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Magnesium sulphate as a technique of hypotensive anaesthesia

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Background. This randomized, double-blind, placebo-controlled study was designed to assess the effect of perioperatively administered i.v. magnesium sulphate as a technique of hypotensive anaesthesia.

Methods. Sixty patients (25 female) undergoing functional endoscopic sinus surgery were included in two parallel groups. The magnesium group received magnesium sulphate 40 mg kg^{-1} i.v. as a bolus before induction of anaesthesia and 15 mg kg^{-1} h^{-1} by continuous i.v. infusion during the operation. The same volume of isotonic solution was administered to the control group. Intraoperative bleeding was evaluated using a quality scale.

Results. In the magnesium group , there was a reduction in surgical time [68.1 (15.6) min *vs* 88.1 (10.7) min], although the anaesthetic time was 10 min longer and thus presuming a prolongation in anaesthetic emergence. There was a significant reduction of blood loss [165 (19) ml *vs* 257 (21) ml]. The anaesthetic requirements (fentanyl, vercuronium and sevoflurane), mean arterial blood pressure ($P<0.005$) and heart rate ($P<0.005$) were also significantly reduced.

Conclusion. Magnesium sulphate led to a reduction in arterial pressure, heart rate, blood loss and duration of surgery. Furthermore, magnesium infusion alters anaesthetic dose requirements and emergence time.

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Functional endoscopic sinus surgery is used for treatment of patients with sinus pathology. Intraoperative bleeding reduces visibility in the operative field.[1] General anaesthesia is often preferred because of the discomfort and incomplete block that may accompany topical anaesthesia as well as providing hypotensive anaesthesia.[1]

I.V. magnesium sulphate may be a good agent for deliberate hypotension because magnesium intervenes in the activation of membrane Ca ATPase and Na–K ATPase involved in transmembrane ion exchanges during depolarization and repolarization phases, and thus act as a stabilizer of cell membrane and intracytoplasmic organelles.[2] Magnesium also exerts its effects on L-type calcium channels in membranes and the sarcoplasmic reticulum. By inhibiting the calcium activation dependent upon the sarcoplasmic channel, magnesium limits the outflow of calcium from the sarcoplasmic reticulum.[3] In addition, magnesium sulphate acts as a vasodilator by increasing the synthesis of prostacyclin, as well as inhibiting angiotensin converting enzyme activity.[4] Magnesium sulphate has small, dose-dependent myocardial depressant effect.[5] Recently, the antagonist effect of magnesium at *N*-methyl-D-aspartate (NMDA) receptors has led to studies of its adjuvant effect in perioperative analgesia.[6 7]

This randomized, placebo-controlled, double-blind study was designed to assess the effect of perioperatively administered i.v. magnesium sulphate technique of hypotensive anaesthesia.

Methods

The protocol was approved by the Institutional Medical Board and patients gave written informed consent. Sixty patients admitted during a 1 yr period to Ain-shams University Hospitals, ASA physical status I and II patients undergoing functional endoscopic sinus surgery, were allocated to one of two parallel groups (control, $n=30$; magnesium, $n=30$).

Exclusion criteria included major hepatic, renal or cardiovascular dysfunction, atrioventricular block, known allergy to magnesium sulphate or other study drugs, haematological disorders, morbid obesity, history of neuromuscular disease, diabetic neuropathy, pregnancy, prior treatment with calcium channel blockers, opioids and anticoagulants, and patients receiving magnesium supplementation, or drugs known to have a significant interaction with NMDAs.

The patients were assigned randomly by using computerized program to one of the two groups. The magnesium group received 10% magnesium sulphate and the control group received 0.9% sodium chloride in a double-blind fashion. The solutions were prepared by the coordinator of the study, and the anaesthetist who was in charge of the patients during the operation was unaware of the study medication. Before induction of anaesthesia, routine monitoring (ECG, pulse oximetry, and noninvasive blood pressure monitoring every 5 min (Drager Infinity kappa, Germany) was started and an i.v. line was sited. Muscle relaxation was monitored with a nerve stimulator (Fisher Paykel, model NS242).

Study protocol

Heart rate (ST segment was observed), mean arterial pressure (MAP) and arterial oxygen saturation (Sp_{O_2}) were recorded before induction of anaesthesia. The magnesium group received magnesium sulphate 40 mg kg^{-1}, administered as a slow i.v. bolus over a 10 min period before the induction of anaesthesia, and 15 mg kg^{-1} h^{-1} by continuous i.v. infusion during the operation. The same volume of isotonic saline was administered to the control group. After preoxygenation of 5 min, anaesthesia was induced with fentanyl 1 μg kg^{-1} and propofol in increments of 20 mg every 5 s. After induction of anaesthesia, supramaximal train-of-four (TOF) stimulation was measured at 20 s intervals. When a stable twitch response (at least three successive equal responses to TOF stimulation) had been established, vecuronium 100 μg kg^{-1} was administered via a fast-flowing i.v. infusion over 5 s. The time from the start of anaesthesia induction and the time to 80% (T1=20%) single-twitch depression after administering vecuronium were recorded. Orotracheal intubation was performed when T1=0%, then a further set of recordings was made.

Anaesthesia was maintained with 30% oxygen in nitrous oxide, sevoflurane and intermittent i.v. bolus doses of fentanyl 0.5 μg kg^{-1}. Dose adjustments of sevoflurane and fentanyl were based on standard clinical signs and haemodynamic measurements. Signs of inadequate analgesia, defined as an increase in heart rate and MAP of more than 20% from baseline, deliberate hypotension was defined as a MAP of 50–60 mm Hg. During the perioperative period, both groups received i.v. fluid (lactated Ringer solution) at 5 ml kg^{-1} h^{-1}. Muscle relaxation was achieved with an infusion of vecuronium adjusted to provide complete depression of the first twitch after TOF stimulation. Hourly infusion rate of vecuronium was recorded as μg kg^{-1} h^{-1}.

The lungs of all patients were ventilated mechanically with an oxygen/N_2O mixture to maintain adequate oxygenation and a Pa_{CO_2} level between 4.6 and 5.3 kPa. Normothermia was maintained during the whole procedure.

Intraoperative bleeding was measured by collecting blood with the pump graded with the precision of 25 ml. For evaluation of the visibility of the operative field during functional endoscopic sinus surgery (FESS) the quality scale proposed by Fromm and Boezaart[8] was used:

0: no bleeding.
1: slight bleeding—blood evacuation not necessary.
2: slight bleeding—sometimes blood has to be evacuated.
3: low bleeding—blood has to be often evacuated. Operative field is visible for some seconds after evacuation.
4: average bleeding—blood has to be often evacuated. Operative field is visible only right after evacuation.
5: high bleeding—constant blood evacuation is needed. Sometimes bleeding exceeds evacuation. Surgery is hardly possible.

Bleeding in the operative field was subjectively evaluated by the same surgeon every 15 min.

Approximately 30 min before the end of surgery, the vecuronium infusion was discontinued, the patients were allowed to recover spontaneously until the return of T1=25%. Then a combination of atropine 0.01 mg kg^{-1} i.v. and prostigmine 0.02 mg kg^{-1} was administered to reverse the neuromuscular block. The times for return of T1 to 25% and return of the TOF ratio (T4/T1) to 70% were recorded. Sevoflurane was discontinued on nasal packing and the patients were allowed to wake up. The trachea was extubated and the time to recovery recorded.

Each patient was observed continuously after the termination of anaesthesia and times of events were recorded by the anaesthetist. After transfer to the recovery area, patients were assessed neurologically for any sign of hypermagnesaemia. Any adverse events or side-effects were recorded during the perioperative and postoperative periods.

Statistical analysis

Comparisons between the control and the study groups were conducted using ANOVA by using multivariate ANOVA test, one-way ANOVA test, repeated measures ANOVA and Kruskal–Wallis ANOVA test as well as comparing mean and standard deviation. A *P*-value below 0.05 was considered significant.

Results

Sixty patients ASA physical status I and II patients (25 female) undergoing functional endoscopic sinuses surgery were included (control, *n*=30; magnesium, *n*=30).

Table 1 Age, sex, duration of surgery and anaesthesia, weight and perioperative fluid intake

Patient characteristic data	Control group	Magnesium sulphate group
Age [mean (range)]	39.1 (18–65)	29.2 (18–65)
(15–25)	4	12
(26–36)	11	11
(37–47)	7	6
(48–65)	8	1
Sex (male/female)	19/11	16/14
Duration of surgery (min)	88 (10)	68 (15)
Duration of anaesthesia (min)	106 (12)	96 (16)
Weight (kg)	72.1 (11.3)	74.7 (10.6)
Perioperative i.v. fluid intake (ml)	639 (124)	604 (149)

Table 2 MAP [mean (SD)] in both the magnesium and control groups (multivariate ANOVA)

Time (min)	Group	Mean (SD)	*P*-value
Preanaesthetic	Control	86.9 (12.4)	0.102
	Magnesium	92.5 (13.6)	
Preoperative	Control	81.7 (10.5)	0.716
	Magnesium	82.8 (12.0)	
5 min	Control	74.5 (8.6)	<0.001
	Magnesium	66.3 (8.1)	
15 min	Control	71.8 (6.8)	<0.001
	Magnesium	58.2 (7.0)	
30 min	Control	69.7 (5.4)	<0.001
	Magnesium	55.7 (4.9)	
45 min	Control	69.3 (5.3)	<0.001
	Magnesium	55.1 (4.6)	
60 min	Control	71.2 (6.6)	<0.001
	Magnesium	58.2 (6.2)	
End of surgery	Control	79.6 (9.0)	0.001
	Magnesium	71.9 (7.3)	

The groups were comparable with respect to age (the age group ranged from 16 to 61, the mean age group is 34.15, with SD 13.46), weight range is between 40 and 95 kg [mean 73.43 (10.97)], ASA status, duration of surgery and anaesthesia (Table 1). All patients underwent the same type of surgery, performed by the same surgeon. There was a significant reduction in surgical time ($P<0.001$) of 88.1 (10.7) *vs* 68.1 (15.6) min. The anaesthetic time was 10 min longer in the magnesium group denoting a longer emergence time, as the anaesthetic requirements (fentanyl, vercuronium and sevoflurane) were significantly reduced in the magnesium group.

The preanaesthetic ($P=0.102$) and preoperative ($P=0.716$) MAP were not significantly different (Table 2), between the groups, but at 5, 15, 30 and 60 min and at end of surgery they were significantly lower in the magnesium group ($P<0.005$). A similar pattern was seen with heart rate (Table 3).

There were no episodes of hypotension (MAP<50 mm Hg), arrhythmia or reflex tachycardia during magnesium sulphate infusion, and no patient had rebound hypertension upon discontinuing magnesium sulphate infusion. Clinical assessment in the recovery room showed that patients had normal ventilatory frequency, adequate tidal volume and normal pupil size.

Table 3 Heart rate [mean (SD)] in the magnesium and control groups (multivariate ANOVA)

Duration (min)	Group	Mean (SD)	*P*-value
Preanaesthetic	Control	83.2 (6.9)	0.175
	Magnesium	80.5 (8.0)	
Preoperative	Control	80.9 (6.6)	0.003
	Magnesium	74.9 (8.3)	
5 min	Control	78.7 (6.7)	<0.001
	Magnesium	67.1 (8.4)	
15 min	Control	71.0 (7.1)	<0.001
	Magnesium	60.5 (7.0)	
30 min	Control	68.6 (6.9)	<0.001
	Magnesium	58.6 (5.9)	
45 min	Control	71.6 (8.4)	<0.001
	Magnesium	59.6 (5.9)	
60 min	Control	76.1 (8.1)	<0.001
	Magnesium	61.9 (4.3)	
End of surgery	Control	79.1 (8.4)	<0.001
	Magnesium	65.1 (5.8)	

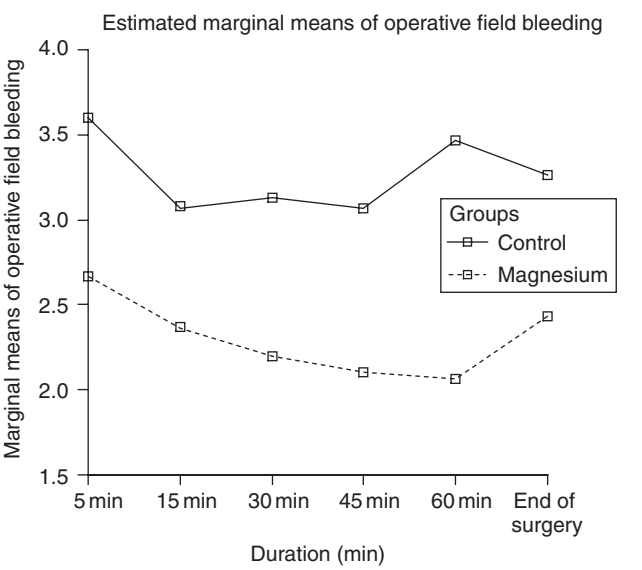

Fig 1 Quality of the operative field in both groups, evaluated using the quality scale proposed by Fromm and Boezaart.[8]

The operative field conditions were significantly better in the magnesium group at 5, 15, 30, 45 and 60 min and the end of surgery (Fig. 1) The mean blood loss in the magnesium group was reduced [165 (19) ml *vs* 257 (21) ml].

There was a significant reduction in the total dose of fentanyl, sevoflurane and vecuronium (Table 4) in the magnesium sulphate group. The time from cessation of vecuronium to T1=25% [41.7 (5.6) min *vs* 32.8 (4.2) min, $P<0.001$] and T4/T1$\geqslant$70% [52.2 (5.0) min *vs* 43.6 (4.3) min, $P<0.001$] were significantly longer in the magnesium group.

Discussion

This study evaluated magnesium sulphate as a hypotensive anaesthesia technique in the magnesium group; there was an

Table 4 Doses of vecuronium, fentanyl and sevoflurance during anaesthesia (ANOVA and repeated measures ANOVA)

Anaesthetic requirements	Group	Mean (SD)	*P*-value
Vecuronium ($\mu g\ kg^{-1}$)	Control	139.6 (9.0)	0.001
	Magnesium	131.9 (7.3)	
Fentanyl ($\mu g\ kg^{-1}$)	Control	2.4 (0.34)	<0.001
	Magnesium	1.1 (0.30)	
Sevofurane (% during the operation)	Control	2.7 (0.03)	<0.001
	Magnesium	1.8 (0.03)	

objectively better operative field, reduction in the duration of surgery and reduced blood loss. The anaesthetic requirements were reduced in the magnesium group but there was a longer emergence time. The possible mechanisms for reduction of the anaesthetic requirements include; antagonism of NMDA receptors in the CNS by magnesium,[6] and reduction of catecholamine release by sympathetic stimulation, thus decreasing peripheral nociceptor sensitization or the stress response to surgery.[6] In addition, the actions of magnesium at the neuromuscular junction include: a reduction in acetylcholine release from motor nerve terminals, a decrease in the depolarizing action of acetylcholine at the endplate and depression of muscle fibre membrane excitability.[6 7 9]

In our study, the magnesium group received magnesium sulphate 40 mg kg^{-1} as a slow i.v. bolus in a 10 min period before the induction of anaesthesia and 15 mg kg h^{-1} by continuous i.v. infusion during the operation. This resulted in a steady and smooth reduction in MAP and reduced heart rate, with no episodes of severe hypotension. Invasive arterial pressure monitoring was not and i.v. fluid was given, in both groups, at 5 ml kg^{-1} h^{-1}. No patient had rebound hypertension when the magnesium sulphate infusion was stopped which can occur with hypotensive anaesthesia techniques using arterial vasodilators.

Magnesium sulphate was chosen as it is a vasodilator with minimal myocardial depression.[4 5] It produces a dose-dependent depressant effect on cardiac contractility and it has been shown that the depressant effect of magnesium on cardiac function is offset by lowering of the peripheral vascular resistance, thus maintaining cardiac pump function.[10] A study using magnesium sulphate during sevoflurane anaesthesia at doses of 30, 60 and even more than 120 mg kg^{-1} concluded that magnesium did not have a deleterious effect on atiroventricular (AV) conduction time and surface ECG during 1 minimal alveolar concentration (MAC) of sevoflurane; and recommended the use of high doses of magnesium sulphate in patients with cardiac arrhythmia and hypertension during sevoflurane anaesthesia.[11] Magnesium causes an increase in cerebral blood flow velocity,[12] which would be beneficial in a hypotensive anaesthesia technique. However, there are potential risks of using magnesium as it has multiple sites of action and can potentiate the actions of opioids and neuromuscular blocking drugs and cause prolongation of emergence time.

The role of magnesium, given before operation, in controlling intraoperative hypertension has been studied in hypertensive patients undergoing cataract surgery with local anaesthesia,[13] and was shown to reduce the intraoperative variability in arterial pressure. In cardiac surgery, magnesium was as effective as nicardipine in controlling arterial pressure during cardiopulmonary bypass procedures.[14]

The use of different doses of magnesium to produce deliberate hypotension has been studied. In a study of patients undergoing cerebral-aneurysm clipping,[5] an initial magnesium sulphate dose of 40 g h^{-1} was used until MAP of 70 mm Hg was reached, followed by 20 g h^{-1} until the target MAP was reached, and then 10 g h^{-1} for the remaining time. The serum magnesium levels were high, and there was prolonged postoperative sedation;[5] however, anaesthesia had been maintained with a total i.v. technique using fentanyl and midazolam. Lower serum magnesium concentrations were found in a study[4] of patients undergoing major oral and maxillofacial surgery, where magnesium was given at a rate of 40 g h^{-1} after induction until the MAP reached 55 (5) mm Hg, followed by a maintenance dose of 5 g h^{-1} until 30 min before the end of surgery, without loss of the hypotensive effect. The total magnesium sulphate dose was 20–51.5 g (mean 33.5 g). This study[4] also compared deliberate hypotension induced by sodium nitroprusside with that produced by magnesium sulphate. The magnesium sulphate infusion showed poorer control of arterial pressure and had a slower onset, taking 28 (12) min to reach the desired MAP. As in our study, there was no rebound hypertension or reflex tachycardia associated with magnesium sulphate infusion, but this occurred in the sodium nitroprusside group. This may be attributed to hypermagnesaemia producing inhibition of angiotensin-converting enzyme activity, sympathetic blockade, slowing of sino-atrial node transmission, depression of carotid baroreceptors, and diminished release of adrenal catecholamines.[4] All patients in that study[4] were drowsy after operation; possibly as magnesium is known as a central nervous system depressant, but this did not prove to be a problem clinically, and all patients were awake and alert within 6 h. This differs from our study as a result of the difference in the duration of and the total dose of magnesium sulphate used.

We conclude that continuous infusion of magnesium sulphate led to a useful reduction in MAP, heart rate, blood loss and duration of surgery. In addition, magnesium infusion alters anaesthetic dose requirements and emergence time. Further studies of this technique are warranted.

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