Premedication with Oral Paracetamol for Reduction of Propofol Injection Pain: A Randomized Placebo-Controlled Trial

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Abstract

Background To compare premedication with 2 doses of oral paracetamol on the incidence and severity of propofol injection pain. Methods The 324 patients (18-65 years old) were randomly allocated into 3 groups. The groups Pb, P500 and P1000, participants were premedicated 1 hour prior to transferal to the operation with oral placebo, 500 or 1000 mg of paracetamol, respectively. Propofol (2 mg/kg) was injected at a rate of 600 ml/hr. After 1/4 of the calculated dose, the syringe pump was temporarily paused, and patients were asked to rate pain at the injection site using a verbal numerical rating score (VNRS) from 0-10. Results The incidence of pain was less in the P1000 group (70.4%) compared with the P500 (86.1%) and the Pb groups (99.1%) (P<0.001). Same as the median VNRS, 2 (0-3), 4 (2-5), and 8 (7-10) (P<0.001), respectively. The incidences of mild (VNRS of 1-3), moderate (VNRS of 4-6) and severe pain (VNRS of 7-10) were also in the same manner, 47.2%, 23.2%, and 0% (P1000), 28.7%, 50%, and 7.4% (P500) and 0%, 22.2%, and 76.9% (Pb) (P<0.001). No significant complications were found in any group. Conclusions Premedication with oral paracetamol, on a dose-dependent basis, can reduce propofol injection pain without causing any complications. As propofol injection pain is common and remains a concern for the comfort of the patients, and oral paracetamol is well-tolerated, available and economic, the results of this study provide the basis for continuing or changing practice with a positive impact on patient care.

Background

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 [1]. The incidence of injection pain has been shown to vary between 28% and 90% which might be severe [2,3] and the data from Songklanagarind Hospital found the high incidence of pain as 83%.

Pain upon injection of some anesthetic agents are thought to be a direct irritant effect by the non-physiological osmolality or pH of their preparations [4]. Nonetheless, propofol is nearly isotonic, nonhyperosmolar and has a pH from 6 to 8.5. Hence, this concept cannot explain for the pain produced by the injection of propofol [1]. Propofol injection pain may be caused by an effect via the kinin cascade [5]. In addition, many factors seem to contribute to the incidence of injection pain including site [6] and speed of injection [7], size of vein [7,8], rate of intravenous fluid infusion [9], concentration of propofol in the aqueous phase [4] as well as blood buffering effects [10].

A number of approaches have been proposed to lessen the injection pain such as injection of propofol at an antecubital fossa, fast injection [7] and pretreatment with lidocaine [11], opioids [12], or non-steroidal anti-inflammatory drugs (NSAIDs) [13]. The effective technique is a combination of lidocaine pretreatment together with venous occlusion (a modified Bier's block) [3]. However, this inflated arm tourniquet technique is quite difficult. From a systematic review and meta-analysis, the most 2 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 [14].

Canbay et al. [15] 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. [16] compared the effect of injection of different paracetamol doses with lidocaine. They found that paracetamol 2 mg/kg administered intravenously 1 minute before propofol was more effective than paracetamol 1 mg/kg and lidocaine in reducing propofol injection pain. However, since intravenous paracetamol formulation is not available in Thailand, we used oral paracetamol in this study. We hypothesized that the oral form of the drug can also reduce the severity of injection pain.

Additionally, Seymour et al. [17] demonstrated that a 1000-mg dose was more effective than 500 mg in reducing postoperative pain after third molar surgery. In regard to this study, we aimed to compare the efficacy of paracetamol 500 mg versus 1000 mg for reduction of propofol injection pain.

Methods

This study was a double-blinded randomized controlled trial. It was approved by the Faculty of Medicine, Prince of Songkla University Ethics Committee and registered with Thai Clinical Trial Registry (TCTR20150224002: registered on February 24, 2015). The principal investigator was Dr. Nimmaanrat. The data were collected from June 2015 until February 2016 at Songklanagarind Hospital (Faculty of Medicine, Prince of Songkla 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.

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.

We recruited 324 patients with the American Society Anesthesiologists (ASA) physical status I-III of who were aged between 18-65, scheduled for elective surgeries under general anesthesia, and having an intravenous catheter number 20G at a hand dorsum.

Exclusion criteria included patients who weighed < 50 kg with either chronic pain, hypertension, cardiovascular disease or cerebrovascular disease, difficulty in communicating, cirrhosis or abnormal liver function test result (aspartate transaminese (AST), alanine transaminase (ALT) $\geq$ 2 times of normal range), renal failure or creatinine clearance (CrCl) $\leq$ 10 umol/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, patients were randomly allocated by using a blocked randomization of 6 method into 3 groups of 108 patients each. The drugs were prepared by one of the

investigators (MJ), with both the patient and an independent assessor blinded. The groups Pb, P500 and P1000, patients were premedicated with oral placebo, 500 or 1000 mg of paracetamol, respectively 1 hour prior to transferal to the operating room. Each patient received either 2 tablets of placeco (Pb group), 1 tablet of placebo and 1 tablet of paracetamol 500 mg (P500), or 2 tablets of paracetamol 500 mg (P1000). Both placebo and paracetamol 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, propofol (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.

The patients were carefully evaluated for paracetamol's side effects in the operating room and postanesthesia care unit.

Statistical analysis was performed by using R software 2.14.1. Continuous variables were analyzed by ANOVA F- test or Kruskal-Wallis test. Categorical variables were analyzed by ANOVA F-test, Fisher's exact test or Chi-square test. Post-hoc analysis was carried out by using a comparison by pairs. P value less than 0.05 was considered as statistical significant. Continuous variables were presented as median and interquartile range (IQR) or mean and standard deviation (SD). Categorical variables were presented as number of patients and percentages. The power of this study was 0.9.

Results

A total of 834 patients were assessed for eligibility from June 2015 to February 2016. Five 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.

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)

The overall incidence of pain during propofol injection among the 3 groups is shown in Figure 2. The incidence of pain was less in the P1000 group (70.4%) compared with the P500 (86.1%) and the Pb groups (99.1%) ($P<0.001$). The incidences of mild (VNRS 1-3), moderate (VNRS 4-6) and severe pain (VNRS 7-10) were also significantly different in the P1000 group (47.2%, 23.2%, and 0%, respectively) in comparison to those in the P500 (28.7%, 50%, and 7.4%, respectively) and the Pb groups (0%, 22.2%, and 76.9%, respectively) ($P<0.001$). (Table 2) [Chi-square test revealed P-value < 0.001 among the 3 groups.

The post-hoc analysis using Chi-square test revealed P-value < 0.001 when compared the Pb group with the P500 group and the Pb group with the P1000 group. Fisher's exact test revealed P-value < 0.001 comparing the P500 group with the P1000 group.]

The median pain score showed a significant reduction in the P1000 group compared with the P500, and the Pb groups. Those were 2 (0-3), 4 (2-5), and 8 (7-10), respectively (P<0.001). (Figure 3) [Kruskal-Wallis test revealed P-value < 0.001 among the 3 groups. The post-hoc analysis using Ranksum test revealed P-value < 0.001 when compared the Pb group with the P500 group, the Pb group with the P1000 group and the P500 group with the P1000 group.]

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

Table 1 Patient demographic data

Patients	Pb (n = 108)	P500 (n = 108)	P1000 (n = 108)	P-value
Gender, n (%)	24 (22.2)	33 (30.5)	36 (33.3)	0.16
- Male	84 (77.8)	75 (69.5)	72 (66.7)	0.54
- Female	42.7 (11.5)	43 (12.2)	44.3 (10.3)	0.96
Age (yr), mean (SD)	62.5 (9.6)	62.8 (9.8)	62.8 (9.1)	0.67
Weight (kg), mean (SD)	159.5 (7.4)	160.3 (7.3)	159.5 (8.2)	0.80
Height (cm), mean (SD)	24.6 (3.6)	24.4 (3.4)	24.8 (3.5)	0.19
BMI (kg/m2), mean (SD)	19 (17.6)	28 (25.9)	23 (21.3)	0.35
ASA classification, n (%)	84 (77.8)	79 (73.1)	81 (75)	
- I	5 (4.6)	1 (1)	4 (3.7)	
- II	65.1 (32.1)	66.5 (28.3)	70.8 (28.9)	
- III				
IPP*, mean (SD)				

*IPP = interval between ingestion of paracetamol to injection of propofol (minutes)

Data are presented as the number of patients (%) and mean ± SD values

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

Severity of pain n (%)	Pb group (n = 108)	P 500 group (n = 108)	P 1000 group (n = 108)
No pain	1 (0.9)	15 (13.9)	32 (29.6)
Pain	107 (99.1)	93 (86.1)	76 (70.4)
- Mild (VNRS 1-2)	0 (0)	31 (28.7)	51 (47.2)
- Moderate (VNRS 4-6)	24 (22.2)	54 (50)	25 (23.2)
- Severe (VNRS 7-10)	83 (76.9)	8 (7.4)	0 (0)

*P-value < 0.001 among the 3 groups

Pb = placebo, P500 = parecetamol 500 mg, P1000 = paracetamol 1000 mg

VNRS = verbal numerical rating score

Data are presented as the number of patients (%)

Discussion

In this study, we found that an oral paracetamol was effective in decreasing the incidence and severity of propofol injection pain when compared with a placebo. Premedication with 1000 mg of paracetamol was also more effective in reducing propofol injection pain than 500 mg.

The factors which are thought to responsible for propofol injection pain include its concentration in the aqueous phase [4,10], site of injection [6], size of vein [7,8], and rate of propofol injection (a slow administration leads to higher pain than a fast bolus) [7]. To regulate these contributing factors, we used an emulsion of 1% propofol in a mixture of long-chain and medium-chain triglycerides, and injected via a catheter no. 20G in a dorsum of hand at a rate of 600 ml/hr in every case.

It has been speculated that an indirect effect via the kinin system causes delayed propofol injection pain which is felt between 10-20 seconds after administration [8]. The lipid solvent of propofol activates the kallikrein-kinin cascade in plasma and generates bradykinin which alters the local vein through its vasodilatory and hyperpermeability effects. This modification in the local vein increases contact between the aqueous phase of propofol and free nerve endings, leading to intensification of injection pain [5]. It was revealed that propofol produces vascular pain which happens in response to prostaglandins, predominantly prostaglandin E2 [18].

NSAIDs exerts its effects by blocking the cyclooxygenases (COX) resulting in reduction of prostaglandin production [19]. A systematic review and meta-analysis conducted by Jalota et al. [14] showed that pretreatment with NSAIDs was effective. However, due to its mechanism of action, NSAIDs can cause

serious adverse events such as gastrointestinal side effects (bleeding, perforation, obstruction) [19], bleeding from platelet dysfunction, renal impairment, etc. Paracetamol is a well-tolerated analgesic and causes fewer side effects in comparison to NSAIDs [20].

Paracetamol is one of the most popular and frequently used pain killer throughout the world. The mechanisms of action are sophisticated and cover both peripheral and central antinocciceptive manners. The pain relief effect provided by paracetamol is via inhibition of the cyclooxygenase pathway centrally and peripherally, reducing the production of prostaglandins [20]. Nevertheless, its antiinflammatory effects are weak, probably due to poor effectiveness when the concentration of peroxidases is high at the area of inflammation [19]. Paracetamol has been postulated to be classified to the group of the so-called atypical NSAIDs, determined as peroxide sensitive analgesic and antipyretic drugs (PSAAD) [21]. It has been shown that paracetamol is a selective cyclooxygenase-2 inhibitor *in vivo* [22]. Other proposed possible modes of action are an endogenous cannabinoid effect [23] and a modulatory effect on the descending serotoninergic inhibitory pathway [24]. Pain relieving effect of paracetamol might also be a result of inhibition of nitric oxide (NO) formation. The synthesis of NO is through activation of L-arginine/NO pathway by substance P (SP) and N-methyl-D-aspartate (NMDA) receptors. NO is an important neurotransmitter involved in nociceptive process of the spinal cord [25,26].

Paracetamol has been found as effective for reducing propofol injection pain. Canbay et al. [15] showed that the incidence of propofol injection pain was 64% in the control group and 22% in the intravenous paracetamol pretreatment group. Khouadja et al. [27] also showed similar results, 85% in the control group and 36.6% in the intravenous paracetamol group.

In our study, the overall incidence of pain during propofol injection was higher than other studies. The previous 3 studies [15,27,28] used intravenous paracetamol, not oral tablet as we did. Oral form of paracetamol exerts different pharmacokinetics and pharmacodynamics in comparison to intravenous form. This is why our results (using oral paracetamol) somewhat differed from other previous studies (using intravenous paracetamol) in terms of incidence and severity of propofol injection pain. Singla et al. [29] has shown that intravenous paracetamol has earlier and higher plasma level compared with oral paracetamol. After administration, plasma concentration of intravenous paracetamol reaches its peak rapidly within 15 minutes as shown by a very steep part of its graph. Plasma concentration of oral paracetamol at any time of measurement (0.25, 0.5, 0.75, 1, 2, 3, 4 and 6 hours) is much lower than that of intravenous paracetamol at 15 minutes. The intravenous route provides a 76% higher maximum concentration (Cmax) than the oral route.

The other reasons that the incidence of propofol injection pain in the paracetamol group in previous studies was lower than ours may be from inserting a bigger venous catheter [27] and/or using a venous occlusion technique [15,27]. It has been demonstrated that this tourniquet technique can help to increase the effectiveness of intravenous paracetamol in reducing propofol injection pain [28]. Canbay et al. [15] occluded their patient's vein and gave pretreatment of intravenous paracetamol over 10 seconds. The patient's vein was further occluded for 2 more minutes before releasing. Propofol was given after the

patient's vein had been released. Pain was measured during 5 seconds of paracetamol injection. The patients in Canbay et al.'s study rated their pain within the period of the highest plasma concentration of paracetamol.

With similar methods, Khouadja et al. [27] gave pretreatment with intravenous paracetamol over 10 seconds into an occluded vein and released the occlusion 2 minutes after the completion of paracetamol injection. Propofol was then administered over 20 seconds. Their patients' pain was measured during the 20 seconds of propofol injection. Again, the patients in Khouadja et al.'s study graded their level of pain within the period of the highest plasma concentration of paracetamol.

A study done by Ozkan et al. [28] comparing intravenous paracetamol with or without tourniquet for propofol injection pain, has demonstrated that paracetamol administration with tourniquet provides better analgesia than paracetamol without use of a tourniquet.

On the other hand, we gave premedication of paracetamol either 500 or 1000 mg per oral 1 hour before transferal to the operating room. Our patients rated their propofol injection pain while their plasma concentration of paracetamol was much lower than that of intravenous paracetamol in the other studies. We think that the differences of pharmacokinetic parameters (much rapid and higher peak plasma concentration of intravenous paracetamol) account for different results of our study in comparison to the other studies.

According to the severity of pain, the incidence of mild, moderate, and severe pain was also significantly different in our P1000, P500 and Pb groups. These findings indicate that premedication with oral paracetamol reduce propofol injection pain by means of a dose-dependent fashion.

Interestingly, our results of pain intensity also differed from the previous studies as we have found higher incidence of mild, moderate and severe levels of propofol injection pain. Different form and method of administration may explain these different findings. We gave premedication with 'oral' paracetamol to our patients. The other studies gave pretreatment with 'intravenous' paracetamol to a patient's occluded vein. The other studies used a more sophisticated (and may be better) technique to administer paracetamol. However, as previously mentioned, there was no intravenous paracetamol available in our country when we did this study. We decided to perform this study using oral paracetamol because it is readily and widely available, practically simple and convenient to use as well as economic wise.

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 0-10 (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). As pain intensity is always subjective so the patients' own rating is the best way to measure it. Patients' self-report is the gold standard of assessing their pain severity. The method of pain measurement that we used in our study, VNRS, is reliable, valid, sensitive to change, and easy to administer. [30] We did not use behavioral assessment at all because it is less reliable (eg. no pain complain does not mean no pain experienced).

Even paracetamol usually has no side effect, all of the patients were carefully evaluated for paracetamol's adverse events in the operating room and postanesthesia care unit including serious allergic reaction (rash, edema and unstable hemodynamic status). None of them sustained paracetamol's adverse consequences.

Strengths of this study are utilization of a simple analgesic (paracetamol) and administered it to the patients in a simple way (oral route). Considering that oral paracetamol has been shown to increase the incidence of no pain as well as to reduce the incidence of severe pain upon propofol injection, the results of this study are clinically useful and applicable to daily practice.

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. 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 oral paracetamol can reduce propofol injection pain without causing any adverse effect. Moreover, premedication with paracetemol 1000 mg reduces the severity of injection pain more than 500 mg. As propofol injection pain is common and remains a concern of anesthesia providers for the comfort of their patients, and oral paracetamol is well-tolerated, available and economic, the results of this study provide the basis for continuing or changing practice with a positive impact on patient care.

Abbreviations

VNRS: verbal numerical rating score

NSAIDs: non-steroidal anti-inflammatory drugs

ASA: American Society of Anesthesiologists

AST: aspartate transaminase

ALT: alanine transminase

IQR: interquartile range

SD: standard deviation

BMI: body mass index

COX: cyclooxygenase

PSAAD: peroxide sensitive analgesic and antipyretic drugs

NO: nitric oxide

SP: substance P

NMDA: N-methyl-D-aspartate

Cmax: maximum concentration

Declarations

Ethics approval and consent to participate

This study was approved by the Faculty of Medicine, Prince of Songkla University Ethics Committee with the reference number 57-358-08-1.

It was also registered with Thai Clinical Trial Registry with the reference number TCTR20150224002.

All participants were informed and asked for written informed consent.

Consent to publication

Not applicable

Availability of data and material

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SN and MJ participated in protocol writing, collecting data, statistical analysis, interpretation of results and manuscript writing. SP participated in protocol writing, interpretation of results and manuscript writing. MO did the statistical analysis and reviewed the manuscript. All authors read and approved the final manuscript.

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Figures

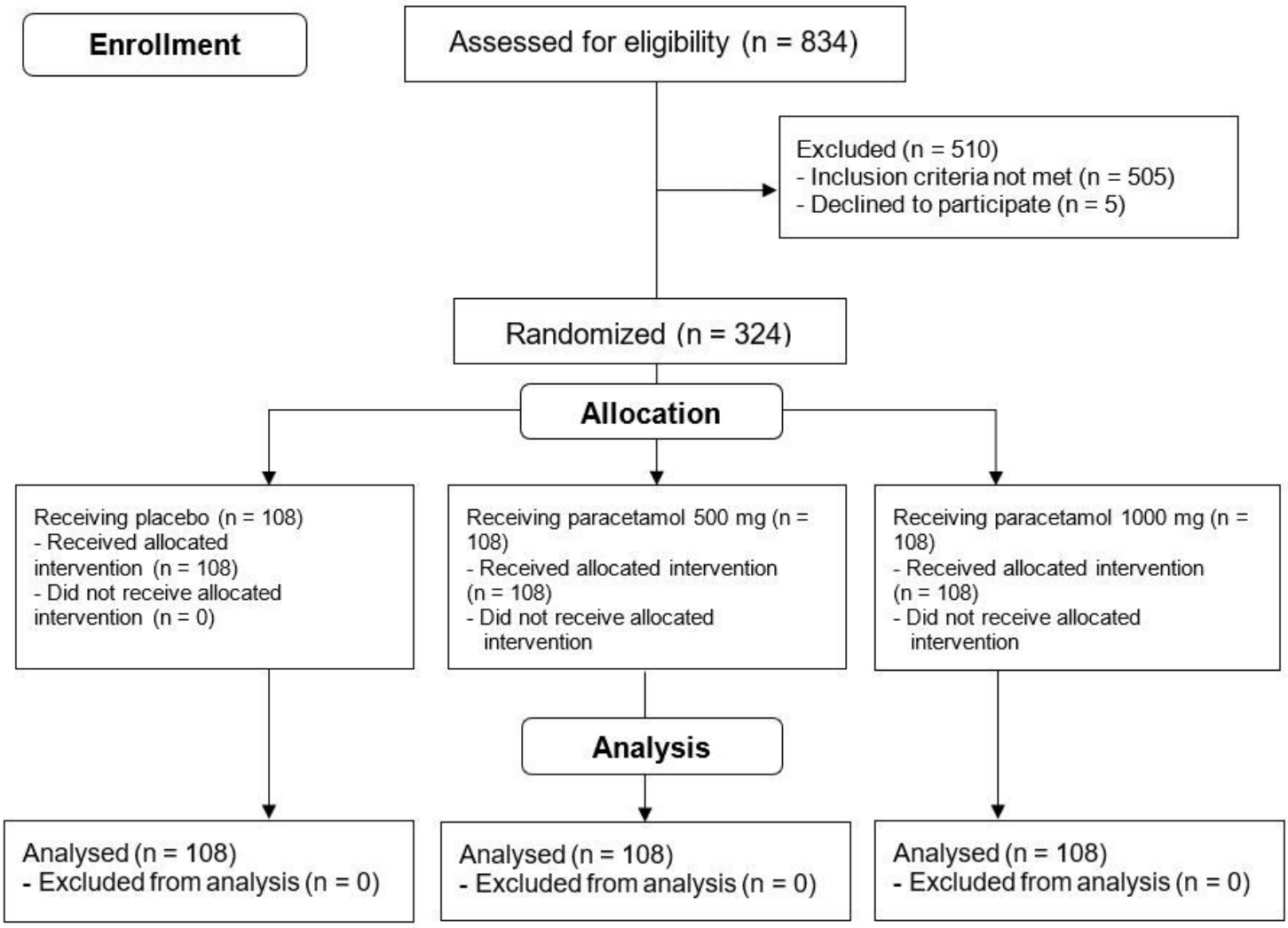
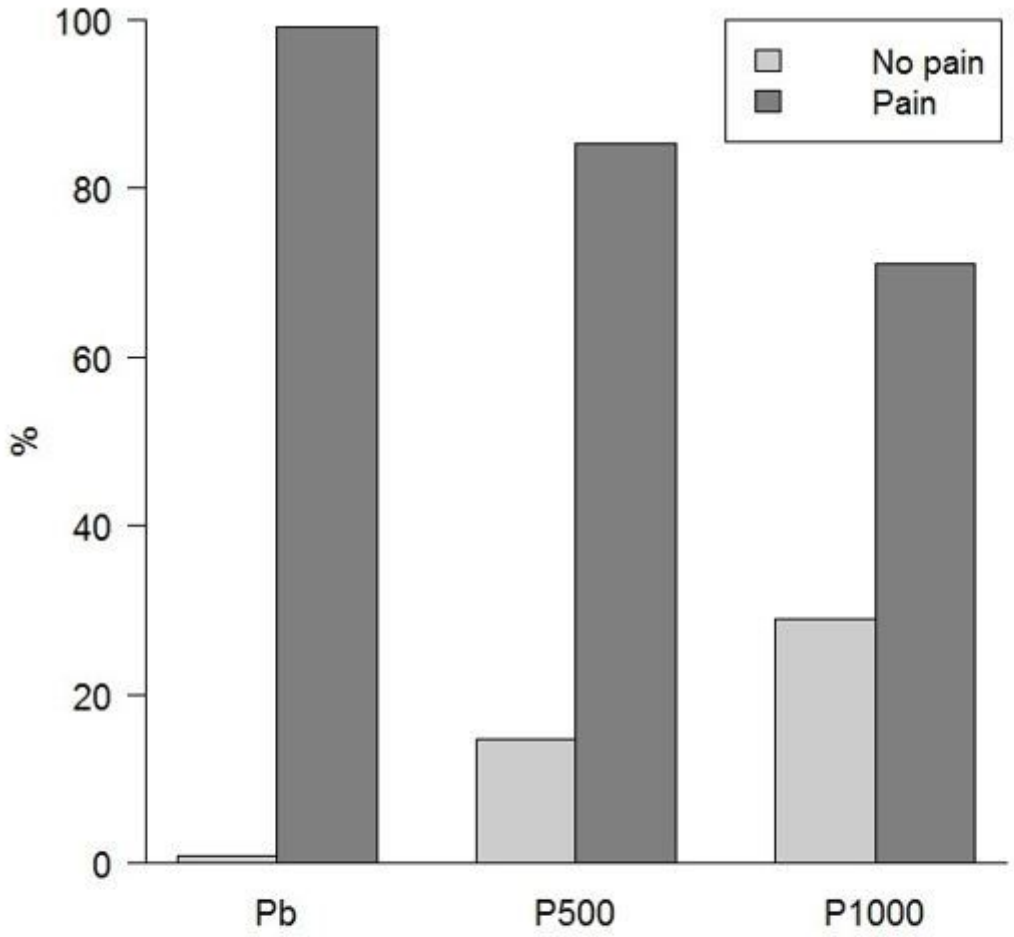


Figure 1

Consort flow diagram of this study

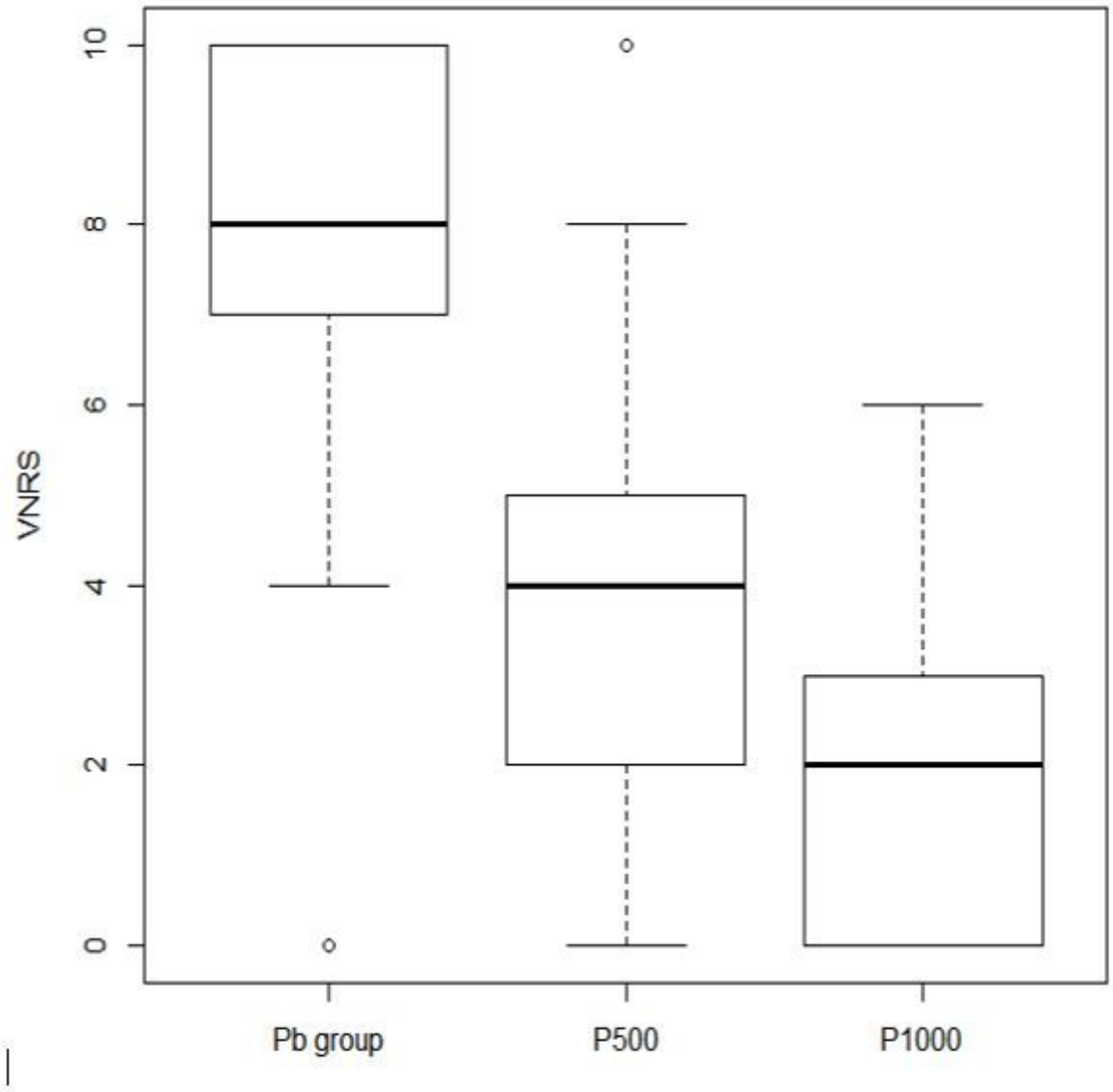


P-value <0.001

Pb = placebo, P500 = parecetamol 500 mg, P1000 = paracetamol 1000 mg

Figure 2

Incidence of injection pain among the 3 groups



P-value < 0.01

Pb = placebo, P500 = parecetamol 500 mg, P1000 = paracetamol 1000 mg

Figure 3

Median pain score with premedication

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplement1.doc