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Original Article

The effects of parecoxib sodium and flurbiprofen axetil injection on postoperative shivering: a randomized, double-blinded clinical trial

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Abstract: Objective: Postoperative shivering can cause patients serious adverse events and influence their outcomes after general anesthesia. To date there is no ideal drug which can be used to prevent post operative shivering. The aim of this randomized controlled trial was to examine the efficacy and accompanying side effects of prophylactic flurbiprofen along with parecoxib or placebo for reducing postoperative shivering. Methods: 145 patients with American Society of Anesthesiologists physical status I-II, who were scheduled for colorectal surgery under general anesthesia were selected. Subjects were randomly assigned to receive flurbiprofen 50 mg (Group F), parecoxib sodium 40 mg (Group P) or normal saline (Group S) 40 minutes before the end of surgery. Heart rate and mean blood pressure were recorded. The occurrence of shivering, visual analogue score (VAS), ramsy sedation scale (RSS), postoperative nausea and vomiting were recorded an hour after extubation. Results: The incidence and severity of postoperative shivering were significantly lower in Groups *P* (18.75%) and F (20.41%) than in Group S (50%, $P<0.01$). The visual analogue score was significantly lower in Groups P and F than in Group S at the time of extubation, 30 minutes after extubation and 60 minutes after extubation ($P<0.01$). There was no significant difference between Groups P and F. Compared to Group S, there were no significant difference in the sedation scores and the incidence of postoperative nausea and vomiting in Groups P and F. Conclusions: Intraoperative intravenous administration of flurbiprofen (50 mg) or parecoxib sodium (40 mg) is effective in decreasing the incidence and severity of postoperative shivering in patients undergoing colorectal surgery under general anesthesia, and does not pose significant risk of side effects.

Keywords: Postoperative shivering, parecoxib sodium, flurbiprofen, randomized controlled trial

Introduction

Shivering after the general or local anesthesia is one of the most frequent complications in patient recovery [1], the incidence of which varies between 5 and 65% [2]. Postoperative shivering has the potential to cause serious adverse events and influence patient outcomes. Furthermore, shivering can cause physiological disturbances such as increased oxygen consumption, carbon dioxide production, lactic acidosis production, left ventricular systolic work index, intraocular pressure on the eye and brain, fluctuations in the blood pressure and decreased tissue oxygenation [3, 4]. Hence, the early prevention of shivering is necessary. Prophylactic pharmacologic means are the most common treatment. To date, there is no ideal drug for the prevention of postoperative shivering to date.

Parecoxib sodium and flurbiprofen, a nonsteroidal anti-inflammatory drugs (NSAID) and Cyclooxygenase 2 (COX-2) inhibitor, may be able to control the postoperative pain with few side effects. Because COX-2 and prostaglandin E2 (PGE2) are the main heating mediums of the hypothalamus [5], it is possible that the COX-2-PGE2 pathway plays a critical role in body temperature and the shivering process. As far as we know, there have been no reported studies on the use of flurbiprofen for the prevention of postoperative shivering. Therefore, in this randomized, placebo-controlled, double-blinded study we assessed the effects of preoperative intravenous parecoxib sodium and flurbi-

profenon patients undergoing colorectal surgery under general anesthesia.

Materials and methods

This randomized controlled trial protocol was approved by the Ethics Committee of Affiliated Tumor Hospital of Guangxi Medical University, P. R. China. Written consent was obtained from each study participant. We allocated the patients randomly to either the treatment or control group using a computer. This study is followed and fulfilled the CONSORT criteria [6]. Our ethics committee approved the trial on March 26, 2014.

166 American Society of Anesthesiologists' (ASA) physical status 1 or 2, patients, undergoing colorectal surgery were selected in the prospective, randomized, double-blinded clinical study. All patients were from 21 to 62 years old, had body mass indexes between 19-35, and had been admitted to the affiliated tumor hospital of Guangxi Medical University (a state-run hospital) between April 2014 and April 2015.

Patients with cardiac, pulmonary, hepatic, renal, thyroid, or neuromuscular disease, as well as chronic drug and/or alcohol abusers were excluded. Patients with hypertension, gastrointestinal bleeding, an initial core temperature over 37.5°C or less than 36.5°C, a history of allergies to non-steroidal anti-inflammatory drugs (NSAIDs) or other agents to be used, and inability to cooperate were also excluded from the study. Additionally, patients with blood loss during surgery of over 400 mL, those who needed blood transfusions during surgery, those whose operations exceeded 4 hours, and those whose surgical procedures required changes were excluded.

All patients selected tracheal intubation general anesthesia, received monitoring ECG, and had their temperature, blood pressure, heart rate and pulse oximetry monitored just after they went into the operating room. Operating room temperature was held constantat 23°C. Patients also received lactated Ringer's solution. Anesthesia was induced with intravenous midazolam 0.01 mg kg^{-1}, propofol 2 mg kg^{-1}, fentanyl 3 ug kg^{-1} and vecuronium bromide 0.10 mg kg^{-1}, which were administered to facilitate tracheal intubation. Anesthesia was maintained with propofol 4-6 mg $kg^{-1}h^{-1}$ and remifentanil 0.1-0.2 ug $kg^{-1}min^{-1}$. Fentanyl 1 ug kg^{-1} was intermittently administrated to maintain blood pressure. Repeated doses of vecuronium 0.05 mg kg^{-1} were administrated as required. Tidal volume was setting at 9 ml kg^{-1}, and the respiratory rate was 12 every minutes. Mechanical ventilation was used to keep end tidal carbon dioxide tension between 4.7 and 6.0 kPa. Propofol and remifentanil were used continuously until the operation was finished. After surgery, patients were transferred to the intensive care unit (ICU), and all patients received respiratory support with mechanical ventilation, and monitored in the ICU. After sufficient spontaneous breathing, reflexes and responsiveness returned, tracheal extubation was conducted. After extubation patients were observed for one hour, and then sent back to the ward.

Using a computer-generated random number, patients were divided into three groups: a parecoxib sodium group (P) (n=48), a flurbiprofen group (F) (n=49) and a saline group (S) (n=48). They each received intravenous injection of Parecoxib sodium 40 mg, flurbiprofen 50 mg and the same volume of saline infusion saline 5 mL respectively approximately 40 minutes before surgery ended. The study drugs were diluted to a volume of 5 mL and preparedin coded syringes by a nurse anesthetist who did not manage the patients. Neither the patient nor the anesthetist treating them were aware of the identity of the test drug or the group to which the patients had been allocated.

Nasopharyngeal temperature was observed continuously during the operating period, and the temperatures at the start and end of surgery were recorded. Heart rate and mean arterial pressure were recorded before anesthesia induction (T0), at the start (T1) and end (T2) of surgery, at the time of extubation (T3), 30 minutes after extubation (T4) and 60 minutes (T5) after extubation. Duration of anesthesia, and duration of surgery were also recorded, respectively. In addition extubation time (from termination of propofol and remifentanil to extubation) was recorded. Three trained ICU nurses who were supervised by an attending anesthesiologist and blind to the group status, evaluated and recorded evaluated and recorded the incidence and severity of shivering, the pain intensity score (VAS from 0-100 mm) and the

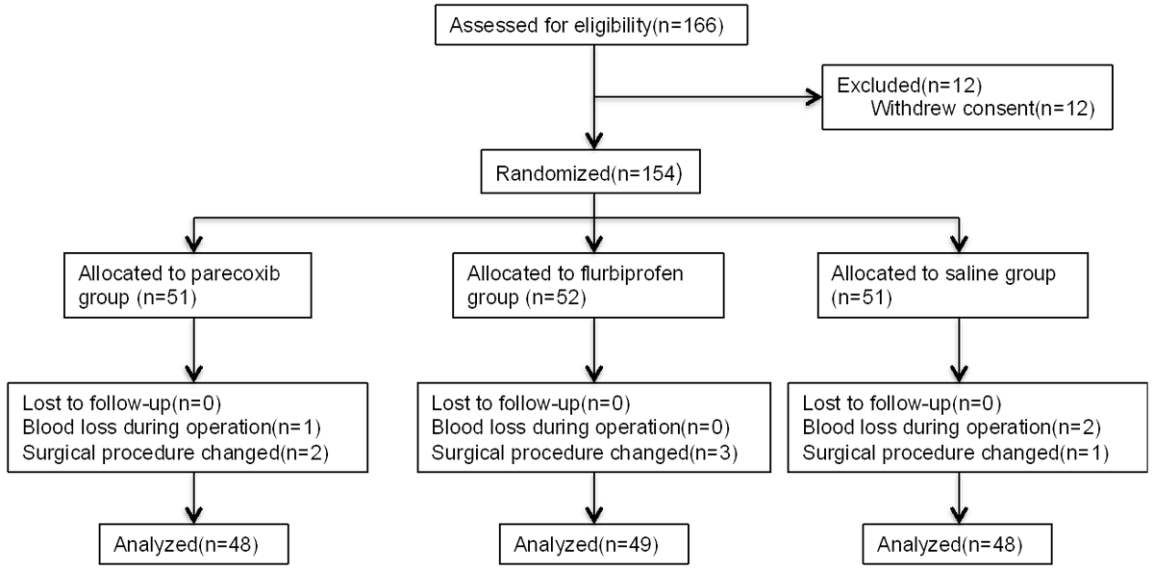

Figure 1. Flow Chart.

ramesay sedation scores at T3, T4 and T5 time points. Severe adverse effects (nausea, vomiting, sedation, and respiratory suppression) were recorded. The shivering was graded as followed: 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. The ramesay sedation scores were recorded as followed: 1, anxious patient; 2, cooperative and tranquil; 3, sleepy but responding to command; 4, brisk response to stimuli; 5, sluggish response to stimuli; 6, response to stimuli. Scores from 2-4 were indicative of calmness and 5-6 were indicative of excessive sedation.

Severe shivering (a score over 2) was treated with a bolus of pethidine (50 mg) IV. Patients with a pain intensity score (VAS) greater than 40 mm received a single dose of fentanyl IV (0.05 mg). Patients who suffered from severe nausea and vomiting were given a dose of metoclopramide IV (10-30 mg according to the condition of patient).

Statistical analysis

The data shown as the mean ± standard deviation in the study were assessed by a two-tailed independent t-test or an analysis of variance for repeated measures as needed. The data shown as absolute number (n) or percentages were analyzed by the Wilcoxon rank sum test, and the significant differences in categorical data were assessed with either the chi-squared test or the Fisher exact test. For all tests, a value of $P<0.05$ was accepted as statistically significant. All statistical analyses were performed using the GraghPad Prism 6 statistical package.

Results

During the recruitment period, 166 patients were eligible to enroll in the trial, however 12 were excluded because they refused to participate and voluntarily withdrew from the study. Another 3 patients were excluded because the blood loss during their operation exceeded 400 mL. Another 6 patients were excluded because their surgical procedures had been changed. In total, 48 patients were selected in the parecoxib sodium group, 49 in the flurbiprofen group and 48 in the saline group (**Figure 1**). There were no significant differences in patients' age, sex, weight, body mass index, ASA physical status, duration of surgery, duration of anesthesia, extubation time, volumes of intravenous fluid, consumption of remifentanil and fentanyl, or change of nasopharyngeal temperature at the beginning and end of surgery among the three groups (**Table 1**). In addition, there were also no significant differences in heart rate and mean arterial pressure (MAP) at each time point among the groups (**Table 2**). In the saline group,

Table 1. Demographic characteristics and perioperative data

	Group P	Group F	Group S	*P*		
	n=48	n=49	n=48	P vs. F	P vs. S	F vs. S
Age (years)	51.5±8.3	49.2±9.5	50.3±8.6	0.2076	0.4884	0.5516
Sex (male/female)	27/21	27/22	26/22	0.9094	0.8374	0.9263
Weight (kg)	55.3±7.8	54.3±8.9	52.6±9.3	0.5579	0.1266	0.3600
Body mass index (kg/m^2)	22.6±4.2	21.6±4.6	22.7±4.5	0.2666	0.9106	0.2369
ASA 1/2	20/28	23/26	21/27	0.6013	0.8365	0.7525
Duration of surgery (min)	188.5±15.5	192.4±17.2	186.7±16.5	0.244	0.583	0.0992
Duration of anesthesia (min)	215.2±14.2	220.1±16.2	218.6±12.4	0.1168	0.2146	0.6103
Extubation time (min)	11.4±3.2	12.3±3.6	11.7±2.9	0.1966	0.6314	0.3689
Volume of i.v. fluid (mL)	1483.5±74.6	1465.3±68.8	1454.8±81.4	0.2146	0.0749	0.494
Propofol (mg)	1195.7±95.8	1225.6±86.7	1215.6±89.9	0.1102	0.2967	0.5784
Remifentanil dose (mg)	1.491±0.076	1.485±0.085	1.511±0.091	0.7150	0.2455	0.1491
Fentanyl dose (mg)	0.305±0.053	0.296±0.043	0.311±0.049	0.3603	0.5611	0.1122
Nasopharyngeal temperature						
Start of surgery (°C)	36.8±0.5	36.9±0.4	36.8±0.4	0.279	>0.9999	0.2213
End of surgery (°C)	36.4±0.7	36.4±0.6	36.3±0.7	>0.9999	0.4857	0.4515

Data are expressed the as mean ± standard deviation or number of patients, ASA = American Society of Anesthesiologists.

Table 2. Hemodynamic parameters

		Group P	Group F	Group S	*P*		
		n=48	n=49	n=48	P vs. F	P vs. S	F vs. S
HR (beats/min)	T0	78.3±10.3	77.9±10.9	78.5±11.3	0.8531	0.928	0.7907
	T1	82.4±11.6	81.3±12.2	82.1±11.9	0.6502	0.9007	0.7445
	T2	80.6±12.5	80.3±11.9	81.8±11.6	0.9039	0.627	0.5312
	T3	81.6±10.2	81.1±11.6	84.2±10.9*	0.8223	0.2306	0.1784
	T4	81.7±11.4	80.8±12.1	83.9±11.9*	0.7071	0.3574	0.2065
	T5	79.7±12.2	78.9±12.1	83.4±10.9*	0.7465	0.1205	0.0575
MAP (mmHg)	T0	73.4±12.3	73.9±11.5	72.5±12.1	0.8366	0.7186	0.5605
	T1	75.5±13.3	75.7±13.1	77.1±12.8	0.9407	0.5496	0.5958
	T2	75.6±12.4	75.4±11.8	76.2±12.5	0.9353	0.8139	0.7465
	T3	75.1±12.8	76.5±11.5	79.9±12.9*	0.5721	0.0704	0.1736
	T4	74.7±14.9	75.8±13.5	78.5±14.4*	0.7039	0.207	0.3431
	T5	74.5±14.3	74.9±13.9	78.1±13.1*	0.8892	0.2016	0.2464

Data are shown as the mean ± standard deviation. HR = heart rate; MAP = mean arterial pressure; T0 = before induction of anesthesia; T1 = commencement of surgery; T2 = end of surgery; T3 = time of extubation; T4 = 30 min after extubation; T5 = 60 min after extubation. *P<0.05 vs. T0 in Group S.

heart rate and MAP was significantly lower at T0 compared with T3-5 (P<0.05), and there were no significant differences at each time point in the parecoxib sodium or flurbiprofen groups.

The total incidence of postoperative shivering was significantly lower in Group P (18.75%) and Group F (20.41%) than among the patients who had received the saline (50.00%) (P<0.01) (**Table 3**). The number of patients who received pethidine was significantly higher in Group S than in Groups P and T (P<0.05). One patient in Group P, one in Group F and ten in Group S received rescue pethidine. In addition, the severity of postoperative shivering (shivering score of 2 or 3) was also significantly decreased by parecoxib sodium and flurbiprofen (P<0.05). However, there were no significant differences in the incidence and severity of postoperative shivering between parecoxib sodium and flurbiprofen.

Table 3. Shivering scores and the number of patients receiving pethidine

Group		Shivering scores					Number of patients shivering	Number of patients receiving pethidine rescue
		0	1	2	3	4		
Group P	n=48	39	6	2	1	0	9 (18.75%)	1
Group F	n=49	39	7	2	1	0	10 (20.41%)	1
Group S	n=48	24	4	10	8	2	24 (50.00%)	10
P	P vs. F	0.8370	0.7963	0.9832	0.9882	1	0.8370	0.9882
	P vs. S	0.0013	0.7783	0.0308	0.0356	0.4947	0.0013	0.0104
	F vs. S	0.0023	0.5457	0.0280	0.0330	0.2423	0.0023	0.0094

Values are patient numbers (percent).

Table 4. RSS and VAS

	Group	Group P	Group F	Group S	*P*		
		(n=48)	(n=49)	(n=48)	P vs. F	P vs. S	F vs. S
RSS	T3	2.7±0.8	2.8±0.7	2.7±0.9	0.5137	>0.9999	0.5423
	T4	2.5±0.7	2.6±0.6	2.6±0.7	0.4516	0.4857	>0.9999
	T5	2.4±0.6	2.5±0.7	2.3±0.8	0.4523	0.4901	0.193
P	T3 vs. T4	0.1956	0.1322	0.5449			
	T3 vs. T5	0.0404	0.0365	0.0236			
	T4 vs. T5	0.4542	0.4496	0.0535			
VAS	T3	14.8±7.8	13.3±7.9	25.8±8.1	0.3492	<0.0001	<0.0001
	T4	13.5±6.6	12.2±6.9	23.9±7.1	0.3456	<0.0001	<0.0001
	T5	12.3±7.6	11.9±7.1	22.6±8.9	0.7893	<0.0001	<0.0001
P	T3 vs. T4	0.3803	0.4647	0.2247			
	T3 vs. T5	0.1151	0.3585	0.0686			
	T4 vs. T5	0.4109	0.8325	0.4309			

Data are shown as the mean ± standard deviation. RSS = ramesay sedation scale; VAS = visual analog scale.

Table 5. Incidence of adverse events within 60 minutes after extubation

Adverse events	Group P	Group F	Group S	*P*		
	n=48	n=49	n=48	P vs. F	P vs. S	F vs. S
Nausea, n (%)	13 (27.1)	11 (22.4)	15 (31.3)	0.5969	0.6534	0.3279
Vomiting, n (%)	9 (18.8)	7 (14.3)	8 (16.7)	0.5536	0.7892	0.7457
Strokes	0	0	0	1	1	1
Myocardial infarction	0	0	0	1	1	1

Data are presented as the number (percent).

Table 4 shows the visual analogue score (VAS) and ramsy sedation scale (RSS) of the three groups. The VAS was significantly higher in Group S than in Groups P and F after the time of extubation, 30 minutes and 60 minutes after extubation ($P<0.01$). However, there were no significant differences in RSS among the three groups at the three time points. There were no patients with RSSover4. None of the patients in the three groups experienced respiratory depression during the study period.

13 patients in Group P (27.1%), 11 patients in Group F (22.4%) and 15 patients in Group S (31.3%) experienced nausea (**Table 5**). 9 patients in Group P (18.8%), 7 patients in Group F (14.3%) and 8patients in Group S (16.7%) experienced vomiting. However, there was no significant difference in the incidence of nausea and vomiting among the three groups. No other serious adverse events such as strokes or myocardial infarction were observed during the study period.

Discussion

This study suggests that parecoxib sodium and flurbiprofen can significantly decrease the incidence of postoperative shivering, without severe adverse effects, during the postoperative period. There were not significantly differences in the incidence of shivering between the parecoxib sodium group and the flurbiprofen group.

Shivering is an uncontrolled somatic motor response that occurs in skeletal muscles in several conditions [7]. Postoperative shivering occurs after operation and general anesthesia, and is very common. However, the mechanism of postoperative shivering is unclear. It is widely

accepted that postoperative shivering is caused by a variety of risk factors, such as the vasodilation caused by anesthesia drugs which makes body heat rapidly conduct from the interior to the periphery, the redistribution of body heat making the core temperature drop, the release of pyrogenic mediums during surgery, the administration of volatile anesthetics, blood loss, and duration of surgery. Cold liguid input is an important reason for postoperative shivering. Additionally, pain can also cause patient shivering. In this study, body temperature of all the patients was controlled at around 36.5°C, so that we could exclude the influence of body temperature on shivering among all groups. The MAP in each group at each time point were within the range of 70 to 80 mmHg, which means that all patients had normal blood pressure at each time point, and therefore this would not have caused shivering.

Postoperative shivering can be managed by numerous means including insulation, heating liquid input, and the prevention of the use of drugs such as pethidine, ketamine, tramadol, clonidine, fentanyl, dexamethasone, and ondansetron [8-11]. Preventive pharmacologic methods are also commonly used as therapy.

Recent studies have [12-15] shown prophylactic administration of parecoxibcan control shivering with few side effects. Our study has obtained similar results, and has shown that patients had more stable of hemodynamics in the parecoxib sodium group than in the saline group. Furthermore, our study demonstrates that flurbiprofen is an effective drug in reducing postoperative shivering, and is well-tolerated with respect to the side effects of sedation, nausea and vomiting. To our knowledge, there have been no previous studies on the use of flurbiprofen for the prevention of postoperative shivering. Our study shows that there were no significant differences in the incidence of shivering between the flurbiprofen group and the parecoxib sodium group.

The exact mechanism by which flurbiprofen and parecoxib sodium prevent shivering is still unclear. Both are known to produce analgesia by inhibiting cyclooxygenase-2 (COX-2) expression, and have been recommended for postoperative analgesia. Flurbiprofenisa non-selective COX-2 inhibitor, and parecoxib sodium is a selective COX-2 inhibitor. The synthesis of prostaglandin E2 (PGE2) is stimulated by COX-2 in the brain. It is likely that PGE2, one of the main mediators of the hypothalamus, causes shivering after anesthesia via a central mechanism [13]. In addition, it has been accepted that the two drugs have certain anti-inflammatory effects, and that they prevent the release of inflammatory cytokines during the surgery. Shivering, for example febrile shakes may be related to the activated inflammatory response and cytokine release that occur during an operation [16]. Cytokines may induce peripheral vasoconstriction, and postoperative fever. Because they can modify the inflammatory response, and produce analgesia, flurbiprofen and parecoxib sodium have been recommended for postoperative analgesia [17-19]. Therefore, it is speculated that flurbiprofen and parecoxib sodium prevent shivering via these pathways.

One limitation of this study is that the time of observing these adverse effects of flurbiprofen and parecoxib sodium was short, possibly because of our trial protocol. Further studies are needed so that a longer duration can be used to observe these adverse effects of flurbiprofen and parecoxib sodium in the prevention of postoperative shivering. Whether flurbiprofen and parecoxib sodium have a treatment effect on postoperative shivering should also be addressed.

In conclusion, intraoperative intravenous administration of flurbiprofen 50 mg or parecoxib sodium 40 mg is effective in decreasing the incidence and severity of postoperative shivering in patients undergoing colorectal surgery under general anesthesia. It does not pose any severe side effects. Between the two groups, there were not any significant differences. Although the mechanism of the reduced incidence of postoperative shivering is unclear, the administration of flurbiprofen or parecoxib sodium can be an alternative for the prevention of postoperative shivering.

Disclosure of conflict of interest

None.

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