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Intraoperative high-dose remifentanil increases post-anaesthetic shivering

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Key points

- Patients administered high dose of remifentanil are prone to shivering after its sudden discontinuation at the end of surgery.

- Remifentanil-induced post-anaesthetic shivering (PAS) does not appear to be related to perioperative hypothermia or postoperative pain.

- PAS after higher doses of remifentanil may reflect acute opioid tolerance and stimulation of N-methyl-D-aspartate receptors, similar to hyperalgesia in this setting.

Background. Remifentanil is associated with increased incidence of post-anaesthetic shivering (PAS). The aim of this study was to compare the effects of intraoperative high and low doses of remifentanil on PAS.

Methods. We investigated 50 consecutive patients, aged <60 yr, who underwent gynaecological laparotomy. Patients who underwent prolonged surgery (>4 h) were excluded from the study. Anaesthesia throughout surgery was maintained with i.v. propofol and remifentanil, and epidural ropivacaine, and no nitrous oxide was used. Fifty patients were randomly assigned to receive intraoperative remifentanil at 0.1 μg kg^{-1} min^{-1} (low-dose group, $n=25$) or 0.25 μg kg^{-1} min^{-1} (high-dose group, $n=25$) until the end of surgery. Intraoperative analgesia was achieved by a fixed infusion rate of remifentanil and titrated epidural ropivacaine. PAS was evaluated by nursing stuff over the first hour after surgery.

Results. PAS occurred more frequently in the high-dose group than in the low-dose group (60% *vs* 20%, $P=0.009$). None of the patients complained of pain during the observation period due to epidural analgesia. There were no significant differences in rectal or palm skin temperature after extubation between the two dose groups.

Conclusions. Remifentanil-induced PAS is not a phenomenon of intraoperative hypothermia. The higher incidence of PAS with higher doses of remifentanil probably reflects acute opioid tolerance and stimulation of N-methyl-D-aspartate receptors, similar to hyperalgesia. We conclude that patients administered high doses of remifentanil are sensitive to shivering after sudden drug withdrawal.

Keywords: gynaecological laparotomy; post-anaesthetic shivering; remifentanil

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Remifentanil is a short-acting opioid associated with predictable and rapid recovery.[1] In Japan, remifentanil has been widely used clinically for intraoperative analgesia since it became commercially available in 2007. However, we often encounter post-anaesthetic shivering (PAS) in our patients after discontinuance of remifentanil. A number of studies have also reported increased incidence of PAS with remifentanil administration.[2–6] The mechanisms underlying PAS are considered to include acute opioid tolerance of short-acting narcotics,[7] which is closely related to activation of N-methyl-D-aspartate (NMDA) receptor.[8–10] The present study was designed to examine the effects of high doses of intraoperative remifentanil on PAS in surgical patients.

Methods

The study protocol was approved by the Human Ethics Review Committee of Kansai Denryoku Hospital, and a signed consent form was obtained from each subject. We investigated consecutive patients who underwent gynaecological laparotomy from June 2008 to August 2009 at Kansai Denryoku Hospital. Patients with ASA physical status III, aged more than 60 yr, undergoing emergency surgery and scheduled radical hysterectomy were excluded from the study. When surgery was prolonged more than 4 h, the study was discontinued and the patient was excluded from this study because duration of surgery is reported to correlate with the incidence of PAS.[11 12] The selection of a cut-off value of 4 h was based on our previous work, indicating that the incidence of PAS in patients who have undergone more than 4 h gynaecological laparotomy is 74%, despite the anaesthetic regimen. The duration of simple hysterectomy or myomectomy, which are typical surgical procedures for benign gynaecological disease, is 3 h in our institution for uneventful surgery.

In accordance with the standard of our hospital, a premedication dose of i.m. midazolam (2.5–5 mg) was administered 15 min before arrival in the operating theatre. An epidural catheter was placed at the T12/L1 or L1/L2 interspace before general anaesthesia, which was subsequently

induced with propofol 1.5–2 mg kg^{-1} and remifentanil 0.25–0.5 μg kg^{-1} min^{-1}. Vecuronium bromide 0.1 mg kg^{-1} was administered for tracheal intubation. Patients were ventilated using oxygen in air ($F_{I_{O_2}}$ 0.4). Nitrous oxide was not used during surgery. Anaesthesia was maintained with propofol 5–10 mg kg^{-1} h^{-1}, remifentanil, and vecuronium bromide. Intraoperative remifentanil and propofol were discontinued at the end of surgery. Epidural ropivacaine was administered at 12.5–25 mg h^{-1} intraoperatively and at 8 mg h^{-1} after operation. Fentanyl 100 μg was administered via the epidural catheter after closure of the peritoneum. Droperidol 1.25 mg was administered to prevent postoperative nausea and vomiting at the end of surgery.

Body temperature was measured at the rectum and palm skin surface (thumb). Ambient temperature was 22–24°C during surgery and 25–27°C post-surgery. The lower extremities were covered by an air-forced blanket at 32°C, and warming was discontinued when rectal temperature reached 37°C. Acetated Ringer's solution was infused at ambient temperature.

Protocol

Fifty patients without exclusion criteria were randomly (envelope randomization) assigned to receive either intraoperative remifentanil at 0.1 μg kg^{-1} min^{-1} (low-dose group, n=25) or intraoperative remifentanil at 0.25 μg kg^{-1} min^{-1} (high-dose group, n=25). At the beginning of the study in June 2008, we prepared sequentially numbered (from 1 to 50) envelopes that contained the group assignment (25 in each group). On the morning of the surgery, the anaesthetist in charge of the surgery opened the envelope. In the case of prolonged surgery (more than 4 h), the patient was excluded from the study and a new envelope containing the same group assignment from which the patient was excluded was added at random to the unopened envelopes.

Intraoperative remifentanil infusion rates were fixed in each group; therefore, intraoperative analgesia was performed by titrating epidural ropivacaine based on systolic arterial pressure to between −20% and 0% of systolic arterial pressure measured at preoperative anaesthetic interview. Intraoperative sedation was performed by titrating propofol with a target of BIS values of 30–50.

Unfortunately, we did not either have post-anaesthetic care unit or dedicated special nursing staff for postoperative care. The operating theatre staff checked the patients for PAS while in the theatre for 30 min after emergence from anaesthesia, followed by a similar 30 min observation by the nursing staff in the ward. The nursing staff judged PAS using a five-point rating scale described by Wrench and colleagues[13] (0, no shivering; 1, peripheral vasoconstriction without visible muscular activity; 2, visible muscular activity confined to one muscle group; 3, visible muscular activity in more than one muscle group; 4, gross muscular activity involving the entire body). Grades 3 and 4 represented the occurrence of PAS and the 'Incidence of PAS' was written in the postoperative record by the nursing staff. The anaesthetist in charge was absent during PAS assessment to avoid bias related to knowledge of the anaesthetic regimen. PAS was treated initially using a warm blanket, and then if the shivering persisted for more than 15 min in spite of warming, pentazocine 15 mg was administered. Patients who developed PAS in the theatre were not returned to the ward until the disappearance of PAS.

Sample size and statistical analysis

On the basis of the previously published study by Röhm and colleagues,[5] we estimated an incidence of PAS grade 3 or 4 of 55% in patients receiving remifentanil 0.25 μg kg^{-1} min^{-1}. Unfortunately, there are no reports that have described the incidence of PAS in patients receiving a smaller dose of remifentanil (0.1 μg kg^{-1} min^{-1}) with propofol. Therefore, we estimated the incidence of PAS to be 15% in patients receiving small dose of remifentanil (0.1 μg kg^{-1} min^{-1}) based on our past-anaesthetic records in patients undergoing gynaecological laparotomy with sevoflurane–fentanyl anaesthesia. Power analysis indicated a minimum sample size of 23 patients in each group would be necessary to detect this difference with a power of 80% and an α of 0.05. Normality (Kolmogorov–Smirnov) and equal-variance tests were applied to all data. If these tests confirmed normal data distribution, data were expressed as mean (SD) and Student's t-test was used for comparisons of two groups. When the data had a skewed distribution, the results were expressed as median values (inter-quartile range) and the Mann–Whitney U-test was used for comparisons. χ^2 and Fisher's exact tests were also used to compare category data of the two groups. Repeated-measures ANOVA was performed to compare time lapse of rectal and palm skin temperatures during general anaesthesia between the two groups. Differences between the groups were considered statistically significant when the P-value was <0.05.

Results

Seventy-two patients were approached. Twenty-two patients were excluded before operation based on age, emergency surgery, ASA physical status, and surgical procedure. All patients undergoing emergency surgery did not receive epidural anaesthesia. One patient was evaluated as ASA physical status III due to massive ascites and pleural effusion. Thus, the study subjects numbered 50 patients. Three patients were later excluded due to prolonged surgery after the start of our protocol, and thus we added to the study one patient in the low-dose group and two patients in the high-dose group (Fig. 1). There were no important differences in preoperative patients' characteristics (Table 1). In spite of continuous infusion of high doses of remifentanil until the end of surgery, time until extubation after surgery was similar in the high- and low-dose groups, while there was a significant difference in the administration of epidural ropivacaine between the two groups. PAS was noted both in the operating theatre and in the gynaecological ward (Table 2), although no patients shivered both in the theatre and in
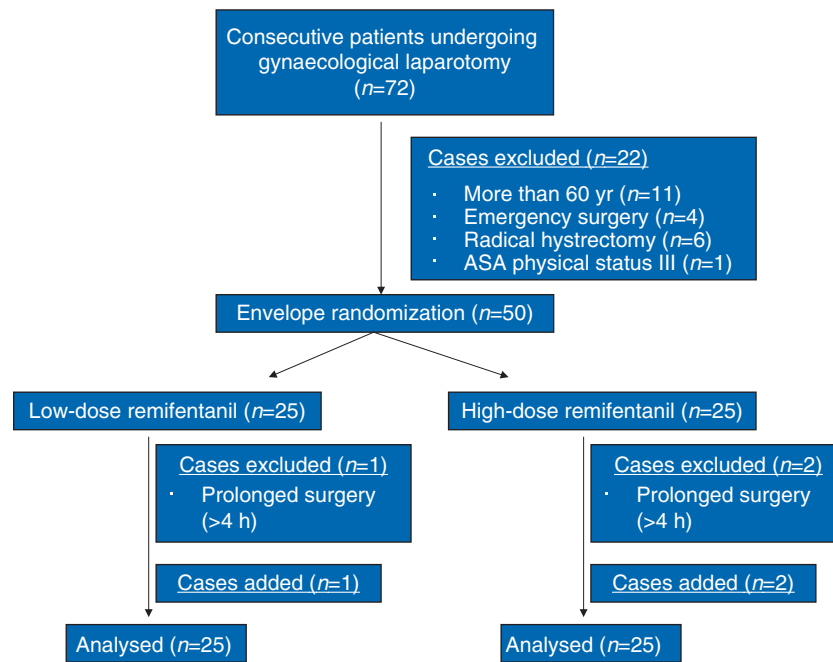
Fig 1 A flow diagram of inclusion and exclusion criteria according to CONSORT (Consolidated Standards of Reporting Trials) statement. One patient in the low-dose remifentanil group and two patients in the high-dose remifentanil group were later excluded from this study due to prolonged surgery after the start of our protocol.

Table 1 Comparison of perioperative clinical variables between the low-dose and high-dose groups. Values are mean (SD) or median (inter-quartile range). *$P<0.05$. Mean arterial pressure, heart rate, and mean bispectral index are mean values measured every 5 min

	Low-dose group	High-dose group
n	25	25
Preoperative factors		
Age (yr)	43 (40–46)	41 (37–45)
Weight (kg)	56 (10)	54 (7)
Diagnosis		
Benign disease (myoma, ovarian cyst, endometriosis)	21	22
Carcinoma	4	3
Intraoperative factors		
Duration of surgery (min)	148 (42)	151 (41)
Blood loss (ml)	151 (74–327)	156 (79–353)
Infusion (ml)	1300 (1200–1662)	1350 (1087–1687)
Total propofol (mg)	1081 (297)	1064 (289)
Total remifentanil (mg)	1.1 (0.9–1.3)	2.3 (2.0–2.9)*
Epidural ropivacaine (mg)	50 (42–71)	40 (35–48)*
Mean arterial pressure (mm Hg)	92 (85–101)	92 (87–100)
Mean heart rate (beats min^{-1})	56 (7)	53 (5)
Mean bispectral index	40 (4)	40 (3)
Time until extubation after surgery (min)	15 (15–20)	15 (15–20)

the ward. PAS during the first post-surgical hour occurred more frequently in the high-dose group (*n*=15, 60%) than in the low-dose group (*n*=5, 20%, *P*=0.009, a power of 0.839, Table 2). One patient in the high-dose group whose PAS persisted for more than 15 min in the ward was treated with pentazocine 15 mg. There were no significant differences in rectal or palm skin temperature throughout anaesthesia between the two groups. All patients of both groups were evaluated pain as pain free (visual analogue scale 0 cm) just after surgery in the operating theatre and

Table 2 Comparison of the incidence of PAS and intraoperative temperatures between the low-dose and high-dose groups. Values are reported as median (inter-quartile range). *$P<0.05$

	Low-dose group	High-dose group
Post-anaesthetic shivering		
Incidence in the theatre [n (%)]	2 (8)	8 (32)
Incidence in the ward [n (%)]	3 (12)	7 (28)
Total incidence [n (%)]	5 (20)	15 (60)*
Rectal temperature at the beginning of surgery (°C)	36.7 (36.6–36.8)	36.6 (36.4–36.7)
1 h after beginning of surgery (°C)	36.4 (36.0–36.6)	36.2 (36.0–36.4)
After extubation (°C)	36.4 (36.2–36.6)	36.4 (35.9–36.5)
Palm skin temperature at the beginning of surgery (°C)	33.6 (32.5–34.6)	33.7 (32.7–34.6)
1 h after beginning of surgery (°C)	32.8 (31.6–34.9)	33.8 (32.9–35.1)
After extubation (°C)	32.5 (31.9–33.8)	33.0 (32.6–34.4)

no patients in both groups complained of pain during the PAS observation period on the gynaecological ward.

Discussion

PAS is a frequent postoperative side-effect of general anaesthesia, affecting 5–65% of patients.[14] Besides the obvious discomfort in the recovery period, PAS increases oxygen consumption, carbon dioxide production, and catecholamine release,[15] resulting in increased cardiac output, heart rate, and arterial pressure.[16] Hence, PAS should be avoided in patients with diminished cardiopulmonary reserve. PAS is a frequent occurrence after discontinuation of remifentanil since this drug has become available in Japan, and some reports have associated the use of remifentanil with increased incidence of PAS.[2–6] None of these reports, except that of Röhm and colleagues,[5] discussed in detail why PAS caused by remifentanil occurred more frequently than with other opioids. Our current study is the first report implicating the infusion rate of remifentanil with PAS.

Three possible mechanisms may account for PAS after remifentanil administration.[17] First, remifentanil is eliminated faster than other opioids. Opioids inhibit thermoregulatory responses, thus shivering does not occur during surgery because the threshold of shivering decreases below body temperature.[18] It is possible that the threshold returns to normal immediately after discontinuance of remifentanil due to the drug's unique kinetics.[1] When the threshold increases faster than the increase in body temperature during recovery from general anaesthesia, shivering is triggered. However, this first explanation does not account for two aspects of the current study findings. If remifentanil produces a marked and linear decrease in

the dose-dependent shivering threshold in the same way as alfentanil,[18] the shivering threshold in patients who have received low doses would be expected to return to the pre-anaesthesia level faster than with higher doses of remifentanil. If remifentanil-induced PAS was related to body temperature and shivering threshold, PAS would occur more frequently in the low-dose remifentanil group. In addition, our results showed that rectal and palm skin temperatures throughout anaesthesia were similar between the two groups. We thus concluded that remifentanil-induced PAS is not a phenomenon of intraoperative hypothermia.

The second possibility is that shivering is mediated by pain.[19] However, this mechanism is also not supported by our results. All patients in both groups evaluated pain as VAS 0 cm probably due to the continuous epidural administration of ropivacaine. Although we did not evaluate pain objectively using VAS in the gynaecological ward, no patient complained of pain and rescue pentazocine was not needed during the PAS observation period because all patients were managed by epidural anaesthesia after operation. There was a significant difference in the dose of epidural ropivacaine between the two groups. This meant that low-dose remifentanil was insufficient to control analgesia during surgical stimuli without epidural ropivacaine in the low-dose group. Epidural anaesthesia itself slightly decreases the threshold-for triggering vasoconstriction and shivering (above the level of the block) by 0.6°C.[20] In addition, Doufas and colleagues[21] reported slight decreases in thresholds during epidural anaesthesia based on an apparent increase in lower body skin temperature. In spite of the larger amount of epidural ropivacaine administered in the low-dose group, the lower extremities were covered using an air-forced blanket at the same temperature in both groups. Hence, we considered that the rate of PAS was not influenced by the epidural anaesthesia itself.

The third mechanism, which we considered most important, is that shivering is a sign of opioid withdrawal caused by acute tolerance. Short-acting opioids like remifentanil could cause acute opioid tolerance and hyperalgesia, especially when higher doses are administered continuously.[7] The NMDA receptors are thought to play a major role in the development of acute opioid tolerance because remifentanil-induced hyperalgesia can be prevented by low doses of ketamine, a typical NMDA antagonist.[22] It was speculated that remifentanil stimulates the NMDA receptors, and that μ-receptors,[8] δ-receptors of remifentanil,[9] or glycine as an additive in the remifentail dose[10] could directly stimulate NMDA receptors and prophylactic ketamine was reported to be effective to prevent PAS.[23 24] In addition, magnesium is a non-competitive NMDA receptor antagonist and intraoperative infusion of magnesium sulphate reduced PAS.[25–27] Our study showed that remifentanil at high doses induced PAS more frequently than at low doses. This result accords with hyperalgesia caused by high doses of remifentanil in previous studies,[7 22] and it is conceivable, therefore, that patients administered high doses of remifentanil were sensitive to shivering after sudden discontinuation. The

administration of an NMDA receptor antagonist such as ketamine might have further clarified the mechanism of remifentanil-induced PAS.

We did not include a propofol–fentanyl-based anaesthesia group as a control. If the incidence of PAS in a propofol–fentanyl-based anaesthesia group is lower than that in a remifentanil group, it would be difficult to interpret. If the incidence were to be lower than that of the remifentanil group, one explanation could be that remifentanil infusion itself increases PAS while the other is that fentanyl reduces PAS since intraoperative fentanyl has been reported to be effective in suppressing PAS.[28]

Our observation period of shivering was 1 h, which is in accordance with several reports on PAS.[5 12 29] Unfortunately, there is no post-anaesthetic care unit in our hospital, and PAS occurred in two different places, that is, operating theatre and gynaecological ward. Both the theatre and ward staff assessed PAS using the same scale, to ensure consistency of the evaluation process. However, it is possible that the theatre nursing staff missed some cases of PAS, while the ward staff identified the presence of PAS. All patients in the operating theatre were covered with a warm blanket and transferred to the gynaecological ward within a few minutes. In addition, ambient temperature and humidity were constant in the postoperative care room of the gynaecological ward. But it also remains possible that environmental changes could have influenced the development of PAS.

In summary, intraoperative body temperature does not correlate with remifentanil-induced PAS. The higher incidence of PAS with high doses of remifentanil probably reflects the mechanism of remifentanil-induced PAS, that is, acute opioid tolerance and stimulation of NMDA receptors as in hyperalgesia. Patients administered high doses of remifentanil are sensitive to shivering after sudden discontinuation.

Conflict of interest

None declared.

References

1 Egan TD, Lemmens HJ, Fiset P *et al.* The pharmacokinetics of the new short-acting opioid remifentanil (G187084B) in healthy adult male volunteers. *Anesthesiology* 1993; **79**: 881–92

2 Apfel CC, Korttila K, Abdalla M *et al.* A factorial trial of six interventions of the prevention of postoperative nausea and vomiting. *N Engl J Med* 2004; **350**: 244–51

3 Apitzsch H, Olthoff D, Thieme V *et al.* Remifentanil and alfentanil: sympathetic-adrenergic effect in the first postoperative phase in patients at cardiovascular risk. *Anaesthetist* 1999; **48**: 301–9

4 Crozier TA, Kietzmann D, Döbereiner B. Mood change after anaesthesia with remifentanil or alfentanil. *Eur J Anaesthesiol* 2004; **21**: 20–4

5 Röhm KD, Riechmann J, Boldt J *et al.* Total intravenous anesthesia with propofol and remifentanil is associated with a nearly twofold higher incidence in postanesthetic shivering than desflurane–fentanyl anesthesia. *Med Sci Monit* 2006; **12**: 452–6

6 Möllhoff T, Herregods L, Moerman A *et al.* Comparative efficacy and safety or remifentanil and fentanyl in 'fast track' coronary artery bypass graft surgery: a randomized, double-blind study. *Br J Anaesth* 2001; **87**: 718–26

7 Guignard B, Bossard AE, Coste C *et al.* Acute opioid tolerance—intraoperative remifentanil increases postoperative pain and morphine requirement. *Anesthesiology* 2000; **93**: 409–17

8 Hahnenkamp K, Nollet J, Van Aken HK *et al.* Remifentanil directly activates human *N*-methyl-D-aspartate receptors expressed in *Xenopus laevis* oocytes. *Anesthesiology* 2004; **100**: 1531–7

9 Zhao M, Joo DT. Enhancement of spinal *N*-methyl-D-aspartate receptor function by remifentanil action at δ-opioid receptors as a mechanism for acute-induced hyperalgesia or tolerance. *Anesthesiology* 2008; **109**: 308–17

10 Guntz E, Dumont H, Roussel C *et al.* Effects of remifentanil on *N*-methyl-D-aspartate receptors: an electrophysiologic study in rat spinal cord. *Anesthesiology* 2005; **102**: 1235–41

11 Crossley AW. Six months of shivering in a district general hospital. *Anaesthesia* 1992; **47**: 845–8

12 Eberhart LHJ, Döderlein F, Eisenhardt G *et al.* Independent risk factors for postoperative shivering. *Anesth Analg* 2005; **101**: 1849–57

13 Wrench IJ, Cavill G, Ward JEH *et al.* Comparison between alfentanil, pethidine and placebo in the treatment of post-anaesthetic shivering. *Br J Anaesth* 1997; **79**: 541–2

14 Crossley. Peri-operative shivering. *Anaesthesia* 1992; **47**: 193–5

15 Ciofolo MJ, Clergue F, Devilliers C, Ben Ammar M, Viars P. Changes in ventilation, oxygen uptake, and carbon dioxide output during recovery from isoflurane anesthesia. *Anesthesiology* 1989; **70**: 737–41

16 Sessler DI, Rubinstein EH, Moayeri A. Physiologic responses to mild perianesthetic hypothermia in humans. *Anesthesiology* 1991; **75**: 594–610

17 Komatsu R, Turan AM, Orhan-Sungur M *et al.* Remifentanil for general anaesthesia: systemic review. *Anaesthesia* 2007; **62**: 1266–80

18 Kurz A, Go JC, Sessler DI, Kaer K, Larson M, Bjorksten AR. Alfentanil slightly increases the sweating threshold and markedly reduces the vasoconstriction and shivering thresholds. *Anesthesiology* 1995; **83**: 293–9

19 Horn EP, Schroeder F, Wilhelm S *et al.* Postoperative pain facilitates nonthermoregulatory tremor. *Anesthesiology* 1999; **91**: 979–84

20 Ozaki M, Kurz A, Sessler DI *et al.* Thermoregulatory thresholds during spinal and epidural anesthesia. *Anesthesiology* 1994; **81**: 282–8

21 Doufas AG, Morioka N, Maghoub AN, Mascha E, Sessler DI. Lower-body warming mimics the normal epidural-induced reduction in the shivering threshold. *Anesth Analg* 2008; **106**: 252–6

22 Joly V, Richebe P, Guignard B *et al.* Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology* 2005; **103**: 147–55

23 Dal D, Kose A, Honca M, Akinci SB, Basgul E, Aypar U. Efficacy of prophylactic ketamine in preventing postoperative shivering. *Br J Anaesth* 2005; **95**: 189–92

24 Honarmand A, Safavi MR. Comparison of prophylactic use of midazolam, ketamine, and ketamine plus midazolam for prevention of shivering during regional anaesthesia: a randomized

double-blind placebo controlled trial. *Br J Anaesth* 2008; **101**: 557–62

25 Wadhwa A, Sengupta P, Durrani J *et al.* Magnesium sulphate only slightly reduces the shivering threshold in humans. *Br J Anaesth* 2005; **94**: 756–62

26 Ryu JH, Kang MH, Park KS, Do SH. Effects of magnesium sulphate on intraoperative anaesthetic requirements and postoperative analgesia in gynaecology patients receiving total intravenous anaesthesia. *Br J Anaesth* 2008; **100**: 397–403

27 Ryu JH, Sohn IS, DO SH. Controlled hypotension for middle ear surgery: a comparison between remifentanil and magnesium sulphate. *Br J Anaesth* 2009; **103**: 465–7

28 Buggy DJ, Crossley AWA. Thermoregulation, mild perioperative hypothermia and post-anaesthetic shivering. *Br J Anaesth* 2000; **84**: 615–28

29 Bicer C, Esmaoglu A, Akin A, Boyaci A. Dexmedetomidine and meperidine prevent postanaesthetic shivering. *Eur J Anaesthesiol* 2006; **23**: 149–53