline solution was applied 10 min before surgery and then titrated at an infusion rate of 0.5–1 μg/kg/hour to maintain MAP with in the target range during surgery. These dosages were based on a previous study,[5,10–12] whereas the magnesium and dexmedetomidine infusion rates were chosen to sustain the target MAP and avoid the serious hemodynamic side effects.

Deliberate hypotension was defined as an MAP of 60–70 mmHg[7]; 50 μg nitroglycerine was applied in the presence of MAP exceeding 70 mmHg and 5 mg ephedrine was applied in the presence of MAP under 55 mmHg. Bradycardia was defined as a heart rate decreased by more than 20% of the initial heart rate; 0.5 mg i.v. atropine was applied to patients who developed bradycardia.

Neuromuscular stimulus was monitored via accelometry of the right adductor pollicis muscle in all patients (TOF-Guard®; Biometer, Denmark). After placing the surface electrodes on the ulnar nerve area of the wrist, 2.5 mg/kg propofol and 1 μg/kg fentanyl i.v. were administered in order to induce anesthesia. After achieving unconsciousness, single muscle twitch auto-calibration at the level of 100% was performed with the use of supramaximal stimulus (60 mA) before rocuronium injection. To the patient 0.6 mg/kg i.v. rocuronium was injected and orotracheal intubation was performed after achieving T1 = 0%. Anesthesia was maintained with 50% nitrous oxide and 50% oxygen, and 5–6% desflurane was adjusted to achieve a target Bispectral Index (BIS) between 40 and 60. The BIS electrodes were placed on the forehead and were connected to an A-2000 BIS monitoring system (Aspect Medical System Inc. Natick, MA, USA). The presence of hypertension or tachycardia during anesthesia, while BIS was between 40 and 60, was attributed to insufficient analgesia and a bolus dose of fentanyl 1 μg/kg was given.

Volume-controlled mechanical ventilation was performed with an end-tidal carbon dioxide pressure between 35 and 40 mmHg (Avance S/5, GE Datex-Ohmeda, Helsinki, Finland). Patients were intraoperatively warmed with an underbody heated blanket (Astoped Duo 120 control unit, Stuttgart, Baden-Wurttemberg, Germany). Skin temperature of the patient measured on the adductor pollicis muscle was maintained above 32 °C. An esophageal temperature probe was inserted into the lower esophagus after the intubation for measuring the core temperature, and normothermia was accomplished with the use of warmed intravenous fluids (enFlow IV Fluid/Blood warmer system, Lexington, MA, USA) during the surgery. In the presence of T1 exceeding 25% of the control value, 0.15 mg/kg rocuronium was applied in order to maintain the T1 under 10% during surgery. Magnesium sulfate and dexmedetomidine infusions were discontinued at the end of the surgery. Then, 0.02 mg/kg atropine and 0.04 mg/kg neostigmine was applied in order to antagonize the neuromuscular blockage in the presence of T1 responses exceeding the control value by 25%. The periods between stopping the anesthesia and extubation and between extubation and opening the eyes with a loud verbal stimulus were determined as the extubation duration and eye opening duration, respectively. Patients were extubated when BIS $\geq$ 70. The time passing until an Aldrete post-anesthesia recovery score $\geq$9 was defined as the recovery period.[13] Aldrete score was evaluated by an anesthetist who was 'blind' in terms of patient groups every 15 min for 60 min. Patients with an Aldrete score $\geq$9 were transferred to the ward. All patients were operated by the same surgeon, and surgical site was rated according to a 6-point scale every 5 min by him in terms of bleeding and dryness (Table 1)[14]: 0 = no bleeding; 1 = minor bleeding, no aspiration required; 2 = minor bleeding, aspiration required; 3 = minor bleeding, frequent aspiration required; 4 = moderate bleeding, visible only with the aspiration; and 5 = severe bleeding, continuous aspiration required, very hard to perform surgery. Surgeon satisfaction was scored by the same surgeon with a 4-point scale: 1 = bad, 2 = moderate, 3 = good, 4 = excellent.

All intraoperative and postoperative complications were recorded. Patients with NRS > 4 were treated with 50 mg dexketoprofen i.v., and those with nausea were given 10 mg metoclopramide i.v. Patients who displayed shivering were warmed with heated blankets.

Table 1 Category scale for assessment of intraoperative surgical field and surgeon satisfaction score.

Variable	Group D ($n = 30$) (%)	Group M ($n = 30$) (%)	p-Value
Bleeding score (n; %)			0.002
0	2 (6.6)	0 (0)	
1	21 (70)	10 (33.3)	
2	6 (20)	11 (36.6)	
3	1 (3.3)	5 (16.6)	
4	0 (0)	4 (13.3)	
5	0 (0)	0 (0)	
Satisfaction score (n;%)			0.001
1	0 (0)	4 (13.3)	
2	2 (6.6)	10 (33.3)	
3	8 (26.6)	8 (26.6)	
4	20 (66.6)	8 (26.6)	

Group D, dexmedetomidine group; Group M, magnesium sulfate group
Data show the number of cases and the percentage rate. p value calculated using Chi-square test.
Bleeding score: 0 = no bleeding; 1 = slight bleeding-no suction of blood required; 2 = slight bleeding-occasional suctioning required. Surgical field not threatened; 3 = slight bleeding-frequent suctioning required. Bleeding threatens surgical field a few seconds after suction is removed; 4 = moderate bleeding-frequent suctioning required. Bleeding threatens surgical field directly after suction is removed; 5 = severe bleeding-constant suctioning required. Bleeding appears faster than can be removed by suction. Surgical field severely threatened and surgery not possible.
Satisfaction score: 1 = poor; 2 = moderate; 3 = good; 4 = very good.

Statistical analysis and study sample size calculation

All statistical analyses were performed R 3.0.2 software (www.r-project.org). Student's t test was used for the comparison of hemodynamic parameters and duration of anesthesia, operation, extubation, eye opening, and Aldrete recovery score $\geq$9. Mann–Whitney U test was used for the comparison of NRS values; Chi-square test was used to compare surgeon satisfaction and visibility of the surgical site, while Fisher's exact test was used in comparison of bradycardia, hypotension, vomiting, shivering, and number of patients requiring fentanyl and nitroglycerine administration. To determine the changes over time in each group, we used repeated measures ANOVA, and multiple comparisons were corrected using Bonferroni's method. $p < 0.05$ was defined as statistically significant. Sample size calculation was based on the initial pilot study. Since α, β and average difference values were calculated as 0.05, 0.20 and 0.5, respectively, (1.1 ± 0.56 and 1.6 ± 0.69) for 10 patients in each group in terms of the 20th min bleeding score, a minimum of 25 patients were calculated as necessary for each group.

Results

Sixty patients were enrolled in the study and all patients completed the study. Demographic data, BIS values, total rocuronium necessity, duration of operation and anesthesia were similar in each group ($p > 0.05$) (Table 2). MAP was significantly lower in Group D than in Group M for all measurements except the initial stage, after induction and 5 min after intubation ($p < 0.05$) (Fig. 1). HR was significantly lower in all measurements except the initial stage in Group D compared to Group M ($p < 0.05$) (Fig. 2). Bleeding score was significantly decreased in group D ($p = 0.002$) (Table 1, Fig. 3). Surgeon satisfaction was significantly better in Group D (p: 0.001) (Table 1).

There was no significant difference between the two groups in terms of bradycardia, hypotension, vomiting, shivering and fentanyl necessity. Nitroglycerine necessity was significantly lower in Group D ($p = 0.01$) (Table 2). The two groups were similar in terms of extubation and eye opening duration. The duration until reaching an Aldrete score $\geq$9 was significantly shorter in Group D ($p = 0.001$) (Table 2). There was no difference in terms of the 15th, 30th, 45th and 60th min NRS scores [Group D = 3 (2–6); 3 (2–6); 3(2–5); 3 (2–4); Group M = 3 (1–6); 3 (1–6); 3 (2–5); 3 (2–5) median (min–max) respectively] ($p > 0.05$).

Discussion

This study revealed that dexmedetomidine was more effective in performing controlled hypotension during FESS and that it provided a better surgical site and surgeon satisfaction and a lower necessity of additional hypotensive agent than magnesium sulfate.

In a study assessing the hypotensive effects of dexmedetomidine administered as a 0.4 μg/kg/hour i.v. infusion following a 1 μg/kg i.v. bolus dose in middle ear surgery, it has been reported that surgeon satisfaction was increased and inhalation agent necessity to decrease the MAP by up to 30% was decreased in the dexmedetomidine administered patient group.[15] Secondary decrease in the heart rate and blood pressure due to the inhibiting effects of dexmedetomidine on central sympathetic stimulus and stimulation of the peripheral α_2 adrenoceptors in vascular smooth muscle tissue is considered to be responsible for

Table 2 Perioperative characteristics and data.

	Group D ($n = 30$)	Group M ($n = 30$)	p-Value
Gender (F/M)	22/8	19/11	0.54[a]
Age (year)	45.1 ± 11.1	39.5 ± 11.3	0.77
Body weight (kg)	76.6 ± 6.1	76.7 ± 12.5	0.95
Duration of anesthesia (min)	67.4 ± 20.5	72 ± 17.3	0.39
Duration of surgery (min)	55.9 ± 18.3	61.5 ± 17.3	0.26
Extubation time (min)	4.5 ± 2.3	5.8 ± 2.9	0.08
Eye opening time (min)	4.1 ± 1.9	4.6 ± 2.2	0.39
Time required to reach Aldrete score ≥9 (min)	11.8 ± 2.5	14.8 ± 3.0	**0.001**
Bradycardia	4 (13.3%)	1(3.3%)	0.35[a]
Hypotension	4 (13.3%)	2 (6.6%)	0.66[a]
Vomiting	1(3.3%)	4(13.3%)	0.35[a]
Shivering	1(3.3%)	3 (10%)	0.61[a]
Fentanyl necessity	1(3.3%)	7 (23.3%)	0.052[a]
Nitroglycerine necessity	2 (6.6%)	10 (33.3%)	**0.02**[a]
Total rocuronium necessity (mg)	53.4 ± 11.4	49.9 ± 9.57	0.205

Group D, dexmedetomidine group; Group M, magnesium sulfate group.
Data show the number of cases or mean ± SD and the percentage rate.
p values calculated using Student's t -test and $p < 0.05$ value is shown in bold.
[a] p values calculated using χ^2 test (Fisher's exact test) and $p < 0.05$ value is shown in bold.

this situation. We also observed that bleeding at the surgical site was decreased and surgeon satisfaction improved in the dexmedetomidine study group. Shams et al.[16] demonstrated that dexmedetomidine, administered as a 1 μg/kg i.v. bolus and a 0.4–0.8 μg/kg/h i.v. infusion, was safe for controlled hypotension and is effective in providing ideal surgical field during FESS. In a study by Guven et al.[2] comparing the hypotensive effects of dexmedetomidine and placebo agent, it was concluded that dexmedetomidine is a safe and effective agent in controlled hypotension and can be an alternative to other agents. In another study assessing the effects of dexmedetomidine administered as a 1 μg/kg i.v. bolus and a 0.7 μg/kg/hour i.v. infusion, it was stated that dexmedetomidine decreased bleeding at the surgical site, improved the visibility of the surgical site and decreased the need for intraoperative fentanyl.[10] The analgesic effects of dexmedetomidine can be due to the activation of α_{2B}-adrenoceptors at the level of the dorsal horn of the spinal cord and the inhibition of substance P release.[17] In our study, there was no significant difference in terms of fentanyl need; this lack of necessity was attributed to both agents having analgesic effects.

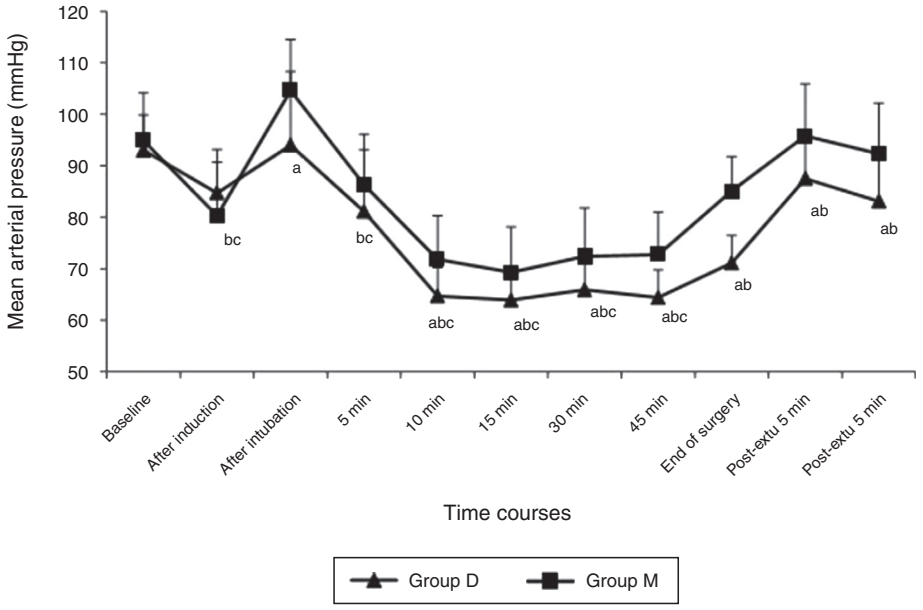

Figure 1 Mean arterial pressure for the groups. [a]$p < 0.05$ significant difference between the groups (Student's t test), [b]p: Group dexmedetomidine, significant difference in the group compared to baseline values, [c]p: Group magnesium sulphate, significant difference in the group compared to baseline values (repeated measures ANOVA test after Bonferroni's test).

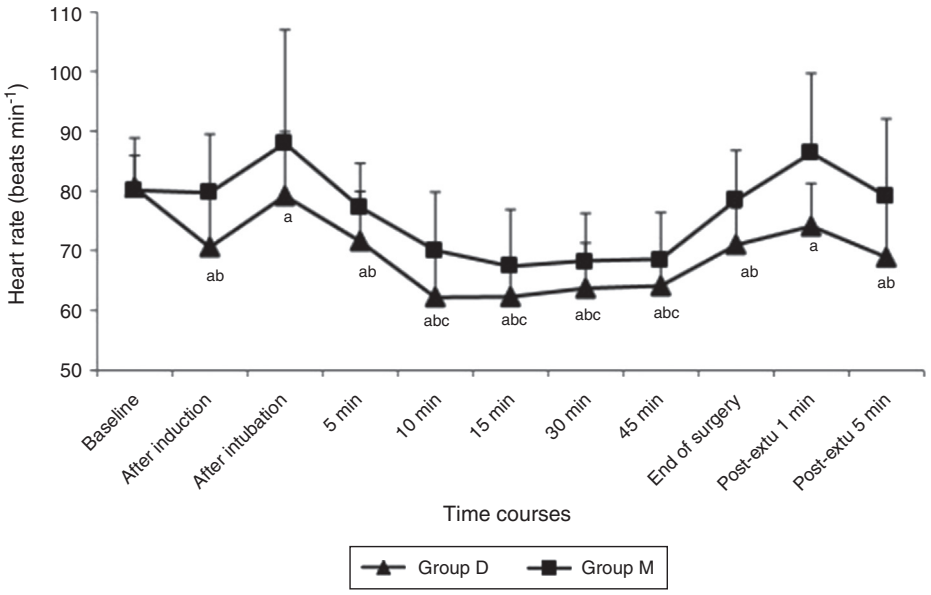

Figure 2 Heart rate values in the groups. [a]$p < 0.05$ significant difference between the groups (Student's t test), [b]p: Group dexmedetomidine, significant difference in the group compared to baseline values, [c]p: group magnesium sulphate, significant difference in the group compared to baseline values (repeated measures ANOVA test after Bonferroni's test).

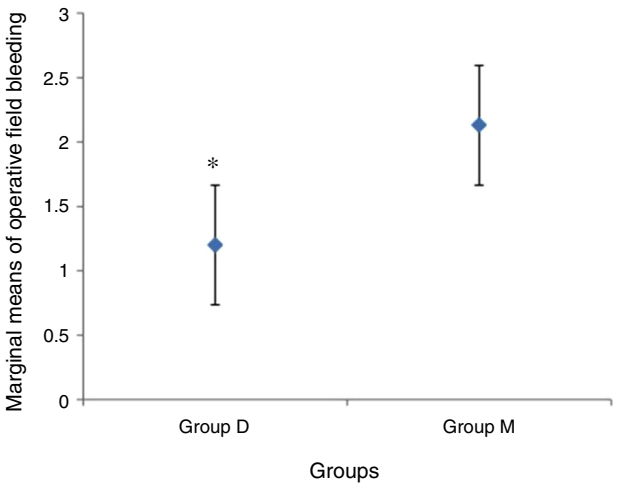

Figure 3 Rating of bleeding quantity. p values calculated using χ^2 test (Fisher's exact test) (*$p = 0.001$).

The use of different doses of magnesium to perform deliberate hypotension has been studied. In a study comparing magnesium sulfate with placebo in patients undergoing FESS, it was stated that controlled hypotension was achieved by using 40 mg/kg i.v. bolus and 15 mg/kg/hour i.v. infusion of magnesium sulfate and that the use of this agent decreased bleeding and duration of surgery.[5] Ryu et al.[7] compared magnesium sulfate with remifentanil in patients undergoing middle ear surgery. Magnesium sulphate was administered as a 50 mg/kg i.v. bolus and 15 mg/kg/hour i.v. infusion in the same study. They stated that controlled hypotension could be achieved with both agents, but that magnesium sulfate provided more effective analgesia in the postoperative period. Since there was no significant difference between the two groups in terms of NRS scores in this study, antinociceptive effects were attributed to both agents. The antagonist effect of magnesium at N-methyl-D-aspartate receptors raised interest in studies searching its adjuvant effect in perioperative analgesia.[18]

Kalra et al.[19] compared magnesium sulfate with clonidine, which is another α_2 receptor antagonist, in patients undergoing laparoscopic surgery; it was stated that the duration until achieving a reply to verbal stimulus was longer in the magnesium sulfate patient group compared to the 1 μg/kg i.v. and 1.5 μg/kg i.v. clonidine groups, which was attributed to the depressor effects of magnesium sulfate on the central nervous system. There was no significant difference in terms of eye opening duration between the two groups. Furthermore the time until achieving an Aldrete score ≥ 9 was shorter in the dexmedetomidine patient group, suggesting that dexmedetomidine results in a sleeping effect on locus coeruleus, similar to that of normal sleeping, and thus results in a faster awakening. There was no difference in terms of adverse effects and patient number requiring fentanyl administration. Nevertheless, the need for an additional nitroglycerine dose in order to obtain adequate hypotension was higher in the magnesium sulfate group, a difference which was attributed to the agent doses used in this study. Additional studies conducted with different doses can contribute to this subject.

In this study, postoperative magnesium sulfate and calcium levels were not measured, which can be considered as one limitation of the study. The administration of a large dose of magnesium sulfate, for example in the treatment of preeclampsia, may cause transient hypocalcaemia due to renal calcium loss or the inhibition of parathyroid function.[20] However, the amount of magnesium sulfate administered in this study was approximately half of the dose for the usual treatment of preeclampsia, and no patient exhibited clinical signs of profound neuromuscular blockade. In another study assessing the hypotensive anesthetic effects of magnesium

sulfate on patients undergoing middle ear surgery, no significant difference was observed between the preoperative and postoperative serum magnesium sulfate levels.[7]

Conclusions

We conclude that dexmedetomidine used at the doses mentioned in the study provided controlled hypotension in a more effective and more stable manner in patients undergoing FESS, and also increased surgeon satisfaction and quality of surgical site, while not prolonging the recovery period.

Conflicts of interest

The authors declare no conflicts of interest.

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