Premedication with parecoxib sodium for reduction of propofol injection pain: a randomized placebo-controlled trial

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Research

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Abstract

Background To compare the effect of premedication with two different doses of parecoxib sodium to prevent pain at propofol intravenous injection. Methods We conducted a double-blind randomized controlled trial in which patients scheduled for induction of general anesthesia with intravenous propofol received either a placebo, 20 mg or 40 mg of parecoxib sodium (P20 and P40, respectively) 30min prior to induction. 2mg/kg of propofol was injected at a rate of 600 ml/hr. After 1/4 of the full dose had been injected, the syringe pump was paused, and patients were asked to rate pain at the injection site using a verbal numerical rating score (VNRS) from 0 to 10. Results Three hundred and twenty-four patients were included. Pain intensity was lower in both P20 and P40 groups (median VNRS [interquartile range] = 2 [0–3] and 4 [3–6], respectively) than in the placebo group (8 [7–10]; P < 0.001)*. The rate of pain was lower in the P40 group (62.9%) than in both the P20 and the placebo group (87.0 and 98.2%, respectively; P < 0.001)*. The respective rates of mild (VNRS 1–3), moderate (VNRS 4–6) and severe pain (VNRS 7–10) were 46.1, 22.3 and 0% in the P40 group, 29.7, 55.4 and 8.5% in the P20 group, and 0, 24.2 and 77.8% in the placebo group (P < 0.001* for between group comparisons). Tolerance was similar in the 3 groups. Conclusions A premedication with parecoxib sodium can dose-dependently reduce pain at propofol intravenous injection. To avoid this common uncomfortable concern for the patients, this well-tolerated, available and cheap treatment appears as an option to be implemented in the current practice.

Background

Propofol is a widely used intravenous anesthetic in clinic. It has the advantages of fast effect, short action time, rapid and complete recovery, etc. but the incidence of injection pain is very high, up to 90%. So far, there have been a lot of attempts to prevent propofol injection pain, the more effective method is to use lidocaine [1].

Although lidocaine is the most commonly used method to prevent propofol injection pain, the preventive effect of lidocaine is not perfect, the incidence of pain is still 32% − 48% [2]. Intravenous injection of propofol can easily cause local injection pain in peripheral veins.Some patients may struggle and avoid the pain caused by propofol injection.

To find better ways to prevent or reduce propofol injection pain has always been a concern for anesthesiologists.

It has adverse effects on smooth induction of anesthesia and aggravates stress Reaction.Shen et al. [3]study have shown that the incidence of propofol injection pain can reach 28.3%-90.0%. In addition, propofol alone has a higher dose and higher incidence of circulatory depression, apnea and respiratory depression.

Zeng LingQuan et al. [4] considered that the factors of propofol injection pain were complex and main.It is because propofol is insoluble in water, has high fat solubility, and propofol is a fat solvent.It can stimulate the intima, mucosa and skin of blood vessel and activate the pancreatic vasopressin-kallikrein

system in plasma to produce bradykinin. In addition, propofol can act on local venules to increase their dilatation and permeability. In veins affected by bradykinin, intravenous pain can be caused by the contact of propofol with free nerve endings outside the vascular endothelium.Therefore, how to reduce the incidence of propofol injection pain has become an important problem for anesthesiologists.

At present, many clinical studies have explored measures to alleviate propofol injection pain, including ketamine, lidocaine, lappaconitine, remifentanil and fentanyl before propofol administration.Gotoda et al. [5] showed that lidocaine could excite cell membrane and alleviate local stimulation, which could effectively promote K + outflow from cardiac myocytes and reduce myocardial autonomy, and had no effect on myocardial contraction, atrioventricular conduction and electrical activity of cardiac myocytes.Lidocaine belongs to phthalocyanine local anesthetics. It has the characteristics of strong permeability, wide dispersion and quick onset. It is a cascade reaction stabilizer of kallikrein, which can effectively reduce the production of kallikrein and can be released after intravenous local administration.

To reduce the incidence of propofol injection pain, the effect of nerve swing block was used to prevent the transmission of peripheral pain.

Parecoxib sodium is a long-acting analgesic drug widely used at present. It can selectively inhibit the central and external organs after hydrolysis.

The expression of cyclooxygenase-2 blocked the pain effect caused by cyclooxygenase-2 [6].

We hypothesized that premedication with Parecoxib sodium can reduce the severity of propofol injection pain. Our primary endpoint was pain intensity measured by verbal numerical rating score upon propofol injection. In regard to this study, we aimed to compare the efficacy of Parecoxib sodium 20 mg versus 40 mg for reduction of propofol injection pain.

Methods

This study was a double-blinded randomized controlled trial (RCT).All patients participating in the trial were approved by the ethics committee of the Affiliated Hospital of Guangdong Medical University and signed the informed consent before operation. The trial was registered prior to patient enrollment at clinicaltrials.gov (Effects of dexmedetomidine combined with parecoxib sodium in patients undergoing endoscopic nasal surgery rapid rehabilitation and prognosis, Principal investigator:GU Xiao-Xia, Date of registration:16 January 2017). Trial's clinical trial registration number is ChiCTR-OPN-17010444 .The principal investigator was Dr. Gu. The data were collected from June 2017 until December 2018 at Affiliated Hospital of Guangdong Medical University. The authors prepared this trial report in accordance to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The full protocol is accessible on request.

We recruited 324 patients with the American Society Anesthesiologists (ASA) physical status I-II of who were aged between 20 and 50, scheduled for elective surgeries under general anesthesia, and having an

intravenous catheter number 20G at a hand dorsum. Exclusion criteria included weight less than 50 kg, chronic pain, hypertension, cardiovascular disease or cerebrovascular disease, difficulty in communicating, cirrhosis or abnormal liver function test result (aspartate transaminese (AST), alanine transaminase (ALT) ≥ 2 times of normal range), renal failure or creatinine clearance (CrCl) ≤ 10umol/L,paracetamol and/or propofol allergy. Exclusion criteria also included patients who were not using propofol for an induction, using an intravenous catheter that was not on a hand dorsum, or whereas the size of the catheter was not 20G and had to have a rapid sequence induction.

After obtaining a written informed consent, a randomization was performed by using a block of 6 method. The drugs were prepared by one of the investigators (XJ-T), with both the patient and an independent assessor (anesthesiologist in-charge) blinded. The groups Pb, P20 and P40, patients were premedicated with placebo, 20 or 40 mg of Parecoxib sodium, respectively 30 min prior to transferal to the operating room. Each patient received either 2 ml of placeco (Pb group), 2 ml of Parecoxib sodium 20 mg (P20), or 2 ml of Parecoxib sodium 40 mg (P40). Both placebo and Parecoxib sodium were identical in shape, size, color and weight. None of them received any other analgesic or sedative drug. A 20G intravenous catheter was inserted into a superficial vein on the hand dorsum and intravenous fluid at a rate of 80 ml/hr. was infused into each patient.

After preoxygenation, an emulsion of 1% propofol in a mixture of long-chain and medium-chain triglycerides (Lipuro®, B Braun) 2 mg/kg (for obese patients, dose was calculated by using lean body weight) was intravenously administered into each patient with a syringe pump at a rate of 600 ml/hr. (10 ml/min). After 1/4 of the calculated dose of propofol had been delivered, the infusion pump was temporarily paused and the patient was asked to rate his/her pain at the injection site using an 11-point verbal numerical rating score (VNRS) when 0 is not pain and 10 is the worst pain imaginable. None of them was heavily anesthetized and unable to give the VNRS. The residual dose of propofol was then given, followed by opioids and neuromuscular blocking agent as per usual.

SPSS 18.0 statistical software(SPSS Institute, Chicago, IL, USA) was used for analysis. The measurement data of normal distribution are expressed as mean (). The comparison among groups is based on one-way ANOVA, while the comparison within groups is based on the ANOVA of repeated measurement design. Chi - square test was used to analyze the categorical data and for testing the association between the variables. Nonparametric tests (Wilcoxon signed rank tests [two - tailed]) were used whenever the mean value was less than two times the standard deviation.$P < 0.05$ showed statistical significance.

For sample size calculation, we collected pain intensity by using the 11-point verbal numerical rating score (VNRS) in 30 patients who received propofol for an induction, without having paracetamol for premedication. The mean VNRS in this group of patients was 5.7. Anticipating that patients premedicated with paracetamol would have 25% less pain (VNRS of 4.2), a number of patients per each group was calculated to be 96. With 10% drop out, the definite number of patients per each group was 108.

Results

A total of 324 patients were assessed for eligibility from June 2017 to December 2018. Three hundred and ten patients were excluded and 324 patients were randomly allocated to each group. Each group equally had 108 patients. All participants were completely analyzed. (Fig. 1)

There were no differences between the groups regarding gender, age, weight, height, body mass index (BMI), ASA physical classification and interval between ingestion of paracetamol and injection of propofol. (Table 1). In all cases, it was possible to achieve a clear response from the patients before they became anesthetized. The overall incidence of pain during propofol injection among the 3 groups is shown in Fig. 2. The incidence of pain was less in the P40 group (75.4%) compared with

Table 1
Patient demographic data. All data are n(%) or mean(SD)

Patients	**Pb(n = 108)**	**P20(n = 108)**	**P40(n = 108)**	**P-value**
Gender,n(%)-male	55(50.9)	51(47.2)	56(51.8)	0.58
Age(yr),mean(SD)	41.6(11.2)	43.2(12.1)	42.7(10.5)	0.51
Weight(kg),mean(SD)	61.8(8.6)	62.1(9.1)	61.6(8.7)	0.98
Height(cm),mean(SD)	159.8(8.8)	160.5(7.6)	159.6(8.2)	0.68
BMI(kg/m^2),mean(SD)	24.3(3.2)	24.8(3.6)	24.6(3.3)	0.78
ASA-Ⅰ,n(%)	28(25.9)	33(30.5)	29(26.8)	
ASA-Ⅱ,n(%)	80(74.1)	75(69.5)	79(73.2)	
IPP[a], mean(SD)	66.8(25.5)	68.6(27.9)	69.8(27.5)	0.32
IPP[a]=interval between ingestion of parecoxib sodium to injection of propofol(minutes)				
Data are presented as the number of patients(%) and mean ± SD values				

the P20 (84.1%) and the Pb groups (99.4%) ($P < 0.001$).

The incidences of pain by categories of intensity (mild/ moderate/severe) were lower in the P40 group in comparison to those in the P20 and the Pb groups ($P < 0.001$). (Table 2).

Table 2
Number of patients experiencing propofol injection pain among the 3 groups

Severity of pain n(%)	Pb group(n = 108)	P20 group(n = 108)	P40 group(n = 108)
None (VNRS 0)	2(1.8)	14(13.0)	40(37.1)
Mild(VNRS 1–3)	0 (0)	30(28.8)	48(44.4)
Moderate(VNRS 4–6)	26(24.1)	52 (48.1)	20 (18.5)
Severe(VNRS 7–10)	80(74.1)	12 (11.1)	0 (0)
P-value < 0.001 among the 3 groups and *P-value* < 0.001 for Pb vs P20, *P-value* < 0.001 for Pb vs P40,*P-value* < 0.001 for P20 vs P40			
Pb placebo, P20 parecoxib sodium 20mg, P40 parecoxib sodium 40mg,VNRS verbal numerical rating score			
Data are presented as the number of patients(%)			

The median pain score showed a significant reduction in the P40 group compared with the P20, and the Pb groups. Those were 2(0–3), 4(3–6), and 8 (7–10), respectively (P < 0.001). (Fig. 3).

There was no incidence of complications such as; rashes or edema of the tissue in each group at the recovery room.

Discussion

Our results show that the frequency of propofol injection pain in the control group was 98.2%, which is consistent with data from other studies [7–10]. Pretreatment with parecoxib 40 mg was effective in reducing propofol injection pain in frequency and severity. Pretreatment with parecoxib 20 mg reduced the severity of propofol injection pain significantly but did not reduce the frequency of pain compared with the control group. We compared two different doses with a control group, as no study regarding the dose of parecoxib was available for this purpose.

The exact mechanism of pain during propofol injection remains obscure. Propofol (di-isopropylphenol) is the most frequently used agent for the induction of general anesthesia because of its rapid onset and short duration of action. However, pain from the injection is a common problem [11]. The incidence of injection pain has been shown to vary between 28 and 90% which might be severe [12, 13]

A number of approaches have been proposed to lessen the injection pain such as injection of propofol at an antecubital fossa, fast injection [14] and pretreatment with lidocaine [15], opioids [16], or non-steroidal anti-inflammatory drugs (NSAIDs) [17]. The effective technique is a combination of lidocaine pretreatment together with venous occlusion (a modified Bier's block) [13]. However, this inflated arm tourniquet technique is quite difficult. From a systematic review and meta-analysis, the most two effective procedures to decrease propofol injection pain are injecting through an antecubital vein and

pretreatment with lidocaine together with venous occlusion when a hand vein is used [18]. Canbay et al. [19] showed that intravenous acetaminophen (paracetamol) could diminish injection pain. The incidence of pain was significantly reduced to 22% as compared to a control group but less than lidocaine.

Borazan et al. [20] compared the effect of injection of different paracetamol doses with lidocaine. They found that paracetamol 2 mg/kg administered intravenously 1 min before propofol was more effective than paracetamol 1 mg/kg and lidocaine in reducing propofol injection pain. The issue of pain at propofol injection pain should be addressed and managed accordingly. In this study, we found that premedicated with Parecoxib sodium was effective in decreasing the incidence and severity of propofol injection pain when compared with a placebo. Premedication with 40 mg of Parecoxib sodium was also more effective in reducing propofol injection pain than 20 mg.

Parecoxib, the prodrug of valdecoxib, was reported to successfully treat postoperative pain in many surgical settings [21–24] with opioid-sparing effects [21]. Recently, parecoxib (5 mg) improved pain in patients with complex regional pain syndrome (CRPS) type I when it was combined with lidocaine/clonidine as the IV regional analgesia [25]. The authors suggested that parecoxib may be effective through a local mechanism by CYP3A4-NADPH cytochrome P450 reductase in peripheral vessels in these study conditions [25].

However, the authors mentioned that the doses of paracoxib 40 mg and 20 mg resulted in transient superficial thrombophlebitis after first application and were no longer used. No thrombophlebitis was reported with 10 mg or 5 mg IV locoregional parecoxib in their study [25]. We followed our patients and checked the injection site for 24 hours after surgery, and did not notice thrombophlebitis in any patient.

According to the severity of pain, the incidence of mild, moderate, and severe pain was also significantly different in our P40, P20 and Pb groups. These findings indicate that premedication with Parecoxib sodium reduce propofol injection pain by means of a dose dependent fashion. Different method of assessing pain severity may also explain our different results on severity of propofol injection pain. We used a Verbal Numerical Rating Score (VNRS) ranging from 0 to 10 (11 points) to measure our patients' pain. All of our patients verbally reported their pain by themselves ('subjective' assessment). The other studies used a 4-point scale (0 = none, 1 = mild, 2 = moderate and 3 = severe). They did not mainly ask their patients to verbally rate the level of pain upon propofol injection but they principally observed their patients' pain behaviors ('observational' assessment): 0 = none (negative response to questioning), 1 = mild pain (pain reported only in response to questioning with no behavioral signs), 2 = moderate pain (pain reported in response to questioning and accompanied by a behavioral sign or pain reported spontaneously without questioning), and 3 = severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawals or tears). Measuring pain by the VNRS is reliable, valid, sensitive to change, and easy to administer [26].

We did not use behavioral assessment because it is not subjective and less reliable. This study found no adverse consequence of Parecoxib sodium.

Limitations of our study are a subjective method of pain intensity measurement and the fractional dose of given propofol. The intensity of propofol injection pain was rated by using the verbal numerical rating score (VNRS), although patient's self-assessment is the gold standard of pain intensity measurement but it is subjective and depends of each individual. Because propofol is a powerful induction agent, we could not inject the entire dose of propofol to each patient before measuring the pain intensity as a significant number of them felt asleep and were unable to give the pain rating.

Conclusions

Premedication with Parecoxib sodium can reduce propofol injection pain on a dose-dependent basis, without causing any adverse effect. As propofol injection pain is common and remains a concern of anesthesia providers for the comfort of their patients, and early administration of Parecoxib sodium is pharmacologically sensible, easy to apply, well-tolerated, available and economic, the results of this study provide the basis for changing practice with a positive impact on patient care.

Abbreviations

ALT: Alanine transminase; ASA: American Society of Anesthesiologists;

AST: Aspartate transaminase; BMI: Body mass index; Cmax: Maximum concentration;

SD: Standard deviation; SP: Substance P; VNRS: Verbal numerical rating score

Declarations

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Availability of data and materials

The datasets generated and/or analyzed during the current study will be available from the corresponding author on reasonable request.

Authors' contributions

XX-G and WM-H participated in protocol writing, collecting data, statistical analysis, interpretation of results and manuscript writing. JJ-W participated in protocol writing, interpretation of results and manuscript writing. Y-L did the statistical analysis and reviewed the manuscript. All authors read and approved the final manuscript

Ethics approval and consent to participate

This study was approved by the Affiliated Hospital of Guangdong Medical University Ethics Committee with the reference number PJ2016118. It was also registered with Thai Clinical Trial Registry with the reference number ChiCTR-OPN-17010444.

All participants were informed and asked for written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Conflicts of Interests/Financial Disclosures: NONE

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Figures

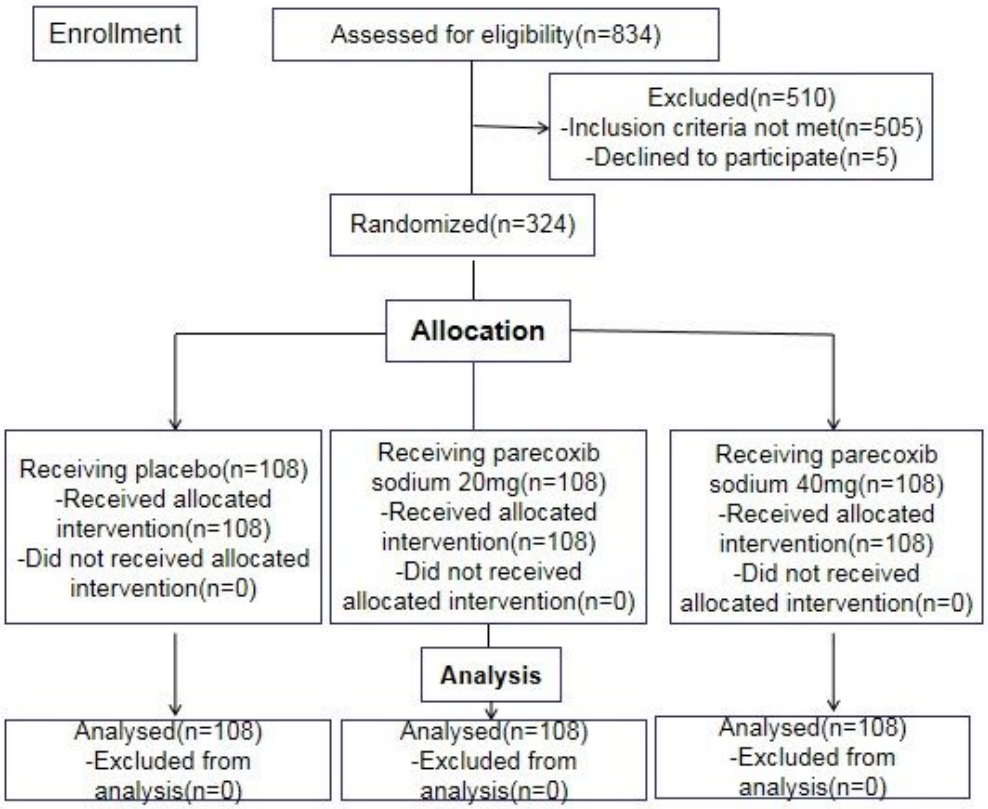
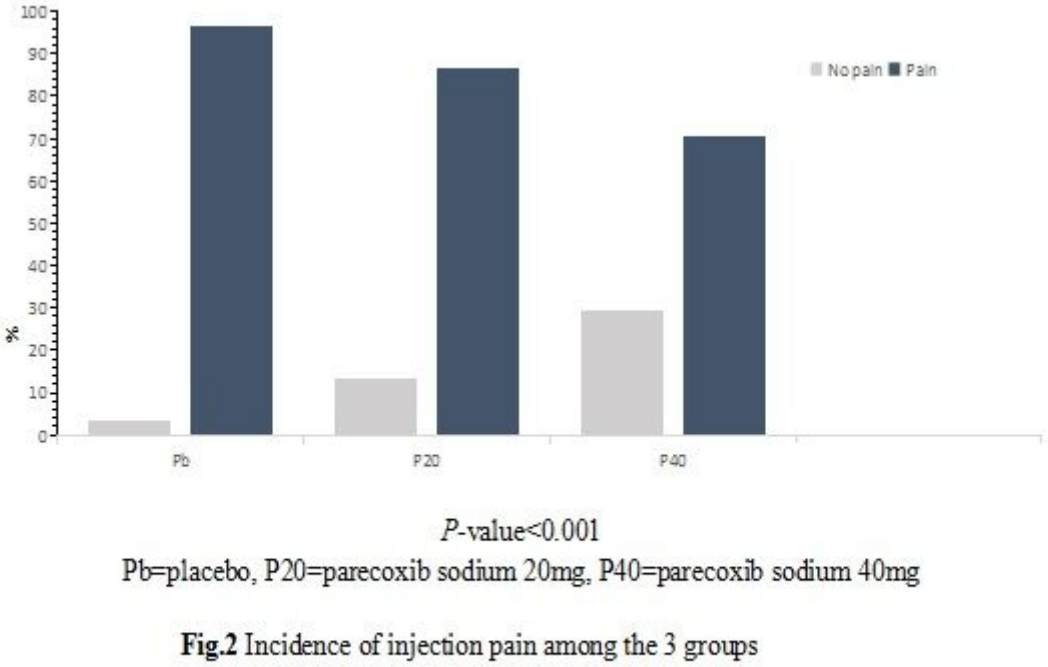


Figure 1

Figure 1



P-value<0.001

Pb=placebo, P20=parecoxib sodium 20mg, P40=parecoxib sodium 40mg

Fig.2 Incidence of injection pain among the 3 groups

Figure 2

Figure 2