

## Controlled hypotension for middle ear surgery: a comparison between remifentanil and magnesium sulphate<sup>†</sup>

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**Background.** This prospective, randomized study was designed to compare remifentanil and magnesium sulphate during middle ear surgery in terms of postoperative pain and other complications.

**Methods.** Eighty patients undergoing middle ear surgery were enrolled in the study. Patients were randomized into two groups of 40 to receive remifentanil (Group R) or magnesium sulphate (Group M) infusion. Propofol 2 mg kg<sup>-1</sup> was administered to induce anaesthesia, which was maintained using sevoflurane. Group R received a continuous infusion of remifentanil titrated between 3 and 4 ng ml<sup>-1</sup> using target-controlled infusion, whereas Group M received an i.v. magnesium sulphate bolus of 50 mg kg<sup>-1</sup> followed by a 15 mg kg<sup>-1</sup> h<sup>-1</sup> continuous infusion to maintain a mean arterial pressure (MAP) between 60 and 70 mm Hg. Haemodynamic variables, surgical conditions, postoperative pain, and adverse effects, such as postoperative nausea and vomiting (PONV) and shivering, were recorded.

**Results.** Controlled hypotension was well maintained in both groups. MAP and heart rate were higher in Group R than in Group M after operation. Surgical conditions were not different between the two groups. Postoperative pain scores were significantly lower in Group M than in Group R ( $P < 0.05$ ). Seventeen patients in Group R (43%) and seven patients in Group M (18%) developed PONV ( $P = 0.01$ ).

**Conclusions.** Both magnesium sulphate and remifentanil when combined with sevoflurane provided adequate controlled hypotension and proper surgical conditions for middle ear surgery. However, patients administered magnesium sulphate had a more favourable postoperative course with better analgesia and less shivering and PONV.

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Controlled hypotension is required for middle ear surgery to achieve a bloodless operative field.<sup>1, 2</sup> Vasodilators (nitroprusside, nicardipine, and nitroglycerine),  $\alpha_2$ A adrenergic agonists (clonidine and dexmedetomidine), beta-adrenergic antagonists (propranolol and esmolol), alpha- and beta-adrenergic antagonists (labetolol), and high doses of potent inhaled anaesthetics (halothane, isoflurane, and sevoflurane) have been used to control hypotension during middle ear surgery.<sup>1</sup> Remifentanil is also well known to induce good surgical conditions by controlling hypotension during tympanoplasty.<sup>2–4</sup> However, intraoperative remifentanil infusion can cause postoperative hyperalgesia,<sup>5</sup> and

early postoperative analgesia is necessary after remifentanil-based anaesthesia.<sup>6</sup>

Magnesium sulphate is a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist with antinociceptive effects and also inhibits the entry of calcium ions into cells.<sup>7</sup> Magnesium sulphate has been investigated in the context of controlling hypotension as a vasodilator,<sup>8, 9</sup> but no comparative study has been performed on the use of magnesium sulphate or remifentanil for controlled hypotension during middle ear surgery. We hypothesized that

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magnesium sulphate would be as effective as remifentanyl for hypotension but might offer better postoperative analgesic effects. We therefore investigated the efficacies of magnesium sulphate and remifentanyl in terms of postoperative analgesia and other complications during and after controlled hypotension for middle ear surgery.

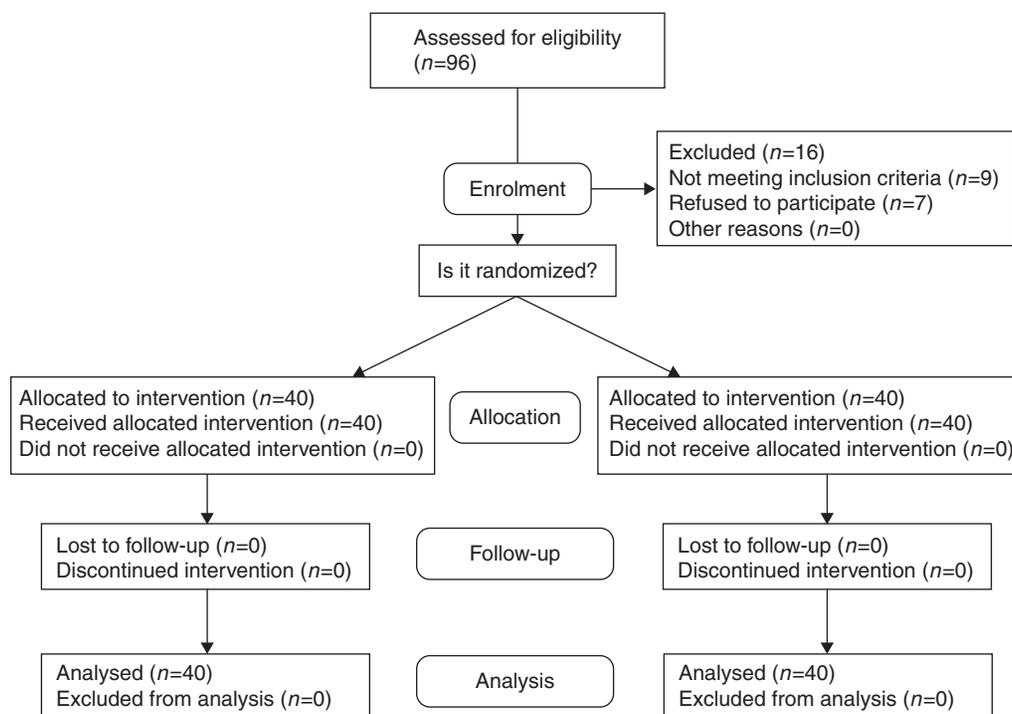
## Methods

In this randomized and prospective trial, 80 adults undergoing middle ear surgery under general anaesthesia were enrolled (Fig. 1). This study was approved by the Institutional Ethics Committee and written informed consents were obtained from all patients. Inclusion criteria were ASA physical status I or II, aged 20–65. Exclusion criteria were allergic reactions to study drugs, renal, hepatic, or cardiovascular diseases, neuromuscular disease, atrioventricular conductance disturbance, opioid or analgesic abuse, and chronic treatment with calcium channel blockers, opioids, or non-steroidal anti-inflammatory drugs.

There was no premedication and perioperative monitoring included standard monitoring with end-tidal concentration of sevoflurane (Solar 8000M<sup>®</sup>, GE medical system, USA) and a bispectral index (BIS<sup>®</sup> XP, A-2000, Aspect Medical Systems, USA). Patients were randomly allocated (sealed envelope method) to receive either remifentanyl (Group R) or magnesium sulphate (Group M). Anaesthetic induction was started with propofol 2 mg kg<sup>-1</sup> (3–4 divided doses) i.v. and study drugs (remifentanyl and magnesium sulphate) were administered using an Orchestra<sup>®</sup> infusion pump

system (Fresenius vial, Brezins, France) in both groups. Using target-controlled infusions with Minto model, patients in Group R were administered with remifentanyl infusion 4 ng ml<sup>-1</sup> during induction of anaesthesia and then the effect-site concentration of remifentanyl was titrated about 3–4 ng ml<sup>-1</sup> during the operation. Group M patients received an i.v. bolus injection of magnesium sulphate 50 mg kg<sup>-1</sup> in saline (total 100 ml) over 10 min during the induction of anaesthesia, and then 15 mg kg<sup>-1</sup> h<sup>-1</sup> by continuous infusion until the end of the operation. This dosage was based on a previous investigation on induced hypotension.<sup>8</sup> After loss of eyelid reflex, patients were ventilated with 2.5 MAC sevoflurane, and rocuronium 0.6 mg kg<sup>-1</sup> was given to facilitate tracheal intubation. Anaesthesia was maintained with sevoflurane targeting BIS (bispectral index score) between 40 and 60 and mean arterial pressure (MAP) between 60 and 70 mm Hg during the operation.<sup>2–4</sup> Patients were ventilated with oxygen and medical air ( $F_{I_{O_2}}=0.5$ ), and nitrous oxide was not used. When surgery was started, muscle relaxation was reversed with atropine 0.02 mg kg<sup>-1</sup> and neostigmine 0.04 mg kg<sup>-1</sup> i.v. for intraoperative monitoring of facial nerve. Neuromuscular block was monitored at the wrist using a peripheral nerve stimulator (TOF Watch SX<sup>®</sup>, Organon Ltd, Dublin, Ireland) to ascertain the reversal of neuromuscular block at the beginning of surgery and during the operation.

MAP, heart rates (HRs), end-tidal concentration of sevoflurane, and BIS were measured at the following time points: before anaesthetic induction, before tracheal intubation, after intubation, at 5, 15, 30, 60, 90, 120 min thereafter, and before and after extubation. If hypertension or



**Fig 1** Consort diagram of the study.

tachycardia over 20% of the preoperative value occurred during anaesthesia while BIS was between 40 and 60, it was assumed to be due to insufficient analgesia and an i.v. bolus of fentanyl  $1 \mu\text{g kg}^{-1}$  was given. If hypotension under 60 mm Hg or bradycardia under 20% of the preoperative HR occurred, while BIS was 40–60, ephedrine 5 mg (for hypotension) or atropine 0.5 mg (for bradycardia) was given i.v. At the end of the procedure, sevoflurane, magnesium sulphate, and/or remifentanyl infusions were stopped. The duration of hypotension and total amounts of remifentanyl and magnesium sulphate administered were recorded. Blood samples for serum magnesium concentration determination were obtained before and immediately after the surgery (the normal range at our institution is  $0.7\text{--}1.3 \text{ mmol litre}^{-1}$ ). Surgical conditions were assessed by the surgeon using a six-point category scale (0–5: 0, uncontrolled bleeding; 5, no bleeding, virtually bloodless field).<sup>10</sup> After surgery, patients were transferred to the post-anaesthesia recovery room (PAR) and evaluated every 15 min using the modified Aldrete scoring system<sup>11</sup> until ready for discharge from the PAR. The criterion used for patient discharge was the achievement of a modified Aldrete score of 9.

In the PAR, postoperative pain and any adverse effects including PONV and shivering were recorded by an anaesthetic nurse who was blinded to the patient's group. Pain and PONV were evaluated using a 100 mm visual analogue scale (VAS, starting from 0, none, to 100, worst). If the VAS was  $>30$ , rescue analgesic (ketorolac 30 mg i.v.) or antiemetic (metoclopramide 10 mg i.v.) was administered as appropriate.

A sample size of 40 in each group was based on a pilot study. We had 20 patients with 11 patients in Group R and nine patients in Group M. The incidence of rescue analgesic at the recovery room was 64% in Group R ( $n=7$ ) and 33% ( $n=3$ ) in Group M. The sample size was calculated to be 40 ( $\alpha=0.05$  and  $\beta=0.2$ ) to achieve 80% power to detect a 30% difference in the incidence of rescue analgesic between the two groups. Information on anaesthesia and surgery and incidence variables (rescue analgesic and rescue antiemetic) were compared using *t*-test or  $\chi^2$  test as appropriate. Repeated-measures ANOVA was used to compare measurements over time (MAP, HR, and end-tidal sevoflurane concentration). To compare the data (MAP, HR, and end-tidal sevoflurane concentration) at each time point, *t*-test was used. Wilcoxon's rank-sum test was used to compare postoperative pain and PONV between the two groups. Values are expressed as counts or as means (SD). *P*-values of  $<0.05$  were considered statistically significant.

## Results

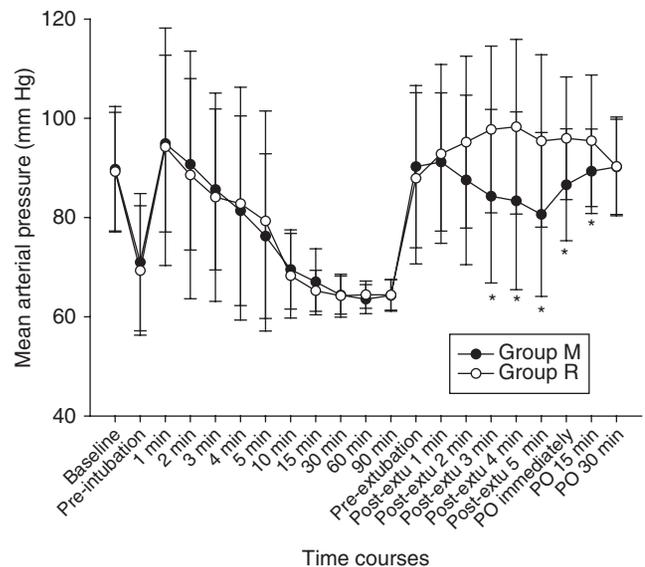
Patient characteristics in both groups were described in Table 1. Postoperative serum magnesium level was higher

in Group M and additional intraoperative fentanyl was not necessary in either group (Table 1).

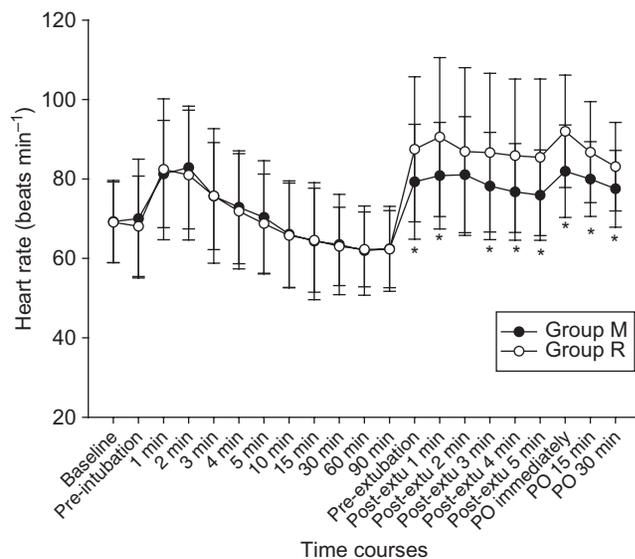
Although there was no statistically significant difference over time in MAP and HR between the two groups, Group R showed higher MAP and HR than Group M after extubation (Figs 2 and 3). Ephedrine was used intraoperatively in 15 patients in Group R and 12 patients in Group M ( $P>0.05$ ). There were significant differences ( $P=0.02$ ) over time in the end-tidal concentration of sevoflurane needed for surgical anaesthesia (BIS 40–60). Patients in

**Table 1** Patients characteristics and information on anaesthesia and surgery. Group R, remifentanyl group; Group M, magnesium group. Values are expressed as mean (range), mean (SD) or number of patients (*n*)

	Group R ( <i>n</i> =40)	Group M ( <i>n</i> =40)
Age (yr)	46.5 (30–62)	49.0 (32–60)
Gender (M/F)	24/16	25/15
Body weight (kg)	64.6 (11.1)	65.1 (8.3)
Height (cm)	164.7 (7.6)	163.2 (7.5)
ASA (I/II)	25/15	27/13
Operation time (min)	199.9 (43.7)	195.9 (56.6)
Anaesthetic time (min)	238.8 (59.6)	242.5 (58.4)
Duration of hypotension (min)	215.0 (49.8)	202.1 (53.5)
Type of surgery		
Mastoidectomy	32	31
Tympanoplasty	8	9
Remifentanyl ( $\mu\text{g kg}^{-1} \text{ min}^{-1}$ )	0.15 (0.02)	0
Rocuronium ( $\text{mg kg}^{-1}$ )	0.6	0.6
Magnesium sulphate ( $\text{mg kg}^{-1} \text{ h}^{-1}$ )	0	31.5 (5.2)
Preoperative magnesium ( $\text{mmol litre}^{-1}$ )	0.95 (0.07)	0.92 (0.11)
Postoperative magnesium ( $\text{mmol litre}^{-1}$ )	0.88 (0.06)	1.52 (0.17)
Fentanyl used intraoperatively ( $\mu\text{g}$ )	0	0



**Fig 2** Perioperative changes in MAP. Values are mean (SD). To compare the data at each time point, *t*-test was used. MAPs in Group M were significantly lower than those in Group R after extubation and after operation ( $P<0.05$ ). Group R, remifentanyl group; Group M, magnesium group. \* $P<0.05$  compared with Group R.



**Fig 3** Perioperative changes in HR. Values are mean (SD). To compare the data at each time point, *t*-test was used. HRs were lower in patients of Group M than those of Group R ( $P < 0.05$ ). Group R, remifentanyl group; Group M, magnesium group. \* $P < 0.05$  compared with Group R.

**Table 2** End-tidal sevoflurane concentrations required for surgical anaesthesia (BIS 40–60). Group R, remifentanyl group; Group M, magnesium group. Values are mean (SD). To compare the data at each time point, *t*-test was used. \* $P < 0.05$  compared with Group R

Minutes after intubation	Group R (n=40)	Group M (n=40)
Pre-intubation	2.27 (0.26)	2.15 (0.35)
1 min	1.67 (0.25)	1.54 (0.36)
2 min	1.36 (0.26)	1.20 (0.34)*
3 min	1.17 (0.22)	1.06 (0.24)
4 min	1.19 (0.21)	1.03 (0.25)*
5 min	1.18 (0.22)	1.03 (0.24)*
10 min	1.19 (0.24)	1.03 (0.24)*
15 min	1.15 (0.25)	1.02 (0.23)*
30 min	1.15 (0.24)	1.05 (0.21)
60 min	1.17 (0.21)	1.05 (0.20)*
90 min	1.12 (0.22)	1.01 (0.20)*

Group M required lower concentration of sevoflurane than those in Group R (Table 2).

Surgical conditions, PAR score, and duration were not different between the two groups (Table 3). The PONV VAS and pain VAS were significantly lower in Group M than those in Group R (Table 3). The use of rescue drugs (antiemetic and analgesic) was also less frequent in Group M (Table 3). Shivering was observed in five patients in Group R and one in Group M ( $P > 0.05$ ). There were no respiratory and circulatory complications in either group.

## Discussion

This study shows that when combined with sevoflurane, remifentanyl and magnesium sulphate produced similar

**Table 3** Recovery profiles. Group R, remifentanyl group; Group M, magnesium group. Values are mean (SD) or number of patients.  $\chi^2$  or Wilcoxon's rank-sum test was used. \* $P < 0.05$  compared with Group R

	Group R (n=40)	Group M (n=40)
Surgical conditions		
0	0	0
1	0	0
2	4	3
3	14	11
4	19	22
5	3	4
PAR score		
Immediately	6.9 (0.5)	7.0 (0.6)
15 min	8.5 (0.7)	8.8 (0.7)
30 min	9.8 (0.4)	9.9 (0.3)
PAR duration (min)	33.0 (6.9)	30.4 (7.0)
PONV (VAS)	30.7 (29.3)	10.7 (16.7)*
Rescue antiemetics	17	7*
Postoperative pain (VAS)		
Immediately	44.7 (24.3)	40.2 (17.7)
15 min	53.5 (23.6)	41.7 (19.2)*
30 min	53.5 (24.2)	34.3 (17.8)*
Rescue analgesics	23	13*
Shivering	5	1

intraoperative conditions and haemodynamics during middle ear surgery. However, our results demonstrate that magnesium sulphate has more advantages during the emergence and postoperative periods, and that its usage was associated with more stable perioperative haemodynamics (smaller increases in MAP and HR) and better recovery profiles (less postoperative pain and fewer PONV incidents) than remifentanyl.

Controlled hypotension is commonly used to decrease intraoperative blood loss and avoid transfusions. During middle ear surgery, control is required for a clearer operative field,<sup>2</sup> as oozing blood obscures vision during ear microsurgery and can make correct graft placement difficult during tympanoplasty.<sup>12</sup> The target MAP range used in this study was 60–70 mm Hg, as has been used in previous investigations during tympanoplasty.<sup>2–4</sup> In the present study, the majority of patients in both groups had a surgical condition score of 3–5, indicating at least a good operative field. Furthermore, surgeons did not complain of surgical bleeding or of interference during procedures.

Hypotensive agents have several disadvantages, which include reflex tachycardia and tachyphylaxis,<sup>2</sup> and thus, an agent with predictable, dose-dependent effects was needed.<sup>3</sup> Remifentanyl, an ultra-short-acting  $\mu$ -agonist opioid receptor, has recently been reported to provide appropriate surgical conditions during middle ear surgery with controlled hypotension.<sup>2–4</sup> However, large doses of intraoperative remifentanyl have been associated with difficult postoperative pain management and hyperalgesia.<sup>5</sup> Furthermore, this phenomenon has been linked with NMDA receptor activation.<sup>13</sup> Similarly, in the present study, patients in the remifentanyl group had higher MAP and HR levels and required more rescue analgesics during the postoperative period.

Magnesium sulphate is a non-competitive NMDA receptor antagonist, and has been investigated as a possible adjuvant for intra- and postoperative analgesia.<sup>14 15</sup> In addition, magnesium sulphate is used as a vasodilator to control hypertension, and thus, reduce blood loss during endoscopic sinus surgery.<sup>8</sup>

In the present study, anaesthesia was maintained during surgery with sevoflurane. Furthermore, the low solubility of sevoflurane makes it a good agent for rapid induction and fast emergence from anaesthesia with reduced airway irritability. In addition, a previous investigation showed that although sevoflurane has a hypotensive effect, it does not alter cerebral blood flow, whereas propofol has less protective effect on inner ear microcirculation.<sup>16</sup> Many studies have concluded that magnesium sulphate reduces anaesthetic and analgesic requirements for surgery. Steinlechner and colleagues<sup>17</sup> found that magnesium sulphate lowered cumulative remifentanyl requirements after cardiac surgery, and Telci and colleagues<sup>15</sup> showed that magnesium sulphate reduced propofol, remifentanyl, and vecuronium consumption. The results of the present study suggest that magnesium sulphate has a more powerful anaesthesia-potentiating effect than remifentanyl.

Middle ear surgery is associated with a high incidence of PONV, which can approach 80%.<sup>18</sup> This problem can be managed by adopting a total i.v. anaesthesia technique incorporating propofol, by administering antiemetics such as dexamethasone or a serotonin 3A receptor antagonist, or by both.<sup>18</sup> In the present study, patients in the magnesium sulphate group had a lower incidence of PONV than those in the remifentanyl group, which we suspect may be related to a lower consumption of sevoflurane during anaesthesia,<sup>19</sup> since remifentanyl itself had no overall impact on PONV.<sup>20</sup> In a previous study, middle ear surgery was performed as a day-case procedure, and only one-third of patients could be discharged on the day of surgery, primarily because of PONV.<sup>21</sup> Accordingly, because PONV can be a barrier to early recovery and discharge, the use of intraoperative magnesium sulphate may be beneficial in patients undergoing middle ear surgery. In addition to PONV, patients in the magnesium sulphate group tended to experience less postoperative shivering, which concurs with previous investigations on the subject.<sup>22 23</sup>

It is well known that magnesium sulphate potentiates the neuromuscular block induced by non-depolarizing neuromuscular blocking agents,<sup>24 25</sup> and thereby reduces neuromuscular blocking agent consumption.<sup>15 23</sup> However, intraoperative monitoring of the facial nerve during middle ear surgery requires that the patient is unparalysed immediately after the start of surgery.<sup>26</sup> In the present study, reversal of neuromuscular block was performed about 40 min after anaesthetic induction and was not impeded by magnesium sulphate infusion, as confirmed by a peripheral nerve stimulator at the wrist. Additional neuromuscular blocking agents were not administered.

In summary, it appears that both magnesium sulphate and remifentanyl can induce adequate hypotensive anaesthesia in patients undergoing middle ear surgery. However, magnesium sulphate was found to be associated with a more favourable course during the immediate postoperative period in terms of analgesia and reducing the incidence of shivering and PONV.

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