Efficiency and safety of ondansetron in preventing postanaesthesia shivering

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ABSTRACT

INTRODUCTION Shivering is one of the most frequent complications of operation during the postanaesthesia period. Ondansetron has been proved to be valid in preventing postanaesthesia shivering (PAS) in several studies. However, its efficiency and safety are still disputable. We therefore performed an updated meta-analysis of randomised controlled trials (RCTs) for evaluation and to clarify this issue.

METHODS A literature search using the PubMed, Embase™ and Cochrane Library databases was performed (from inception to January 2015). RCTs that evaluated the efficiency and safety of ondansetron in the prevention of PAS were included in the meta-analysis. The primary outcome measure was incidence of PAS, and secondary outcomes included subgroup analysis and the side effects of ondansetron.

RESULTS A total of 8 RCTs containing 905 subjects were identified as suitable for this review. Compared with placebo, ondansetron was associated with a significant reduction of PAS (relative risk [RR]: 0.33, 95% confidence interval [CI]: 0.19–0.58, $p=0.0001$) while no difference was detected between ondansetron and pethidine (RR: 0.89, 95% CI: 0.41–1.94, $p=0.78$). There was no significant difference between ondansetron and placebo or pethidine in terms of risk of bradycardia but ondansetron was associated with a lower risk of hypotension (RR: 0.26, 95% CI: 0.08–0.79, $p=0.020$) than placebo. There was no difference in hypotension when ondansetron was compared with pethidine.

CONCLUSIONS Ondansetron can prevent PAS effectively and reduce the risk of hypotension.

KEYWORDS

Ondansetron – Pethidine – Shivering – Meta-analysis

Accepted 21 October 2015

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It is estimated that 234.2 million major surgical procedures are undertaken every year worldwide.¹ Postanaesthesia shivering (PAS) is a relatively frequent, unpleasant, stressful and occasionally distressing complication in the postoperative period after modern advanced anaesthesia.^{2,5} According to previous studies, the incidence ranges from 6.5% to 66% after general anaesthesia and the mechanism is still poorly understood.^{4–7}

PAS is defined as detectable tremor or fasciculation involving the head, neck, trunk, shoulders and extremities, or generalised and visible shaking resembling normal thermogenic shivering.^{4,8} It not only causes discomfort and aggravates physical pain but also induces serious complications, implicating the cardiopulmonary systems, increasing cardiac output, peripheral resistance, intraocular and intracranial pressures, oxygen consumption, carbon dioxide production and, ultimately, lactic acidosis.^{9–15} In addition, it disturbs surgical care and is associated with an adverse effect on cases requiring postoperative immobilisation such as nerve and vascular anastomoses.¹⁴ Consequently, prevention of PAS will not merely have a beneficial effect on patients but will also automatically promise a better prognosis.¹⁵

Raising the theatre temperature and skin surface rewarming could prevent PAS effectively but is insufficient.^{16,17} Medical treatment is therefore imperative and there are numerous effective drugs for preventing or stopping PAS. These include alpha-2 agonists, opiates, tramadol, ketanserin, magnesium sulphate, corticosteroids, physostigmine, doxapram, methylphenidate, nefopam and serotonin 5-HT₃ antagonists.^{11,18}

Ondansetron, a 5-HT₃ antagonist, is generally used as an antiemetic but its efficiency and safety in the prevention of PAS remains controversial. A previous meta-analysis concluded it reduces the incidence of PAS without showing an increased risk of bradycardia.¹⁹ However, some new randomised controlled trials (RCTs) have since been published on this topic. Our meta-analysis therefore sought to determine the effectiveness and safety of ondansetron by comparing it with placebo and pethidine in terms of the preventative effect on PAS and also adverse effects.

Methods

The review was conducted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*²⁰ and the

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.²¹ PubMed, Embase™ and the Cochrane Library databases (from inception to January 2015) were searched for potentially relevant articles related to ondansetron and prevention of PAS. The structured search strategies used the following format of search terms: (ondansetron AND shivering). No other restrictions were imposed.

The reference lists of identified studies were checked manually to include other potentially eligible trials. This process was performed repeatedly until no additional articles could be identified. The following inclusive selection criteria were applied: a) study design: RCTs reported in full text; b) study population: patients undergoing a surgical operation with anaesthesia (regardless of whether neuraxial or general); c) intervention: ondansetron to prevent PAS (regardless of type and regimen applied); d) comparison: ondansetron compared with placebo or pethidine; e) outcome measures: including incidence of PAS or reported adverse events.

Data extraction and quality assessment

Two of the authors independently screened the titles and abstracts of retrieved studies to identify those records that appeared to meet the inclusion criteria. The full text of these articles was then obtained for further independent assessment of eligibility. Any disagreement was resolved by discussion and the third author arbitrated when necessary.

The two reviewers used a standardised Excel® spreadsheet (Microsoft, Redmond, WA, US) to record the following from the eligible studies: first author, publication year, number of patients, patient characteristics, ASA (American Society of Anesthesiologists) grade, surgical setting, type of anaesthesia, time and dose of drug administration, definition of PAS, incidence of PAS and adverse events. Again, discrepancies were resolved by discussion and the third author arbitrated when necessary.

The primary outcome was incidence of PAS. In order to determine the best prophylactic dose, subgroup analysis was performed on data from trials investigating ondansetron dosage. Adverse events were also explored as secondary outcomes when information was available.

Risk of bias was assessed according to the Cochrane Collaboration guidelines²⁰ by the two reviewers. Factors examined included adequacy of randomisation, allocation concealment, blinding, attrition, selective reporting and other bias. The studies were rated as having a low, high or unclear risk of bias. Disagreements between the two reviewers were resolved by discussion.

Statistical analysis

All statistical analysis was performed with RevMan version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark). A random effects model was used despite heterogeneity. Statistical heterogeneity among the RCTs included in the meta-

Table 1 Summary of the studies included in the meta-analysis								
Study	Country	Age (yrs)	Male	Surgical setting and ASA grade	Anaesthesia	Comparisons	Administration	Definition of PAS
Powell, 2000 ²⁴	UK	46.7	74.4%	Orthopaedic, general or urological surgery, ASA 1–2	General	Ondansetron IV 4mg Ondansetron IV 8mg Saline IV	3–5 mins before induction of anaesthesia	Readily detectable fasciculations or tremors of the face, trunk or limbs for ≥15 secs
Kelsaka, 2006 ²⁵	Turkey	36.3	74.7%	Elective orthopaedic surgery, ASA 1–2	Spinal	Ondansetron IV 8mg Pethidine IV 0.4mg/kg Saline IV 4ml	Immediately before anaesthesia	Observation of fasciculations of pectoralis major muscles for >10 secs
Shakya, 2010 ²⁶	Nepal	45.7	36.7%	Elective lower abdominal surgery, ASA 1–2	Spinal	Ketamine IV 0.25mg/kg Ondansetron IV 4mg Saline IV	Just after intrathecal injection	0 = no shivering; 1 = piloerection or peripheral vasoconstriction but no visible shivering; 2 = muscular activity in only one muscle group; 3 = muscular activity in more than one muscle group but not generalised; 4 = shivering involving the whole body
Asl, 2011 ²⁷	Iran	25.9	NA	Elective gynaecological surgery, ASA 1–2	General	Ondansetron 4mg Pethidine 0.4mg/kg Normal saline 2ml	2 mins before induction of anaesthesia	Chills for ≥15 secs
Abdollahi, 2012 ²⁸	Iran	63.8	64.5%	Off-pump coronary artery bypass graft, ASA 1–3	General	Pethidine IV 0.4mg/kg Ondansetron IV 8mg Normal saline IV	15 mins before end of surgery	0 = no shivering; 1 = one or more of the following: peripheral vasoconstriction, peripheral cyanosis without any other reason, piloerection without muscle contraction; 2 = visible muscular activity involving only one muscle group; 3 = visible muscular activity involving more than one muscle group; 4 = intensive muscular activity involving the whole body

Study	Country	Age (yrs)	Male	Surgical setting and ASA grade	Anaesthesia	Comparisons	Administration	Definition of PAS
Browning, 2013 ²⁹	Australia	31.5	0%	Elective Caesarean section, ASA 1–2	Combined spinal epidural anaesthesia	Ondansetron IV 8mg	Before anaesthesia	0 = no shivering; 1 = one or more of the following: piloerection, peripheral vasoconstriction, peripheral cyanosis without other cause but 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
						Saline IV 4ml		
Marashi, 2014 ³⁰	Iran	33.9	62.9%	Elective urological, orthopaedic or gynaecological, ASA 1–2	Spinal	Ondansetron IV 6mg Ondansetron IV 12mg Saline IV 20ml	5 mins before anaesthesia	1 = no shivering; 2 = fasciculation in head and neck that was just visible as artefacts on ECG; 3 = obvious tremor on head, neck and limbs; 4 = generalised tremor throughout the body
Safari, 2014 ³¹	Iran	37.3	68.3%	Elective orthopaedic surgery, ASA 1–2	Spinal	Ondansetron IV 8mg Pethidine 0.2mg/kg Saline IV	Before anaesthesia	0 = no shivering; 1 = piloerection or peripheral vasoconstriction but no visible shivering; 2 = muscular activity observed only in one muscle group; 3 = muscular activity observed in more than one muscle group without generalised shivering; 4 = all body shivering
ASA = American Society of Anesthesiologists; PAS = postanaesthesia shivering; IV = intravenous; NA = not available; ECG = electrocardiography								

analysis was assessed using Cochran’s Q statistic ($p<0.1$ was considered indicative of statistically significant heterogeneity) and inconsistency was quantified with the I^2 statistic (values of 25%, 50% and 75% were considered to represent low, medium and high heterogeneity respectively).^{22,23} Differences with a p -value of <0.05 were considered statistically significant except where otherwise specified.

Results

A total of 168 records were identified in the initial electronic search and 1 additional record was found through other sources. Of these, 44 records were excluded for being duplicates, and 107 were identified as irrelevant by reviewing the titles and abstracts. The full text was obtained for 18 articles for further assessment. Overall, 8 studies with a total of 905

subjects met our inclusion criteria and were included in the meta-analysis.^{24–31} A detailed flowchart of the search and selection results is shown in Figure 1.

Study characteristics and quality assessment

A summary of the studies included in the review is shown in Table 1. A total of 905 patients were assigned randomly to different groups for different interventions. The studies selected for our review were published between 2000 and 2014, and the sample size ranged from 75 to 210. The types of anaesthesia used in the studies included spinal, general and combined spinal epidural anaesthesia. Our analysis focused only on three types of intervention: ondansetron compared with pethidine or placebo. All of the RCTs included in our meta-analysis scored highly enough

according to the Cochrane guidelines²⁰ to suggest good quality in terms of risk of bias (Fig 2).

Primary outcome

The pooled results for the eight RCTs showed that compared with placebo, ondansetron was associated with a significant reduction of PAS (relative risk [RR]: 0.33, 95% confidence interval [CI]: 0.19–0.58, $p=0.0001$) while there was no significant difference between ondansetron and pethidine (RR: 0.89, 95% CI: 0.41–1.94, $p=0.78$). The heterogeneity was $I^2=78\%$ and $I^2=34\%$ respectively (Fig 3).

Secondary outcomes

Subgroup analysis of ondansetron dose demonstrated that compared with placebo, both 4mg and 8mg of ondansetron could reduce the risk of PAS significantly (RR: 0.37, 95% CI: 0.19–0.69, $p=0.002$; and RR: 0.47, 95% CI: 0.28–0.80, $p=0.005$ respectively) (Fig 4). There was no statistical difference between ondansetron and placebo or pethidine regarding

the risk of bradycardia (Fig 5) but ondansetron was associated with a lower risk of hypotension (RR: 0.26, 95% CI: 0.08–0.79, $p=0.020$) than placebo. There was no difference in hypotension when ondansetron was compared with pethidine (Fig 6).

Discussion

This meta-analysis of eight RCTs sought to determine the efficiency and safety of ondansetron in the prevention of PAS by comparing it with placebo and pethidine. The results show that ondansetron can significantly reduce the risk of PAS compared with placebo. However, the effects of ondansetron are comparable with pethidine. Ondansetron was significantly associated with a lower risk of hypotension but there was no significant association with bradycardia.

Ondansetron is a specific 5-HT₃ antagonist that is usually recommended for prevention and treatment of nausea and vomiting during or after surgery. Previous studies have

Figure 3 Forest plot comparing the antishivering effect of ondansetron with placebo and with pethidine. A Mantel–Haenszel random effects model was used for meta-analysis. Risk ratios are shown with 95% confidence intervals.

Figure 4 Subgroup analysis by dose of ondansetron: Forest plot comparing ondansetron with placebo. A Mantel–Haenszel random effects model was used for meta-analysis. Risk ratios are shown with 95% confidence intervals.

Figure 5 Bradycardia: Forest plot comparing ondansetron with placebo and with pethidine. A Mantel–Haenszel random effects model was used for meta-analysis. Risk ratios are shown with 95% confidence intervals.

Figure 6 Hypotension: Forest plot comparing ondansetron with placebo and with pethidine. A Mantel–Haenszel random effects model was used for meta-analysis. Risk ratios are shown with 95% confidence intervals.

demonstrated that a biological amine found in the brain and spinal cord, serotonin (5-HT), plays a role in neurotransmission, and several studies have confirmed that the serotonergic system plays an important role in the control of PAS.^{5,52,53} Ondansetron could therefore affect perioperative thermoregulation and prevent PAS. The detailed mechanism by which 5-HT₃ antagonists act in the regulation of body temperature and the prevention of PAS has not been clarified but it might be related to encouraging the inhibiting effect of serotonin reuptake on the preoptic anterior hypothalamus region.^{11,54}

Among the eight studies included in our meta-analysis, only the RCT by Browning *et al* found that prophylactic ondansetron does not prevent PAS or decrease shivering severity as expected.²⁹ This contributes greatly to the heterogeneity in the meta-analysis of the primary outcome. There are two main reasons for this phenomenon. First, the type of anaesthesia was totally different to that in the other studies. The study by Browning *et al* reported on combined spinal epidural anaesthesia while the others used spinal or general anaesthesia.²⁹ It should be noted that shivering following general anaesthesia is different to that following neuraxial

anaesthesia because general anaesthesia only impairs central thermoregulatory control while neuraxial anaesthesia impairs both central and peripheral thermoregulation.⁵⁵ As a result, owing to its mechanism, ondansetron will not have an antishivering effect after neuraxial anaesthesia.

Second, the patients in the study by Browning *et al* differed in a number of ways from the other study populations in that they were all female, pregnant and relatively young.²⁹ There is evidence that shivering in pregnancy and in the peripartum period also differs in many ways to thermoregulatory shivering seen in the non-pregnant population.^{56,57} Ondansetron may not have an antishivering effect in this clinical setting. Consequently, further exploration is needed to determine which patients are appropriate and which conditions are suitable.

Two studies demonstrated that intravenous ondansetron has a dose dependent effect.^{24,50} Both found that ondansetron was associated with a dose dependent reduction of PAS. However, this effect was not observed in the pooled results. As the administration doses of ondansetron did not vary with weight, the real effect might be confounded by the different weights of the participants in different trials.

Ondansetron has been used widely for its antiemetic properties. When ondansetron is used for the prevention of PAS, the haemodynamic profile of the patient does not change, which is beneficial for safety in anaesthesia. Furthermore, our review looked at side effects on the cardiovascular system, namely bradycardia and hypotension. Many drugs are used for treating PAS. We chose to compare ondansetron with pethidine, the most widely used drug for the prevention and treatment of PAS.^{25,38} Our meta-analysis found no difference between ondansetron and pethidine in terms of bradycardia or hypotension. However, when compared with placebo, ondansetron was associated with a lower risk of hypotension although there was no difference for bradycardia.

Several studies have confirmed that pethidine can cause nausea and vomiting, somnolence, delayed emergence from anaesthesia and respiratory depression when used for PAS.^{39,40} The limited data for ondansetron indicate it may produce similar side effects but these were not analysed because of their rarity.

Study limitations

Our review has several potential limitations. First, medium or high heterogeneity was observed among the included studies, mainly due to methodological and clinical heterogeneity (such as different types of anaesthesia, recruitment of subjects and definitions of PAS). Second, a minority of trials in this review were rated as having an unclear risk of bias, which impairs the power. Third, our analysis was based on eight RCTs but four had only a modest sample size ($n < 100$).^{24,25,27,28} The preventative effect of ondansetron on PAS could be overestimated more easily with smaller sample sizes than with larger studies. Finally, the optimal administration dose of ondansetron needs further exploration to determine which dose is most appropriate and whether it should be varied with weight.

Future studies should clarify the mechanism of ondansetron, and also investigate which patient populations are suitable for its use, what range of applications is appropriate and what the optimal effective clinical dose is. Relevant adverse events of ondansetron should be reported to evaluate its safety comprehensively.

Conclusions

Despite several limitations, our meta-analysis is of great clinical value because it suggests that the usage of ondansetron is as effective and safe as pethidine.

References

- Weiser TG, Regenbogen SE, Thompson KD *et al.* An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008; **372**: 139–144.
- Brownridge P. Shivering related to epidural blockade with bupivacaine in labour, and the influence of epidural pethidine. *Anaesth Intensive Care* 1986; **14**: 412–417.
- Macario A, Weinger M, Carney S, Kim A. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. *Anesth Analg* 1999; **89**: 652–658.
- Crossley AW. Six months of shivering in a district general hospital. *Anaesthesia* 1992; **47**: 845–848.
- Joris J, Banache M, Bonnet F *et al.* Clonidine and ketanserin both are effective treatment for postanesthetic shivering. *Anesthesiology* 1993; **79**: 532–539.
- Horn EP, Sessler DI, Standl T *et al.* Non-thermoregulatory shivering in patients recovering from isoflurane or desflurane anesthesia. *Anesthesiology* 1998; **89**: 878–886.
- Panzer O, Ghazanfari N, Sessler DI *et al.* Shivering and shivering-like tremor during labor with and without epidural analgesia. *Anesthesiology* 1999; **90**: 1,609–1,616.
- Kurz A. Physiology of thermoregulation. *Best Pract Res Clin Anaesthesiol* 2008; **22**: 627–644.
- Liem ST, Aldrete JA. Control of post-anaesthetic shivering. *Can Anaesth Soc J* 1974; **21**: 506–510.
- Murphy MT, Lipton JM, Loughran P, Giesecke AH. Postanesthetic shivering in primates: inhibition by peripheral heating and by taurine. *Anesthesiology* 1985; **63**: 161–165.
- Alfonsi P. Postanaesthetic shivering: epidemiology, pathophysiology, and approaches to prevention and management. *Drugs* 2001; **61**: 2,193–2,205.
- Mathews S, Al Mulla A, Varghese PK *et al.* Postanaesthetic shivering – a new look at tramadol. *Anaesthesia* 2002; **57**: 394–398.
- Dal D, Kose A, Honca M *et al.* Efficacy of prophylactic ketamine in preventing postoperative shivering. *Br J Anaesth* 2005; **95**: 189–192.
- Mohta M, Kumari N, Tyagi A *et al.* Tramadol for prevention of postanaesthetic shivering: a randomised double-blind comparison with pethidine. *Anaesthesia* 2009; **64**: 141–146.
- Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. *N Engl J Med* 1996; **334**: 1,209–1,215.
- Camus Y, Delva E, Sessler DI, Lienhart A. Pre-induction skin-surface warming minimizes intraoperative core hypothermia. *J Clin Anesth* 1995; **7**: 384–388.
- El-Gamal N, El-Kassabany N, Frank SM *et al.* Age-related thermoregulatory differences in a warm operating room environment (approximately 26 degrees C). *Anesth Analg* 2000; **90**: 694–698.
- Kranke P, Eberhart LH, Roewer N, Tramèr MR. Postoperative shivering in children: a review on pharmacologic prevention and treatment. *Paediatr Drugs* 2003; **5**: 373–383.
- Tie HT, Su GZ, He K *et al.* Efficacy and safety of ondansetron in preventing postanesthesia shivering: a meta-analysis of randomized controlled trials. *BMC Anesthesiol* 2014; **14**: 12.
- Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0.* London: Cochrane Collaboration; 2011.
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; **8**: 336–341.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1,539–1,558.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–560.
- Powell RM, Buggy DJ. Ondansetron given before induction of anesthesia reduces shivering after general anesthesia. *Anesth Analg* 2000; **90**: 1,423–1,427.
- Kelsaka E, Baris S, Karakaya D, Sarihasan B. Comparison of ondansetron and meperidine for prevention of shivering in patients undergoing spinal anesthesia. *Reg Anesth Pain Med* 2006; **31**: 40–45.
- Shakya S, Chaturvedi A, Sah BP. Prophylactic low dose ketamine and ondansetron for prevention of shivering during spinal anaesthesia. *J Anaesthesiol Clin Pharmacol* 2010; **26**: 465–469.
- Asl ME, Isazadefar K, Mohammadian A, Khoshbaten M. Ondansetron and meperidine prevent postoperative shivering after general anaesthesia. *Middle East J Anaesthesiol* 2011; **21**: 67–70.
- Abdollahi MH, Forouzannia SK, Bagherinasab M *et al.* The effect of ondansetron and meperidin on preventing shivering after off-pump coronary artery bypass graft. *Acta Med Iran* 2012; **50**: 395–398.
- Browning RM, Fellingham WH, O'Loughlin EJ *et al.* Prophylactic ondansetron does not prevent shivering or decrease shivering severity during cesarean delivery under combined spinal epidural anesthesia: a randomized trial. *Reg Anesth Pain Med* 2013; **38**: 39–43.
- Marashi SM, Soltani-Omid S, Soltani Mohammadi S *et al.* Comparing two different doses of intravenous ondansetron with placebo on attenuation of spinal-induced hypotension and shivering. *Anesth Pain Med* 2014; **4**: e12055.

31. Safavi M, Honarmand A, Negahban M, Attari M. Prophylactic effects of intrathecal Meperidine and intravenous Ondansetron on shivering in patients undergoing lower extremity orthopedic surgery under spinal anesthesia. *J Res Pharm Pract* 2014; **3**: 94–99.
32. Dawson NJ, Malcolm JL. Initiation and inhibition of shivering in the rat: interaction between peripheral and central factors. *Clin Exp Pharmacol Physiol* 1982; **9**: 89–93.
33. Hindle AT. Recent developments in the physiology and pharmacology of 5-hydroxytryptamine. *Br J Anaesth* 1994; **73**: 395–407.
34. Hammel HT. Regulation of internal body temperature. *Annu Rev Physiol* 1968; **30**: 641–710.
35. Lenhardt R. The effect of anaesthesia on body temperature control. *Front Biosci* 2010; **2**: 1,145–1,154.
36. Fusi L, Steer PJ, Maresh MJ, Beard RW. Maternal pyrexia associated with the use of epidural analgesia in labour. *Lancet* 1989; **1**: 1,250–1,252.
37. Ravid D, Gidoni Y, Bruchim I *et al*. Postpartum chills phenomenon: is it a feto-maternal transfusion reaction? *Acta Obstet Gynecol Scand* 2001; **80**: 149–151.
38. Casey WF, Smith CE, Katz JM *et al*. Intravenous meperidine for control of shivering during Caesarean section under epidural anaesthesia. *Can J Anaesth* 1988; **35**: 128–133.
39. Dabir S, Jahandideh M, Abbasinazari M *et al*. The efficacy of a single dose of pethidine, fentanyl and morphine in treating postanaesthesia shivering. *Pak J Pharm Sci* 2011; **24**: 513–517.
40. Anaraki AN, Mirzaei K. The effect of different intrathecal doses of meperidine on shivering during delivery under spinal anesthesia. *Int J Prev Med* 2012; **3**: 706–712.