Pharmacological Approach for the Prevention of Postoperative Shivering: A Systematic Review of Prospective Randomized Controlled Trials

Paraskevi K. Matsota, Iosifina K. Koliantzaki, Georgia G. Kostopanagiotou
2nd Department of Anesthesiology, School of Medicine, National and Kapodistrian University of Athens, “Attikon” University Hospital, Athens, Greece

Shivering is a common postoperative complication that occurs after both general and regional anesthesia even in the cases when hypothermia during surgery has been averted. Patients describe it as a highly unpleasant experience, while clinicians are concerned due to its adverse effects such as increased oxygen consumption. In this article, we present a summary of the pathophysiological mechanisms involved in postoperative shivering (POS), risk factors, and inadvertent effects. The major objective of this article was to review the existing literature on the efficiency of various drug interventions as a prophylactic measure against POS. Since α2-adrenergic, opioid, anticholinergic, and serotonergic pathways are thought to play a role in the pathogenesis of POS, a wide variety of drugs has been investigated in this regard. Although the methodological diversity of the study designs and regimens does not support drawing definite conclusions, there is evidence indicating a beneficial effect of dexmedetomidine, ketamine, tramadol, meperidine, dexamethasone, nefopam, granisetron, and ondansetron in the prevention of POS. The purpose of this review is to provide a thorough insight on various drug options and to serve as an aid for clinicians for careful analysis of the advantages and disadvantages of each regimen to decide which regimen will be ideally suited for the medical profile of each patient.

Keywords: drugs, preventing, postoperative shivering

Introduction

Postoperative shivering (POS) is defined as readily detectable fasciculations affecting muscle groups, usually appearing early in the postoperative period. Its prevalence ranges between 5–65% after general anesthesia and 33–66% after regional anesthesia.

Pathophysiology

Shivering is the body’s response to augment heat production commonly perceived as a symptom of hypothermia, although core body temperature does not always seem to correlate with the incidence of shivering after anesthesia. Thus, non-thermoregulatory shivering is believed to be caused by special factors related to surgery, such as stress or pain.

Risk Factors

Risk factors that predispose the patient to hypothermia and shivering include young age, male gender, low body weight, or poor nutritional status, prolonged preoperative fasting, an American Society of Anesthesiologists (ASA) risk class higher than 1, combined general-regional anesthesia and the extent...
of induced sympathetic blockade, \(^8,10\) administration of premedication, volatile anesthetics, and muscle relaxants.\(^11\)

Furthermore, the type and duration of surgery are the surgery-related risk factors for the development of hypothermia. Endoprosthesis and long-lasting abdominal surgery bear a high risk of consequential hypothermia.\(^6\) Likewise, intraoperative use of unwarmed irrigation fluids,\(^12\) transfusion of cold red blood cells and the low temperature of the operating room (OR)\(^13\) predispose the patient to hypothermia.

**Adverse Effects**

Patients describe shivering as a highly disturbing experience. However, the foremost concern of clinicians lies in the fact that shivering can increase oxygen consumption dramatically, by up to 700% in cases of severe shivering.\(^14\) This imposes significant stress on patients, particularly those with burdened cardiorespiratory reserve. Furthermore, shivering increases intraocular\(^15\) and intracranial pressure.\(^16\) Hypothermia, which may be the underlying cause of shivering, is associated with a number of adverse events,\(^17,18\) but discussion on these extends beyond the scope of this review.

Several studies investigating the precautionary measures for shivering have been conducted. This review aims to investigate the existing literature regarding the efficacy of various drugs used to prevent POS.

**Methods**

**Identification of Trials**

Published trials (till the September of 2018) investigating the pharmacological options for the prevention of POS were identified by conducting a search on PubMed and Scopus databases, using the keywords “preventing postoperative shivering” and “preventing shivering after anesthesia.”

**Inclusion Criteria**

We considered solely prospective randomized clinical trials written in English. The investigated drugs had been administered prophylactically at any time between just before the induction of anesthesia till the end of surgery, as a single dose or by infusion, through any parenteral or enteral route.

**Exclusion Criteria**

We did not include data from retrospective analyses or studies without randomization, to avoid any potential bias. Also, data from abstracts, case reports, nonsurgical settings, cardiac surgery or any other type of surgery using induced hypothermia, guidelines, or from experimental studies using volunteers or animals were excluded.

**Results**

**Trials Included**

Of the 244 articles identified initially, only 38 met the selection criteria for this review and were included in the analysis. The flow diagram is illustrated in Fig. 1.

From the 38 included studies, 24 studies had been performed on patients undergoing surgery under general anesthesia and 1 under conscious sedation (Table 1),\(^19-43\) and 13 on patients receiving regional anesthesia (Table 2).\(^44-56\) Information on patients, type of surgery, investigated drugs (doses, routes, and timing of the administration), power of the study and study findings are presented in these Tables.

Since α2-adrenergic, opioid, anticholinergic, and serotonergic pathways are thought to contribute to the pathogenesis of POS, a wide variety of drugs has been investigated regarding their efficacy in its prevention. The route of administration for all the drugs mentioned in this review is mainly intravenous unless stated otherwise.

**α2-Adrenergic Agonists**

The efficacy of α2-adrenergic agonists in the prevention of POS has been extensively investigated. Dexmedetomidine, with an α1/α2 ratio of 1:1,620, is a highly selective and potent drug of this class, as opposed to clonidine, which is a partial agonist with an α1/α2 ratio of 1:220.\(^57\) Due to the selectivity of dexmedetomidine, it is preferred over clonidine in the majority of relevant trials.

**General Anesthesia—Table 1**

Our review revealed that clonidine, administered either as oral premedication (0.2 mg)\(^55\) or as an intravenous bolus dose (2 mcg/kg) at the end of surgery,\(^56\) effectively prevents POS after general anesthesia. Dexmedetomidine (1 mcg/kg) appears...
to be as efficacious against POS as meperidine (0.5 mg/kg), but is inferior to tramadol (1 mg/kg) when administered at the end of surgery. In contrast, Alvarez Corredor reported that 0.4 mg/kg meperidine performed better than 1 mcg/kg dexmedetomidine. However, one must also consider that 70% of the patients in the dexmedetomidine group reported severe postoperative pain, while most of the patients in the other groups reported mild to no pain. Since the presence of postoperative pain can facilitate non-thermoregulatory tremors, coupled with the fact that the mean duration of anesthesia and surgery, volume of intraoperative IV fluids and blood loss were greater in the dexmedetomidine group, the result may be considerably biased against dexmedetomidine. Kim et al. compared three different dosages of dexmedetomidine (0.50, 0.75, and 1.00 mcg/kg) to placebo and found that dexmedetomidine at 0.75 or 1.00 mcg/kg is an effective prophylactic measure against shivering when administered 30 min before the completion of surgery. Furthermore, dexmedetomidine infusion has been successfully used in a placebo-controlled study. Sedation, prolonged extubation time, and a tendency of lower mean arterial pressure and heart rate, all of which are dose-dependent adverse effects, were observed in most of the aforementioned studies, without compromising the outcomes of anesthesia.

**Regional Anesthesia—Table 2**

Only two published studies have investigated
<table>
<thead>
<tr>
<th>Title</th>
<th>Intervention</th>
<th>Study population</th>
<th>Type of surgery/anesthesia</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| Alvarez Corredor    | 1. Dexmedetomidine 1.00 mcg/kg iv  
2. Meperidine 0.40 mg/kg iv  
3. Ketamine 0.50 mg/kg iv  
4. Placebo (0.9% saline solution) iv  
All drugs were given 20 min before skin suture. | 160 patients, ASA I–II, 18–70 years | Both elective and emergency surgery lasted more than 1 h, including open and laparoscopic procedures. General anesthesia. | Meperidine was the most effective drug in preventing POS, while 70% of patients in the group of dexmedetomidine reported severe pain (p < 0.01). 80% power. |
| Sahi et al.         | 1. Clonidine 2 µg/kg iv  
2. Tramadol 1 mg/kg iv  
3. Dexmedetomidine 1 mcg/kg iv  
4. Placebo (0.9% saline solution) iv  
All drugs were given at the beginning of wound closure. | 120 patients, ASA I–II, adults | LPC. General anesthesia.                     | Tramadol was the most effective drug, although all three drugs were more effective than placebo in preventing POS. NM power. |
| Kim et al.          | 1. Dexmedetomidine 0.50 mcg/kg iv  
2. Dexmedetomidine 0.75 mcg/kg iv  
3. Dexmedetomidine 1.00 mcg/kg iv  
4. Placebo (0.9% saline solution) iv  
All drugs were given 30 min before the anticipated completion of surgery. | 132 patients, ASA I–II, 18–60 years, female | Elective laparoscopic total hysterectomy. General anesthesia | Higher doses of dexmedetomidine (0.75 mcg/kg and 1.00 mcg/kg) were effective in preventing POS. 80% power. |
| Bicer et al.        | 1. Dexmedetomidine 1.00 mcg/kg iv  
2. Meperidine 0.50 mg/kg iv  
3. Placebo (0.9% saline solution) iv  
All drugs were given at the time of wound closure. | 120 patients, ASA I–II, 18–50 years | Elective abdominal or orthopedic surgery of about 1–3 h duration. General anesthesia | Both drugs were equally effective in preventing POS. NM power. |
| Karaman et al.      | 1. Dexmedetomidine iv as a loading of 1.00 mcg/kg for 10 min followed by a maintenance infusion of 0.50 mcg/kg/h  
2. Placebo iv (0.9% saline solution given at a similar mode)  
The loading dose was given just after endotracheal intubation. The infusion was stopped at the beginning of the closure of the fascia. | 60 patients, ASA I–II, 20–50 years, female | Elective gynecologic laparoscopy. General anesthesia | Dexmedetomidine was effective in preventing POS. NM power. |
Table 1. Randomized controlled trials investigating drugs to prevent postoperative shivering in patients who received general anesthesia (continued)

<table>
<thead>
<tr>
<th>Title</th>
<th>Intervention</th>
<th>Study population</th>
<th>Type of surgery/anesthesia</th>
<th>Conclusion</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldehayat&lt;sup&gt;7&lt;/sup&gt;</td>
<td>1. Dexmedetomidine 1.00 mcg/kg iv 2. Placebo iv (0.9% saline solution)</td>
<td>70 patients, ASA –II patients, 18-68 years</td>
<td>The type of surgery was not mentioned. General anesthesia anticipated to last 2 to 3 h.</td>
<td>Dexmedetomidine was effective in preventing POS.</td>
<td>NM</td>
</tr>
<tr>
<td>Mohammadi and Seyedi&lt;sup&gt;25&lt;/sup&gt;</td>
<td>1. Clonidine 0.20 mg orally 2. Placebo (0.9% saline solution)</td>
<td>80 patients, ASA I–II, older than 18 years</td>
<td>Elective abdominal surgery. General anesthesia.</td>
<td>Clonidine was effective in preventing POS.</td>
<td>85%</td>
</tr>
<tr>
<td>Petskul et al.&lt;sup&gt;26&lt;/sup&gt;</td>
<td>1. Ketamine 0.25 mg/kg iv 2. Placebo iv (0.9% saline solution)</td>
<td>183 patients, ASA I–II, 18–65 years</td>
<td>Orthopedic surgery. General anesthesia.</td>
<td>Ketamine failed to prevent POS.</td>
<td>80%</td>
</tr>
<tr>
<td>Norouzi et al.&lt;sup&gt;27&lt;/sup&gt;</td>
<td>1. Ketamine 0.125 mg/Kg iv 2. Ketamine 0.250 mg/Kg iv 3. Ketamine 0.500 mg/Kg iv 4. Placebo iv (0.9% saline solution)</td>
<td>120 patients, ASA I–II, 18–65 years</td>
<td>Elective orthopedic surgery. General anesthesia</td>
<td>Higher doses of Ketamine (0.25 mg/kg, 0.5mg/kg) were effective in preventing POS</td>
<td>NM</td>
</tr>
<tr>
<td>Dal et al.&lt;sup&gt;28&lt;/sup&gt;</td>
<td>1. Pethidine 20.0 mg iv 2. Ketamine 0.5 mg kg/kg iv 3. Placebo iv (0.9% saline solution)</td>
<td>90 patients, ASA I–II, 18-65 years</td>
<td>General anesthesia for surgery lasting 60–180 min.</td>
<td>Both drugs were equally effective in preventing POS.</td>
<td>NM</td>
</tr>
<tr>
<td>Zavareh et al.&lt;sup&gt;29&lt;/sup&gt;</td>
<td>1. Pethidine 0.5 mg/kg iv 2. Ketamine 0.5 mg/kg iv 3. Dexamethasone 0.6 mg/kg iv</td>
<td>135 patients, ASA I–II, 18-70 years</td>
<td>Elective surgery. General anesthesia</td>
<td>Pethidine was more effective than the other two drugs in preventing POS.</td>
<td>NM</td>
</tr>
</tbody>
</table>
Table 1. Randomized controlled trials investigating drugs to prevent postoperative shivering in patients who received general anesthesia (continued)

<table>
<thead>
<tr>
<th>Title</th>
<th>Intervention</th>
<th>Study population</th>
<th>Type of surgery/anesthesia</th>
<th>Conclusion</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Köse et al.</td>
<td>1. Meperidine 20.00 mg iv</td>
<td>150 patients, ASA I–II, 18–65 years</td>
<td>General anesthesia for an anticipated duration of 60–180 min</td>
<td>Meperidine 20 mg and ketamine 0.5 mg/kg were effective in preventing POS.</td>
<td>NM</td>
</tr>
<tr>
<td></td>
<td>2. Ketamine 0.10 mg/kg iv</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Ketamine 0.25 iv</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Ketamine 0.50 mg/kg iv</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Placebo iv (0.9% saline solution)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All drugs were given 20 min before completion of surgery.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dar et al.</td>
<td>1. Pethidine 20.0 mg iv</td>
<td>90 patients, ASA I–II, 18–70 years</td>
<td>General anesthesia for an anticipated duration of 120–180 min</td>
<td>Investigated drugs were equally effective in preventing POS.</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td>2. Ketamine 0.5 mg/kg iv</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Placebo iv (0.9% saline solution)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All drugs were given 20 min before the end of surgery.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ogawa et al.</td>
<td>1. Remifentanil</td>
<td>29 patients, ASA I–II, 20–80 years</td>
<td>Laparotomy or laparoscopic gastrointestinal and gynecological surgery lasted more than 2 h. General anesthesia</td>
<td>Remifentanil + Ketamine were effective in preventing POS.</td>
<td>NM</td>
</tr>
<tr>
<td></td>
<td>2. Remifentanil + ketamine 0.5 mg/kg iv</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infusions were started immediately after anesthesia induction, the flow rate was set at 5.0 mcg/kg/min by continuous iv infusion, and they were discontinued approximately 15 min before completion of surgery.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yousuf et al.</td>
<td>1. Propofol groups</td>
<td>124 patients, ASA I–II, 18–60 years</td>
<td>Orthopedic, gynecological, and general surgical procedures with duration of 60–240 min. General anesthesia</td>
<td>Tramadol in a dose of 1 mg/kg with propofol as an induction agent was more effective in preventing POS.</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>a. Tramadol 1 mg/kg iv</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b. Placebo iv (0.9% saline solution)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Thiopentone groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. Tramadol 1 mg/kg iv</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b. Placebo iv (0.9% saline solution)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All drugs were given 15 min before wound closure.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 1. Randomized controlled trials investigating drugs to prevent postoperative shivering in patients who received general anesthesia (continued)

<table>
<thead>
<tr>
<th>Title</th>
<th>Intervention</th>
<th>Study population</th>
<th>Type of surgery/anesthesia</th>
<th>Conclusion</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mohta et al.</td>
<td>1. Tramadol 1.0 mg/kg iv&lt;br&gt;2. Tramadol 2.0 mg/kg iv&lt;br&gt;3. Tramadol 3.0 mg/kg iv&lt;br&gt;4. Pethidine 0.5 mg/kg iv&lt;br&gt;5. Placebo iv (0.9% saline solution)&lt;br&gt;All drugs were given at the time of wound closure.</td>
<td>165 patients, ASA I–II, adults</td>
<td>Elective abdominal surgery performed under general anesthesia with expected duration &gt; 1 h and expected VAS score ≥ 5 cm.</td>
<td>All three doses of tramadol were effective and comparable to meperidine in preventing POS.</td>
<td>80%</td>
</tr>
<tr>
<td>Heid et al.</td>
<td>1. Tramadol 2.0 mg/kg iv&lt;br&gt;2. Placebo iv (0.9% saline solution)&lt;br&gt;All drugs were given 45–30 min before skin closure.</td>
<td>60 patients, ASA I–III, 18–75 years</td>
<td>Lumbar disc surgery under remifentanil-based general anesthesia.</td>
<td>Tramadol 2 mg/kg was more effective in preventing POS.</td>
<td>80%</td>
</tr>
<tr>
<td>Angral et al.</td>
<td>1. Laparoscopic&lt;br&gt; a. Tramadol 1.0 mg/kg iv&lt;br&gt; b. Placebo iv (0.9% saline solution)&lt;br&gt;2. Open&lt;br&gt; a. Tramadol 1.0 mg/kg iv&lt;br&gt; b. Placebo iv (0.9% saline solution)&lt;br&gt;All drugs were given at the time of wound closure.</td>
<td>80 patients, ASA I–II</td>
<td>Laparoscopic or open cholecystectomy General anesthesia.</td>
<td>Tramadol 1.0 mg/kg was effective in preventing POS following both open and laparoscopic surgery.</td>
<td>80%</td>
</tr>
<tr>
<td>Sajedi et al.</td>
<td>1. Tramadol 1.0 mg/kg iv&lt;br&gt;2. Granisetron 40.0 mcg/kg iv&lt;br&gt;3. Meperidine 0.4 mg/kg iv&lt;br&gt;4. Placebo iv (0.9% saline solution)&lt;br&gt;All drugs were given at the end of surgery.</td>
<td>132 patients, ASA I–II, 18–65 years</td>
<td>Elective orthopedic surgery. General anesthesia.</td>
<td>All drugs were equally effective in preventing POS.</td>
<td>NM</td>
</tr>
<tr>
<td>Abdollahi et al.</td>
<td>1. Meperidine 0.4 mg/kg iv&lt;br&gt;2. Ondansetron 8.0 mg iv&lt;br&gt;3. Placebo iv (0.9% saline solution)&lt;br&gt;All drugs were given 15 min before the end of surgery.</td>
<td>90 patients, ASA I–III</td>
<td>OPCABG under general anesthesia.</td>
<td>Ondansetron 8.0 mg was more effective than meperidine in preventing POS.</td>
<td>NM</td>
</tr>
</tbody>
</table>
### Table 1. Randomized controlled trials investigating drugs to prevent postoperative shivering in patients who received general anesthesia (continued)

<table>
<thead>
<tr>
<th>Title</th>
<th>Intervention</th>
<th>Study population</th>
<th>Type of surgery/anesthesia</th>
<th>Conclusion</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhukal et al. [39]</td>
<td>1. Meperidine 0.3 mg/kg iv 2. Meperidine 0.5 mg/kg iv 3. Placebo iv (0.9% saline solution) All drugs were given just before induction of general anesthesia.</td>
<td>60 patients, ASA I–II, 25–35 years, female</td>
<td>Laparoscopic gynecological procedures. General anesthesia</td>
<td>Pre-induction meperidine was not effective in preventing POS.</td>
<td>85%</td>
</tr>
<tr>
<td>Iqbal et al. [40]</td>
<td>1. Meperidine 25.0 mg iv 2. Granisetron 40.0 mcg/kg iv 3. Placebo iv (0.9% saline solution) All drugs were given before induction of anesthesia.</td>
<td>90 patients, ASA I–II, 20–60 years</td>
<td>Laparoscopic surgery. General anesthesia</td>
<td>Both drugs were equally effective in preventing POS.</td>
<td>80%</td>
</tr>
<tr>
<td>Parsa et al. [41]</td>
<td>1. Buprenorphine 3.0 mcg/kg iv 2. Meperidine 0.5 mg/kg iv All drugs were given 30 min before the end of surgery.</td>
<td>60 patients, ASA I–II, 18–40 years</td>
<td>Elective cesarean section. General anesthesia</td>
<td>Meperidine 0.5 mg/kg was more effective in preventing POS.</td>
<td>NM</td>
</tr>
<tr>
<td>Entezariasl and Isazadehfar [42]</td>
<td>1. Dexamethasone 0.1 mg/kg iv 2. Meperidine 25.0 mg iv 3. Placebo iv (0.9% saline solution) All drugs were given after induction of anesthesia.</td>
<td>120 patients, ASA I–II, adults</td>
<td>Orthopedic, and ENT surgeries (mean duration 60 min). General anesthesia</td>
<td>Although both drugs were effective, dexamethasone was superior in preventing POS.</td>
<td>80%</td>
</tr>
<tr>
<td>Bilotta et al. [43]</td>
<td>1. Nefopam 15.0 mg/kg 2. Clonidine 3.0 mcg/kg 3. Placebo iv (0.9% saline solution) All drugs were given 15 min before the procedure.</td>
<td>101 patients, ASA I–III, adults</td>
<td>Elective or emergency interventional neuroradiology with conscious sedation</td>
<td>Both interventions significantly lowered the rate and severity of shivering. However, nefopam was more effective than clonidine.</td>
<td>NM</td>
</tr>
</tbody>
</table>

Table 2. Randomized controlled trials investigating drugs to prevent postoperative shivering in patients who received regional anesthesia

<table>
<thead>
<tr>
<th>Title</th>
<th>Intervention</th>
<th>Study population</th>
<th>Type of surgery/anesthesia</th>
<th>Conclusion</th>
<th>Power</th>
</tr>
</thead>
</table>
| Bozgeyik et al.  | 1. Tramadol 100.0 mg iv  
2. Dexmedetomidine 0.5 mcg/kg iv  
All drugs were given after spinal block. | 90 patients, ASA I–II, 18–60 years | Elective arthroscopic surgery under spinal anesthesia | Both drugs were equally effective in preventing POS. | NM    |
| Usta et al.      | 1. Dexmedetomidine 1 mcg/kg iv over a 10-min period followed by an infusion of 0.4 mg/kg/h  
2. Placebo iv (0.9% saline solution)  
Administration began after intrathecal injection and infusions were stopped at the completion of skin closure. | 60 patients, ASA I–II, 18–50 years | Elective minor surgical operations under spinal anesthesia | Dexmedetomidine was more effective than placebo in preventing POS. | 80%   |
| Kose et al.      | 1. Ketamine 0.25 mg/kg iv  
2. Ketamine 0.50 mg/kg iv  
3. Placebo iv (0.9% saline solution)  
All drugs were given after intrathecal injection. | 90 parturient, ASA I–II, 18–45 years | Cesarean delivery under spinal anesthesia | Ketamine at both doses was effective in preventing POS. | 80%   |
| Sagir et al.     | 1. Ketamine 0.50 mg/kg iv  
2. Granisetron 3.00 mg iv  
3. Ketamine 0.25 mg/kg + Granisetron 1.50 mg iv  
4. Placebo iv (0.9% saline solution)  
All drugs were given after intrathecal injection. | 160 patients, ASA I–II, 18–65 years | Urological surgery under spinal anesthesia | Ketamine alone at the dose of 0.50 mg/kg was the most effective regimen in preventing POS. | 80%   |
| Lakhe et al.     | 1. Ondansetron 4.00 mg iv  
2. Ketamine 0.25 mg/kg iv  
3. Tramadol 0.50 mg/kg iv  
4. Placebo iv (0.9% saline solution)  
All drugs were given after intrathecal injection. | 120 patients, ASA I–II, 18–65 years | Elective general, gynecological and orthopedic surgery under spinal anesthesia | All drugs were equally effective in preventing POS. | NM    |
| Solhpour et al.  | 1. Meperidine 0.40 mg/kg iv  
2. Ketamine 0.25 mg/kg plus midazolam 37.5 mcg/kg iv  
3. Meperidine 0.20 mg/kg plus dexamethasone 0.10 mg/kg iv  
4. Placebo iv (0.9% saline solution)  
All drugs were given immediately after intrathecal injection. | 200 patients ASA I–II, 20–60 years | Orthopedic and urologic surgery under spinal anesthesia | Meperidine 0.20 mg/kg plus dexamethasone 0.10 mg/kg was the most effective regimen in preventing POS. | NM    |
Table 2. Randomized controlled trials investigating drugs to prevent postoperative shivering in patients who received regional anesthesia (continued)

<table>
<thead>
<tr>
<th>Title</th>
<th>Intervention</th>
<th>Study population</th>
<th>Type of surgery/anesthesia</th>
<th>Conclusion</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savafi et al.(^{50})</td>
<td>1. Ondansetron 8.00 mg \text{ iv}</td>
<td>90 patients, ASA I–II, 18–65 years</td>
<td>Lower extremity orthopedic surgery under spinal anesthesia</td>
<td>Investigated drugs were equally effective in preventing POS.</td>
<td>NM</td>
</tr>
<tr>
<td></td>
<td>2. Ketamine 0.25 mg/kg plus midazolam 37.50 \text{ mcg/kg iv}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Placebo iv (0.9% saline solution)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All drugs were given immediately after spinal block.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shakya et al.(^{51})</td>
<td>1. Ketamine 0.25 mg/kg \text{ iv}</td>
<td>120 patients, ASA I–II</td>
<td>Lower abdominal surgery under spinal anesthesia</td>
<td>Ketamine was more effective than ondansetron in preventing POS.</td>
<td>NM</td>
</tr>
<tr>
<td></td>
<td>2. Ondansetron 4.00 mg \text{ iv}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Placebo iv (0.9% saline solution)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All drugs were given just after the intrathecal injection.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Honarmand and Safavi(^{52})</td>
<td>1. Ketamine 0.50 mg/kg \text{ iv}</td>
<td>120 patients, ASA I–II, 18–60 years</td>
<td>Orthopedic surgery under spinal anesthesia</td>
<td>The combination of ketamine plus midazolam was more effective in preventing POS than monotherapy with each drug alone.</td>
<td>NM</td>
</tr>
<tr>
<td></td>
<td>2. Midazolam 75.00 mcg/kg iv</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Ketamine 0.25 mg/kg + midazolam 37.50 mcg/kg iv</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Placebo iv (0.9% saline solution)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All drugs were given just after intrathecal injection.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xue et al.(^{53})</td>
<td>1. Epidural ketamine 0.5 mg/kg</td>
<td>60 patients, ASA I–II, 22–41 years</td>
<td>Elective cesarean section under CSE</td>
<td>Epidural ketamine was more effective than placebo in preventing POS.</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>2. Epidural placebo (0.9% saline solution)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All drugs were given right after epidural catheter placement.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misiran and Aziz(^{54})</td>
<td>1. Midazolam 0.02 mg/kg plus ketamine 0.25 mg/kg \text{ iv}</td>
<td>90 patients, ASA I–II, 18–60 years</td>
<td>Emergency lower limb surgery, spinal anesthesia</td>
<td>Both regimens of midazolam combined with ketamine were equally effective in preventing POS.</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>2. Midazolam 0.04 mg/kg plus ketamine 0.25 mg/kg \text{ iv}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Placebo iv (0.9% saline solution)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All drugs were given after administration of spinal anesthesia.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Randomized controlled trials investigating drugs to prevent postoperative shivering in patients who received regional anesthesia (continued)

<table>
<thead>
<tr>
<th>Title</th>
<th>Intervention</th>
<th>Study population</th>
<th>Type of surgery/anesthesia</th>
<th>Conclusion</th>
<th>Power</th>
</tr>
</thead>
</table>
| Hong et al.\textsuperscript{76} | 1. Electroacupuncture  
2. Nefopam 0.15 mg/kg iv  
3. Placebo iv (0.9% saline solution)  
All interventions were given 30 min before anesthesia. | 90 patients, ASA I–II, 20–65 years | Elective urological surgery under spinal anesthesia | Both interventions were equally effective in preventing POS. | NM    |
| Bilotta et al.\textsuperscript{76} | 1. Nefopan 0.15 mg/kg iv  
2. Tramadol 0.50 mg/kg  
3. Placebo iv (0.9% saline solution)  
All drugs were given immediately before neuraxial anesthesia. | 90 patients, ASA I–II, 45–48 years (age mean) | Lower limb orthopedic surgery under either epidural or spinal anesthesia | Both interventions were effective but nefopam was even more effective than tramadol in preventing POS. | 90%   |

iv: intravenously; ASA: American Society of Anesthesiologists; POS: postoperative shivering; NM: not mentioned; CSE: combined spinal epidural.
the use of dexmedetomidine in the setting of regional anesthesia. The low dose of dexmedetomidine (0.5 mcg/kg), which did not seem to offer significant relief against POS after general anesthesia, was found to be similarly effective in preventing POS as 100 mg tramadol, in patients under spinal anesthesia, although it was associated with a higher level of sedation. A possible explanation for this discrepancy may be the fact that under general anesthesia, there is a greater suppression of the sympathetic nervous system compared to spinal blockade reaching the T8–10 dermatome. Also, continuous infusion of dexmedetomidine was found to be effective in preventing POS resulting from spinal anesthesia. In this case, patients are also sedated, but in cases of regional anesthesia, sedation is many times desirable for patients’ comfort.

**N-Methyl-D-Aspartate Receptor Antagonists**

Research has revealed that N-methyl-D-aspartate (NMDA) receptor antagonists interfere with thermoregulation at various locations within the central nervous system.

**General Anesthesia—Table 1**

Ketamine, a non-competitive NMDA receptor antagonist, administered 20 min before the completion of surgery has been investigated at different dosages in the prevention of POS after general anesthesia. Ketamine (0.100 mg/kg or 0.125 mg/kg) does not appear to offer any advantage in the prevention of POS. Norouzi et al. demonstrated that high doses of ketamine (0.25 mg/kg or 0.50 mg/kg) had similar efficacy in preventing shivering, but the higher dose of ketamine was correlated with an increase in hallucinations and delay in extubation. Petskul et al. disagree with this finding, as the dose of 0.25 mg/kg ketamine used in their study failed to prevent POS. However, in the aforementioned study, the reported overall incidence of shivering was possibly too low to detect a statistically significant difference.

The efficacy of late administration of ketamine in patients under general anesthesia has also been compared with meperidine, with conflicting results. Ketamine at a dose of 0.5 mg/kg performed better than placebo, but was not as effective as meperidine at doses of 0.4 mg/kg or 0.5 mg/kg. On the contrary, three studies concluded that 0.5 mg/kg ketamine is as effective as 30 mg meperidine in preventing POS, without significant side effects. This inconsistency might be attributed to the lower dose of meperidine employed in the previous studies.

Ogawa conducted a study to investigate whether shivering associated with remifentanil-based anesthesia could be prevented by the concomitant use of low-dose ketamine infusion, reaching favorable results. However, the low number of patients recruited reduces the credibility of the conclusion.

**Regional Anesthesia—Table 2**

Two studies on adults undergoing elective surgery demonstrated that 0.25 mg/kg ketamine was more effective than placebo in the prevention of POS after spinal anesthesia. Kose et al. also studied the effects of ketamine on parturients undergoing cesarean section and showed that the prophylactic IV administration of 0.25 mg/kg ketamine was as effective as 0.5 mg/kg ketamine in the prevention of shivering. The drug was administered immediately after intrathecal injection and did not exhibit serious maternal or neonatal adverse effects. Xue et al. revealed that prophylactic epidural administration of 0.5 mg/kg ketamine reduced the incidence and severity of shivering in patients undergoing cesarean section under combined spinal-epidural anesthesia.

The combination of ketamine with midazolam has also been investigated using the rationale that vasoconstriction induced by ketamine is opposed by the effect of midazolam, which impedes tonic thermoregulatory vasoconstriction. The study by Savafi et al. yielded positive results regarding the combination of 0.25 mg/kg ketamine plus 37.5 mcg/kg midazolam, for the prevention of POS after spinal anesthesia. Another study confirmed this finding and even found the aforementioned combination of ketamine plus midazolam to be more effective than monotherapy using either 0.5 mg/kg ketamine or 75.0 mcg/kg midazolam. The same combination was also tested in another study, wherein although it was effective in the prevention of POS, it was found to be inferior to the combination of 0.2 mg/kg meperidine plus 0.1 mg/kg dexmethasone in doing so.

Misiran and Aziz compared the combination of 0.25 mg/kg ketamine with two different doses of midazolam (0.02 mg/kg vs. 0.04 mg/kg), and concluded that the two regimens were equally effective. One peculiarity of this study was that the test group

Drugs Used to Prevent Postoperative Shivering

Asian Journal of Anesthesiology 57(3) 2019 77
consisted of emergency cases, some of which were trauma cases that were resuscitated in the emergency department prior to surgery. Thus, the pathophysiology of these patients is distinctive, due to which the results of this study cannot be compared with the results of other studies.

A different regimen consisting of ketamine and granisetron (a serotonin 5-HT3 receptor antagonist) has been studied by Sagir et al., who observed that 0.5 mg/kg ketamine was more effective than the combination of a lower dose of ketamine (0.25 mg/kg) plus 1.5 mg granisetron, in the prevention of shivering associated with regional anesthesia.47

**Opioids and Tramadol**

It is hypothesized that the anti-shivering effect of opioids is associated with their μ-receptor agonist activity.9,60 It seems more probable that the anti-shivering action of meperidine involves its μ- and κ-receptor agonist activity, in addition to its α2-adrenoreceptor agonist properties and anticholinergic properties.14 The fact that the anti-shivering effect of meperidine is inhibited by high-dose naloxone but not by low-dose naloxone indicates that both μ- and κ-receptors play a major role.61

**General Anesthesia—Table 1**

Most published studies on this topic have investigated the prophylactic effect of meperidine administered at the end of surgery. As mentioned before, meperidine at a dose of 20 mg, administered 20 min before the completion of surgery, is as effective as 0.5 mg/kg ketamine in preventing POS,9,30,31 while higher doses of meperidine (0.4 mg/kg and 0.5 mg/kg) appeared to perform better than 0.5 mg/kg ketamine.19,29 The highest dose of meperidine (0.5 mg/kg) was observed to be as effective as dexamethasone 1 mg/kg.23 Abdollahi et al. compared 0.4 mg/kg meperidine with 8 mg ondansetron in patients undergoing off-pump coronary artery bypass graft who, after the end of surgery, were transferred to intensive care unit (ICU) and remained intubated.38 The shivering scores recorded at the time of ICU admission were in favor of 0.4 mg/kg meperidine and 8 mg ondansetron, compared to placebo.

Three other studies had tested the prophylactic administration of meperidine given before or right after the induction of anesthesia.19,40,42 Entezarialis and Isazadehfar compared the efficacy of 25 mg meperidine with 0.1 mg/kg dexamethasone, both given immediately after the induction of anesthesia. The researchers observed that the incidence of POS was 10% in the dexamethasone group, 37.5% in the meperidine group, and 47.5% in the control group.42 The findings of Iqbal et al. also support the prophylactic administration of meperidine before the induction of anesthesia.60 In contrast, Bhuwal et al. have disputed the pre-induction efficacy of meperidine.39 This inconsistency may be attributed to the fact that they studied only female patients, and intravenous fluids administered were heated to 37°C.39

The study by Parsa et al. is unique in that it compared the efficacy of buprenorphine to meperidine in a group of parturients undergoing cesarean section under general anesthesia.41 The researchers valued buprenorphine for being a partial μ-receptor agonist and a betaine derivative that is attached to κ- and σ-receptors, and observed that although both drugs decreased postoperative pain equally, meperidine performed better as an anti-shivering agent.41

Tramadol acts centrally on μ-opioid receptors, inhibits the reuptake of 5-hydroxytryptamine and norepinephrine, and facilitates the release of 5-hydroxytryptamine. In 2017, a meta-analysis by Li et al. showed that tramadol was an effective cure against POS by significantly reducing the severity of shivering and the need for a rescue agent.62 No adverse events were associated with its use, even when doses as high as 3 mg/kg were employed. In any case, authors of this meta-analysis recommended the dose of 1 mg/kg, in order to avoid the possibility of adverse effects.

Mohta et al. compared different doses of tramadol (1, 2, and 3 mg/kg) for their anti-shivering and analgesic effects.34 Tramadol at a dose of 2 mg/kg, administered at the time of wound closure, appeared to have the best anti-shivering and analgesic effect, without any undesirable adverse effects. It is worth noting that all patients received prophylaxis for postoperative nausea and vomiting (PONV) using 10 mg metoclopramide. The three groups of tramadol were found to be as efficient as 0.5 mg/kg meperidine in terms of POS prevention. Findings of few studies confirm that 1 mg/kg tramadol administered at the end of surgery prevents POS after general anesthesia32 and is equally effective to 0.4 mg/kg meperidine.37
Furthermore, 1 mg/kg tramadol is more efficient than α2-agonists.\textsuperscript{35} Notably, the higher dose of 2 mg/kg was even found to be effective in remifentanil-isoflurane-based general anesthesia, which is associated with a particularly high incidence of POS.\textsuperscript{35}

Angral et al. studied the usage of 1 mg/kg tramadol, administered at the time of wound closure, in open and laparoscopic cholecystectomy.\textsuperscript{36} The incidence of POS was similarly low in the treatment groups, but significantly higher in the control groups.\textsuperscript{36}

**Regional Anesthesia—Table 2**

Even though meperidine is highly valued as an anti-shivering agent, our search revealed only one study that had employed meperidine as anti-shivering prophylaxis for regional anesthesia. According to this study, a combination of 0.2 mg/kg meperidine plus 0.1 mg/kg dexamethasone was more effective than 0.4 mg/kg meperidine alone or combination of 0.25 mg/kg ketamine plus 37.5 mcg/kg midazolam, in the prevention of shivering resulting from spinal anesthesia.\textsuperscript{49}

Tramadol at doses of 0.5 mg/kg has been found to be as effective in preventing POS as 0.5 mg/kg meperidine, with negligible side effects.\textsuperscript{48} Bozgeyik et al. claim that 100 mg tramadol acts as effectively as 0.5 mcg/kg dexmedetomidine.\textsuperscript{44}

**Serotonin 5-HT3 Receptor Antagonists**

The mechanism of action of serotonin 5-HT3 receptor antagonists could be related to the inhibition of serotonin reuptake on the preoptic anterior hypothalamic region. The 5-HT3 receptors may also influence both heat production and heat loss pathways.

**General Anesthesia—Table 1**

Iqbal et al. have shown that the prophylactic use of 40 mcg/kg granisetron is as effective as 25 mg meperidine in preventing POS.\textsuperscript{39} It is worth mentioning that this dose was found to be even equally effective to a higher dose of meperidine (0.4 mg/kg) or to tramadol (1 mg/kg) without prolonging the time of emergence from anesthesia or affecting the respiratory or cardiovascular system.\textsuperscript{17} Likewise, Abdollahi et al. have compared the efficacy of ondansetron (8 mg) to meperidine (0.4 mg/kg) on a population more prone to cardiovascular side effects, and observed no significant difference in the incidence of side effects such as bradycardia, convolution, rash, and myoclonus between groups.\textsuperscript{38}

**Regional Anesthesia—Table 2**

Serotonin 5-HT3 receptor antagonists have been studied for the prophylaxis of POS-related to regional anesthesia and compared to various regimens. Sagir et al. commented that 3 mg granisetron alone or a combination of 0.25 mg/kg ketamine plus 1.5 mg granisetron were inferior to 0.5 mg/kg ketamine in preventing shivering related to regional anesthesia.\textsuperscript{47} Savafi et al. reported that although 8 mg ondansetron was effective in controlling POS, a combination of 0.25 mg/kg ketamine plus 37.5 mcg/kg midazolam performed better.\textsuperscript{50} Ondansetron at a lower dose (4 mg) still appears to be effective but is inferior to 0.25 mg/kg ketamine.\textsuperscript{51} On the contrary, Lakh et al. showed that 4 mg ondansetron is as effective as 0.25 mg/kg ketamine or 0.5 mg/kg tramadol.\textsuperscript{48}

**Dexamethasone**

The available data on dexamethasone efficacy are rare. It has been proposed that dexamethasone decreases the gradient between core and skin temperature and inhibits the release of vasoconstrictors and pyrogenic cytokines released during surgery, through its action on the immune system.\textsuperscript{63}

**General Anesthesia—Table 1**

As mentioned earlier, Entezariasl and Isazadehfar showed that dexamethasone surpassed meperidine’s efficacy in preventing POS, when administered after induction of anesthesia.\textsuperscript{42}

**Regional Anesthesia—Table 2**

Solhpour et al. observed that the combination of meperidine and dexamethasone is superior to meperidine alone, in preventing POS in patients subjected to spinal anesthesia.\textsuperscript{49}

**Nefopam**

Nefopam is a non-opioid, non-steroidal, centrally acting analgesic drug that increases the activity of serotonin, norepinephrine, and dopamine. Furthermore, it acts on the sodium and calcium channels, inhibiting the release of glutamate\textsuperscript{64} and it seems to have a promising role in the prevention of POS.

**Conscious Sedation—Table 1**
We opted for including in our review a randomized control trial that compared the efficacy of nefopam and clonidine on patients undergoing interventional neuroradiological procedures under conscious sedation with midazolam infusion. In such cases, prevention of shivering is essential, as any movement may cause technical difficulties or even complications, such as vessel perforation. Authors concluded that although both drugs are effective in preventing POS, nefopam is more potent than clonidine. In addition, patients receiving nefopam were more hemodynamically stable than patients in clonidine and placebo groups.

Regional Anesthesia—Table 2

According to Hong et al., 0.15 mg/kg nefopam was efficient in preventing POS after spinal anesthesia, but nausea and injection pain were observed. Nefopam even surpassed tramadol’s efficacy in lowering the rate and severity of intraoperative shivering in patients undergoing neuraxial anesthesia for orthopedic surgery, according to Bilotta et al. However, the dose of tramadol (0.5 mg/kg) studied was possible too low to evaluate its full effect in preventing shivering.

Conclusion

Although the published studies on this topic are greatly heterogeneous in factors such as temperature of the OR, type and duration of surgery, anesthetic drugs used, intraoperative fluid replacement, use of active warming measures, as well as the scales used to evaluate shivering, there is evidence that some drugs can effectively prevent POS. However, dose-response studies are required to determine the most appropriate dosing regimen of each drug for the optimal prevention of POS. Studies of cost-effectiveness are also essential.

Regarding α2-agonists, intravenous dexmedetomidine was found to be promising. It appears to have a dose-dependent preventive effect on patients subjected to general anesthesia. Notably, meperidine and tramadol surpass its efficacy in most studies, and the expected side effects associated with α2-agonists, including bradycardia, sedation in the immediate postoperative period, and prolonged extubation time, are observed. Although limited data are available regarding regional anesthesia, it appears that the continuous infusion of dexmedetomidine, or even the low dose of 0.5 mcg/kg, is effective in preventing POS.

Regarding NMDA antagonists, 0.25 mg/kg ketamine has questionable efficacy in preventing POS after general anesthesia, while lower doses do not seem to confer any advantage at all. Ketamine at a dose of 0.5 mg/kg performs better than placebo and possibly, is even equally effective to meperidine. Despite the number of studies concerning regional anesthesia, the diverse regimens used in each study makes it infeasible to draw safe conclusions. In general, the rationale for the use of ketamine in the setting of POS is that it could serve as an alternative drug for patients with bradycardia, hypotension, respiratory depression, nausea, vomiting, or allergic reactions to pethidine. Still, adverse effects (hallucination, nystagmus, sedation, etc.) should always be borne in mind.

As far as opioids are concerned, 0.4–0.5 mg/kg meperidine is effective in the prevention of POS after general anesthesia, when administered at the end of surgery, and possibly, even when administered at the beginning. It appears to be effective in patients with different ASA classifications and undergoing different procedures. There are not enough data available to comment on the efficacy of meperidine after regional anesthesia.

As for tramadol, the dose of 1–2 mg/kg appeared to be effective as anti-shivering prophylaxis after general anesthesia, without adverse effects including PONV. However, most of the studies involved patients that had been administered metoclopramide in advance. Tramadol was found to be effective as a preventive measure for shivering under regional anesthesia, but the ideal dose is not established yet.

Additionally, the use of serotonin 5-HT3 receptor antagonists, such as ondansetron or granisetron, seems promising as a preventive measure against POS. The main advantage of this class of drugs is that they prevent PONV and do not prolong the emergence time from anesthesia or significantly affect the respiratory or cardiovascular system.

Finally, as for dexamethasone, data are limited on reaching definite conclusions. On the contrary, nefopam seems to play an important role in the prevention of POS, since it has been found to surpass tramadol and clonidine’s efficacy and to possess a favorable hemodynamic profile.

In conclusion, even though an association between the occurrence of shivering and an increase in cardiac morbidity has not yet been established, POS should be avoided because it raises the oxygen
Drugs Used to Prevent Postoperative Shivering


Conflicts of Interest

None.

References

9. Bernthal EM. Inadvertent hypothermia prevention:


Drugs Used to Prevent Postoperative Shivering


62. Li S, Li P, Lin X. Efficacy of the prophylactic

Asian Journal of Anesthesiology 57(3) 2019 83
