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Research Article

Effect of parecoxib on remifentanil induced postoperative shivering

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Abstract Remifentanil based anesthesia was found to be associated with high incidence of postoperative shivering. This study was designed to evaluate the effect of preoperative administration of IV parecoxib sodium (a selective COX 2 inhibitor) on remifentanil induced shivering during the first 2 h following surgery.

Method: In a randomized, placebo-controlled, double blind study, sixty-seven patients with ASA physical status I, aged 20–60 years underwent elective lumber discectomy, were randomly allocated to receive either parecoxib sodium 40 mg IV (group P, $n = 33$) or saline IV (group S, $n = 34$) 30 min before induction of anesthesia which was induced with remifentanil 0.5 ug/kg/min, propofol, and cisatracurium and was maintained with remifentanil 0.1–0.3 ug/kg/min, sevoflurane, O_2/N_2O and cisatracurium. The incidence and grades of postoperative shivering were evaluated for 2 h.

Results: The incidence of postoperative shivering was 36% in parecoxib group which was significantly less than that of saline group 64% ($p < 0.05$). Number of patients who developed grade 3 shivering, number of patients received meperidine to treat shivering and postoperative morphine requirement were significantly less in group P than that of group S ($p < 0.05$).

Conclusion: Administration of parecoxib sodium 40 mg IV 30 min before induction of general anesthesia significantly reduced the incidence and severity of remifentanil induced shivering compared to placebo in patients underwent elective lumber discectomy under general anesthesia.

1. Introduction

Shivering is a frequent postoperative complication of general anesthesia [1]. Shivering causes patient discomfort, interruption of monitoring, increases O_2 consumption, CO_2 production, and catecholamine secretion that increase cardiac output, heart rate, and blood pressure [2].

Remifentanil, an ultra-short-acting μ opioid receptor agonist, is widely used intraoperatively to provide good intraoperative analgesia and stable intraoperative hemodynamics. However, a number of studies reported an increase in the incidence of postoperative shivering with remifentanil [3–5] and it is more likely to occur with remifentanil than other opioids [6].

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A wide range of drugs have been reported to be effective in suppressing shivering including meperidine; tramadol; ketamine; ondansetron; clonidine and midazolam [7].

Parecoxib is a prodrug of valdecoxib, a selective cyclooxygenase 2 inhibitor (COX 2 inhibitor), has been found to be effective in reduction of the remifentanil induced hyperalgesia [8,9] and some studies suggested a relationship between remifentanil induced hyperalgesia and postoperative shivering with activation of N-methyl-D-aspartate (NMDA) receptors [4,10]. Therefore, we hypothesized that preoperative administration of parecoxib sodium may prevent the development of remifentanil-induced shivering during the first postoperative 2-h. So, in this randomized, placebo-controlled, double-blind study we evaluated the effects of preoperative intravenous parecoxib sodium given 30 min before induction of anesthesia on postoperative shivering after remifentanil-based general anesthesia

2. Method

After approval of the local ethical committee, a written informed consents were obtained from 70 patients with American Society of Anesthesiology (ASA) physical status I aged 20–60 years old, planned for lumbar discectomy under general anesthesia in Dar Alshifa hospital (State of Kuwait) from August 2013 to April 2014

Patients were excluded from the study if there was any contraindication to parecoxib (cardiovascular disease, peripheral arterial disease, cerebrovascular disease, peptic ulcer, Inflammatory bowel disease, bronchial asthma, hepatic or renal disease), those with history of thyroid dysfunction, known allergy to the study drug or other nonsteroidal anti-inflammatory drugs (NSAID), an initial body temperature >38 °C or <36 °C, BMI $>$ 30 kg/m^2 or who required blood transfusion.

All patients were premedicated with omeprazole 40 mg iv, primperane 10 mg iv and midazolam 5 mg oral 1 h before surgery.

When patients arrived to the operation theater, they were randomly assigned to one of two equally divided groups (35 patients each) by using the closed envelop technique. Parecoxib group (group P) received parecoxib 40 mg iv (Dynastate, Pfizer Manufacturing, Puurs, Belgium) and saline group (group S) received the same volume of saline, and the studied drugs were prepared in 2 ml syringe by an anesthesia nurse unaware of the study as per the envelope and were given to the patients in the anesthesia preparation room 30 min before induction of anesthesia.

The operating room temperature was adjusted at 22 °C.

The patients were shifted to the operating room where they were monitored with electrocardiogram (ECG), non-invasive arterial blood pressure, pulse oximetry (Spo_2), and capnography (after intubation).

General anesthesia was induced with remifentanil 0.5 μg/kg/min for 1 min using syringe pump (Alaris®, Cardinal Health, Switzerland) followed by propofol 1–2 mg/kg and cisatracurium 0.15 mg/kg, and then the patients were intubated with armored cuffed endotracheal tube and mechanically ventilated. After induction, patients were put in prone position with proper padding of the pressure points with gel pads. The anesthesia was maintained by sevoflurane 1–1.5 vol%, O_2/N_2O (50/50%), remifentanil 0.1–0.3 μg/kg/min and cisatracurium 0.03 mg/kg guided by peripheral nerve stimulator.

All through the anesthesia time, the patients were actively warmed by lower body forced air warming device (Bair Hugger_warming unit, Arizant Healthcare Inc., USA) and warm iv fluids using level 1 hot fluid warmer (Rockland, MA, USA) to maintain core temperature above 35.5 °C.

At the end of the procedure, the surgical wound was infiltrated with 20 ml of bupivacaine 0.5% by the surgeon taking all layers including the muscle layer with iv infusion of paracetamol 1 g (perfalgan, Bristol-Myers Squibb, Anagni, Italy).

At the end of the operation the patients were returned to supine position, and remifentanil and sevoflurane were stopped with reversal of residual neuromuscular blockade (neostigmine 0.05 mg/kg and atropine 0.02 mg/kg); the patients were extubated and were shifted to postanesthesia care unit (PACU) where they were monitored and observed for 2 h.

In PACU the ambient temperature was adjusted at 25 °C, O_2 face mask and whole body forced air warming device was applied and the patients complained of pain were treated by IV morphine boluses (2 mg) that repeated every 15 min until patients became pain free.

The following parameters were evaluated in all patients by an anesthesia technician unaware of the study drugs:

(1) Core temperature (tympanic membrane temperature using FirstTemp Genius Model 3000, Sherwood Medical Company, St. Louis, UK) before induction of anesthesia, 1 h after induction of anesthesia, after extubation and in PACU every 30 min for 2 h.
(2) Shivering intensity was graded by using a five-point scale that was used in the study of Nakasuji and colleagues (4):

Grade 0: none;
Grade 1: one or more areas of piloerection but without visible muscular activity;
Grade 2: visible muscular activity confined to one muscle group;
Grade 3: same as Grade 2 but in more than one muscle group;
Grade 4: gross muscular activity involving the entire body).

Shivering grades 3 and 4 were considered postoperative shivering and treated with iv meperidine 20 mg.

(3) The incidence of shivering.
(4) Number of patients requiring meperidine.
(5) Time to first postoperative analgesic requirement.
(6) Postoperative morphine consumption in the first 2 h after surgery.
(7) Postoperative side effects such as

- Nausea and vomiting (treated with metoclopramide 10 mg iv).
- Sedation (graded on a five-point scale: 1: fully awake and oriented; 2: drowsy; 3: eyes closed, arousable to command; 4: eyes closed, arousable to physical stimulation; and 5: eyes closed, unrousable to physical stimulation) [11].

3. Statistical method

Based on the incidence of postanaesthetic shivering with remifentanil from the previous study [4] was 60%, The sample size required to achieve 50% reduction was minimum 33 patients in each group with a power of 80% and an α of 0.05.

Data values were presented as means (SD), or number (%). Numerical data were analyzed by using Student's unpaired *t*-test. Nonparametric data were analyzed by using the Mann Whitney *U*-test. A value of $P < 0.05$ was considered significant. All statistical calculations were done using computer programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA).

4. Results

Seventy patients were included in this study; however, two patients in parecoxib group and one patient in saline group were excluded from the study because they received blood transfusion.

The two groups were comparable regarding the age, weight, Sex, and duration of operation (Table 1).

The incidence of shivering was significantly reduced in parecoxib group being 36% compared to saline group being 64% ($p < 0.05$). Grade 3 shivering was significantly low in group P compared to group S ($p < 0.05$). There was no significant difference between groups in grades of shivering 1, 2 and 4. Patients who received meperidine were significantly low in group P compared to group S ($p < 0.05$) (Table 2).

Core temperature was comparable between the two groups at different times of measurement intraoperative and in PACU ($p > 0.05$) (Table 3).

The time to first postoperative analgesic requirement and morphine consumption during the first 2 h after surgery were significantly less in parecoxib group compared to saline group (Table 4).

The incidence of nausea, vomiting, and sedation were comparable in patients of the two groups ($p > 0.05$) (Table 5).

5. Discussion

This study showed that parecoxib treated patients shivered less than the patients in the saline group with lower grades of shivering and less number of patients received meperidine to stop shivering compared to those of the saline group.

Remifentanil based anesthesia is commonly used intraoperatively because of its ultrashort acting effect that can be rapidly titrated to provide hemodynamic stability and rapid recovery, however postoperative shivering is common after remifentanil discontinuation, but the exact underlying mechanism is unclear. Therefore, there are many theories tried to explain postoperative shivering after remifentanil infusion;

The first theory is intraoperative hypothermia which was prevented in this study by active warming of the patients intraoperatively and in PACU with no difference between groups in core temperature, and this is in agreement with the study of Nakasuji et al. who conclude that remifentanil induced shivering is not related to intraoperative hypothermia [4].

The second theory is pain which is prevented in this study by intraoperative infusion of paracetamol and wound infiltration with local anesthetic and iv morphine titration postoperatively, and this is in line with the study of Nakasuji et al. [4] who suggested that shivering is not related to pain because in this study pain was relieved with epidural analgesia and the study of Heid and colleagues who found that intraoperative tramadol decreased the incidence of postoperative shivering without changing postoperative pain under general anesthesia [12].

The third theory, which is the more likely underlying theory, is that remifentanil induced shivering is related to the remifentanil induced hyperalgesia and it is a sign of opioid induced hyperalgesia with suspected activation of the N-methyl-D-aspartate (NMDA) receptors as it was found that NMDA application in the preoptic anterior hypothalamus (central

Table 1 Demographic data and operation time.

Variables	Group S ($n = 34$)	Group P ($n = 33$)
Age	38.7(5.8)	41.3(7.5)
Weight (kg)	83.3(6.7)	85.2(6.2)
Sex (M/F)	25/9	22/11
Operation time (min)	111.8(10.7)	115.5(13.9)

Group S: saline group, group P: parecoxib group.
Data presented as mean (SD) or number.

Table 2 Incidence and severity of shivering and number of patients received meperidine.

Variables	Group S ($n = 34$)	Group P ($n = 33$)
Total number of shivering patients	22(64)	12(36)*
Grades of shivering		
Grade 0	12(35)	21(64)*
Grade 1	3(9)	2(6)
Grade 2	2(5)	2(6)
Grade 3	17(50)	8(24)*
Grade 4	0(0)	0(0)
Number of patients received meperidine	17(50)	8(24)*

Group S: saline group, group P: parecoxib group.
Data presented as number (%).
* Significant difference ($p < 0.05$) compared to group S.

Table 3 Core temperature (tympanic membrane temperature).

Time	Group S ($n = 34$)	Group P ($n = 33$)
Before induction	36.6(0.1)	36.7(0.2)
1 h After induction	36.5(0.2)	36.4(0.1)
After extubation	36.3(0.2)	36.4(0.2)
PACU 0 min	36.2(0.1)	36.3(0.2)
PACU 30 min	36.2(0.1)	36.1(0.1)
PACU 60 min	36.1(0.2)	36.1(0.1)
PACU 90 min	35.9(0.2)	36(0.2)
PACU 120 min	35.9(0.1)	35.8(0.2)

Group S: saline group, group P: parecoxib group, PACU 0: admission to PACU, PACU 30: 30 min in PACU, PACU 60: 60 min in PACU, PACU 90: 90 min in PACU, PACU 120: 120 min in PACU.
Data presented as mean (SD).

Table 4 Time to first postoperative analgesic requirement and morphine consumption during the first 2 h after surgery.

Variables	Group S (n = 34)	Group P (n = 33)
Time to first postoperative analgesic requirement (min)	7.3(0.9)	10.7(1.1)*
Morphine consumption during the first 2 h after surgery (mg)	6.1(1.1)	3.6(0.9)*

Group S: saline group, group P: parecoxib group,
Data presented as mean (SD).
* Significant difference ($p < 0.05$) compared to group S.

Table 5 Incidence of side effects.

Variables	Group S (n = 34)	Group P (n = 33)
Nausea	6(17)	4(12)
Vomiting	1(2.9)	1(3)
Sedation	20(59)	15(45)

Group S: saline group, group P: parecoxib group.
Data presented as number (%).

control of shivering) increases firing of neurons in rats [13]. This theory was supported by the observation of the previous studies of Röhm et al. [5], Zhao and Joo [10], and Song et al. [13], also both shivering and hyperalgesia could be reduced by NMDA antagonists such as low dose ketamine 0.25 mg/kg iv just before skin incision, followed by 5 μg/kg/min iv until skin closure in the study of Masato et al. [14] and magnesium sulfate 50 mg kg(−1) iv followed by 15 mg kg(−1) h(−1) iv in the study of Ryu et al. [15].

Published Ahead-of-To our knowledge, there were no studies reported the effect of parecoxib on remifentanil induced shivering. The results of this study coincided with the result of Xiuze et al. that showed that iv parecoxib 40 mg before the end of surgery decreased the incidence and severity of postoperative shivering after general anesthesia [16]. Also, the study of *Tröster* et al. [17] showed that parecoxib administration before remifentanil infusion potentiates the analgesic effect of remifentanil and reduced remifentanil hyperalgesia which is in line with our result of increased time to first postoperative analgesic requirement and reduced postoperative morphine consumption. The parecoxib exerts these effects through inhibition of cyclo-oxygenase and prevention of prostaglandins production, and it was found that prostaglandins especially prostaglandin E2 stimulate release of glutamate in spinal cord dorsal horns [18] and the prostaglandins depolarize the deep spinal cord dorsal horn neurons and disinhibit the glycinergic neurotransmission in the superficial layers of spinal cord dorsal horn neurons causing sensitization of the spinal nociceptive system with activation of the NMDA receptors [19].

In this study parecoxib was given 30 min before induction of anesthesia instead of given 30 min before end of surgery in the study of Xiuze et al. [16] and we found that parecoxib treated patients showed less postoperative morphine consumption and longer time to first postoperative analgesic requirement compared to control group as it was found that early administration of iv parecoxib 30 min before starting remifentanil infusion was effective in reducing remifentanil induced hyperalgesia, while parallel administration was ineffective [17].

Morphine was used to treat postoperative pain; it was found that morphine does not have effect on postoperative shivering [20] and the results of the present study showed that patients received meperidine to control shivering; received less doses of morphine than other patients and the sedation was reported after injection of morphine and meperidine.

The incidence of nausea and vomiting was found unexpectedly comparable in patients of both groups; in spite of using morphine and meperidine more in saline group, as parecoxib causes nausea and vomiting.

We concluded that intravenous parecoxib sodium 40 mg administrated 30 min before induction of anesthesia effectively reduced the incidence and severity of remifentanil induced shivering compared to placebo in patients undergoing lumbar discectomy under general anesthesia.

Conflict of interest

None declared.

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