Analgesic effect of preoperative intravenous administration of paracetamol on post-cesarean pain: A randomized clinical trial

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Research article

Keywords: Cesarean Section, Pain, Paracetamol, Meperidine

Posted Date: April 2nd, 2020

DOI: https://doi.org/10.21203/rs.2.18913/v2

Abstract

Background: Pain control after every surgery, especially cesarean is very important, and physicians are striving to discover pain control methods using the least amount of opioid. Paracetamol is a non-opioid analgesic with few complications. The present study was aimed to investigate the analgesic effect of preoperative intravenous administration of paracetamol on post-cesarean pain.

Methods: This randomized double-blind clinical trial was conducted on 240 pregnant women under spinal anesthesia who were candidate for elective cesarean. The patients' weight, height, age and body mass index (BMI) were recorded, and patients were randomly divided into two equal groups (n=120). In the first group, 10 mg/kg paracetamol in 100cc normal saline (paracetamol group) and in the second group 100cc normal saline (control group) administered 15 minutes before surgery intravenously. Blood pressure, pulse rate, chills and nausea were recorded during and 1 hour after surgery, and pain visual analogue scale (VAS) and need for additional analgesic were recorded 1, 2, 4, 6, 12 and 24 hours after surgery.

Results : The mean scores of pain were significantly lower in paracetamol group (4.01±2.22) than control group 6 hours (4.83±2.35) (p=0.008) and 24 hours (2.26±1.85 and 2.67±1.80 respectably) (p=0.038) after surgery. Mean meperidine consumed was lower in paracetamol group than control group but not significantly. No significant difference was found between the two groups in frequency of chills and nausea (p>0.05).

Conclusions : Within the limitations of the current study, preoperative intravenous administration of paracetamol significantly reduced post-cesarean pain within 24 hours.

Trial registration: The proposal of present study approved by the Research Council of Rafsanjan University of Medical Sciences with No. 841 on 2016-11-08 and by the ethics committee of Rafsanjan University of Medical Sciences, with code IR.RUMS.REC.1395.115 on 2016-11-08 (prospectively registered), and approved by the Iranian Registry of Clinical Trial (IRCT) with code IRCT20150519022320N17 on 2019-01-18 (retrospectively registered). https://www.irct.ir

Background

The International Association for the Study of Pain has defined pain as an unpleasant feeling and mental experience associated with potential or real tissue damage. Pain is one of the most common symptoms and signs of diseases that informs an individual of a dysfunction in a part of his body (1). Following all surgical procedures, the patients experience pain unavoidable in various degrees (2).

On the other hand, cesarean is one of the most significant surgical procedures in obstetrics and gynecology (3) that is used as a strategy to save the lives of mother and child in difficult deliveries (4) and is currently a frequently used surgery (3). In cesarean section, there is acute pain due to complex physiologic reaction against to histological damage, visceral stretch and uterine contractions (5, 6). In

poor control and insufficient management of pain, some adverse effect may be occur on different body systems, such as inability to discharge secretions of respiratory system, increased blood pressure and heart rate and prolonged bed rest, thereby increasing the risk of deep vein thrombosis, delayed breastfeeding and inappropriate neonatal nutrition (7).

To relive post-cesarean pain, opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used (8). For a long time, opioids drugs were the main choice for postoperative pain relief (9). Pethidine (meperidine) is the most frequently used opioids during delivery. Meperidine bonds to the opioid receptors of central nervous system, so inhibits the ascending pain pathway and reduces the pain perception (10). But opioids are used less due to adverse effects such as respiratory depression, nausea, vomiting, slow gastrointestinal function and reduced consciousness, which delays rehabilitation and movement. Nowadays, various methods have been suggested for decreasing opioids use, one of them is use of non-opioid drugs along with or as a substitute to narcotic drugs (9).

Recently, paracetamol, which is an analgesic and antipyretic medication, is administered intravenously before, during and after surgery(9). Use of this drug before surgical insision (preemptive) has shown favorable effects on postoperative pain in different studies (9, 11). Unlike opioids, non-opioids analgesics have advantages such as lack of effect on breastfeeding, absence of respiratory weakness, absence of drug abuse potential, low narcotic effects, early return of bowel function and quicker improvement (12, 13).

Paracetamol, is a non-opioid antipyretic and analgesic drug (14, 15) that acts through inhibition of production of prostaglandins. It is one of the highly consumed drugs around the world (16). The onset of its analgesic effect ranges from 5 to 10 minutes, and its maximum effect is one hour, lasting from 4-6 hours (14, 15).

Given the significance of post-cesarean pain control as well as the side effects of opioid analgesics, this study was conducted to determine the preoperative analgesic effect of intravenous paracetamol on post-cesarean pain control.

Methods

The proposal of present study approved by the Research Council of Rafsanjan University of Medical Sciences with No. 841 on 2016-11-08 and by the ethics committee of Rafsanjan University of Medical Sciences, with code IR.RUMS.REC.1395.115 on 2016-11-08, and also approved by the Iranian Registry of Clinical Trial (IRCT) with code IRCT20150519022320N17 on 2019-01-18.

This randomized double-blind clinical trial conducted on 240 pregnant women aged 18-40 years referring to Niknafas maternity hospital in Rafsanjan, Iran for elective cesarean section. The sample size was determined based on the Jabalameli M study(17). Trial design was parallel and the allocation ratio was 1:1. The exclusion criteria consisted of patients with history of cardiovascular diseases, hypertension, diabetes, hepatic and renal failure, psychiatric disorders, specific drug-dependency, drug abuser, and

those prohibited from paracetamol or Meperidine consumption. Exclusion criteria confirmed through questionnaire before surgery. In addition, patients undergoing general anesthesia, receiving meperidine during surgery or having complicated surgery excluded from the study and replaced by new patients.

The study was carried out during 2017-2018. Patient medical history recorded and the study and pain severity measurement method, consumption drugs and their side effects were explained to the patients. Then, a questionnaire, including demographic information and research variables, was completed for each patient, and informed written consent was taken.

The patients who agreed to take part in the study were randomly assigned to two groups of paracetamol (n=120) and control (n=120). We used simple randomized pairing method. Patients with general entry conditions are divided into two groups by throwing coins. The operating room nurse determined the group of each patient and patient's group was recorded in their own record sheet. Surgeon, researcher and patient were not aware about the groups.

All patients kept NPO for 8 hours, during which time the hydration therapy was prepared according to the one, two and four rules using Ringer's solution (Shahid Ghazi pharmaceutical Co, Tabriz, Iran). Paracetamol group was administered intravenous 10 mg/kg paracetamol (Exir Pharmaceutical Co, Borujerd, Iran) dissolved in 100 cc normal saline (Shahid Ghazi, pharmaceutical Co, Tabriz, Iran) 15 minutes before surgery. The control group was administered 100 cc normal saline intravenously 15 minutes before surgery. The patients were blind to the type of group they were assigned to, either case or control. The drug administered by an out of research nurse before surgery, and the patient immediately transferred to the operative room. All patients received 10 cc/kg Ringer's solution before spinal anesthesia and were administered intravenous 10 mg metoclopramide (Daru Pakhsh Co, Tehran, Iran). Spinal anesthesia was performed by spinal needle no 25 (Dr. J, China) and 2.5 cc of Marcaine 5.0% (Mylan, France), totally 12.5 mg, in a sitting position. After performing spinal anesthesia and reaching appropriate anesthetic level (T4), cesarean section was carried out. If the Mean Arterial Pressure (MAP) drop more than 20% of base level, the patients received 5 mg Ephedrine (STEROP, Brussels, Belgium). When the baby was delivered, 1 mg midazolam (Tehran Shimi Co, Tehran Iran) was injected intravenously to all patients. A trained anesthetic technician recorded vital signs at baseline (after placement on the bed and doing anesthesia) and then every 15 minutes until the end of surgery and 1 hour after surgery, nausea, vomiting and chills during and after surgery. All patients underwent spinal anesthesia by one anesthesiologist and one surgeon did the operations. The surgeon and the anesthesiologist were out of research team.

After surgery, Visual Analogue Scale (VAS) were taught by the recovery nurse to the patient. Zero showed no pain and ten indicated the worst level of pain (18). VAS was recorded by trained nurses 1, 2, 4, 6, 12 and 24 hours after surgery. These nurses were blind to the patient groups. Pain score was determined by VAS scoring ruler (Figure 1). If VAS was >5, the patient was visited by a physician and, if prescribed, meperidine (25 mg) was administered by the nurse. Also, the mean dose of meperidine intake was recorded in the first 24 hours. The obtained data were analyzed by SPSS software using parametric and

non-parametric statistical tests (t-test, chi-square, Mann-Whitny). Significance level was determined $P<0.05$ for all analyzes.

Results

All study participants (both the intervention and the control group) received their own therapeutic interventions and remained in the study to the end. The number of participants excluded after the randomization was zero. Therefore, data of all participants was used in all analyzes. Mann-Whitney test was done for the following variables: scores of pain, Meperidine consumption, pulse rate and systolic and diastolic blood pressure.

The results of independent t-test showed no significant difference between the two groups in weight, height, age and BMI (table 1).

The findings of chi-square test showed no significance difference between paracetamol and control groups in frequency of post-surgery chills and nausea (table 2).

The results of statistical test revealed that the mean scores of pain at 6 and 24 hours after surgery were significantly lower in paracetamol group than control group. There was no significant difference between the two groups in the mean scores of pain at the other times. Figure 1 shows the changes of mean scores of pain in both study groups over time (table 3).

Meperidine consumption 24 hours after surgery was lower in paracetamol group than control group although difference between the groups was not statistically significant (table 4).

Mann-Whitney test indicated no significant difference between the two groups in mean pulse rate at all study times (table 5).

The results of statistical test showed no significant difference between the study groups at different times in terms of mean systolic blood pressure (table 6), but a significant difference was seen between two groups in diastolic blood pressure at 15 and 45 minutes after starting the operation (table 7).

There were no unwanted side effects in the participants in the two groups.

Discussion

This study was carried out on 240 pregnant women undergoing cesarean section. The results showed that since postoperative pain was a very common complication, especially in cesarean section, preoperative administration of intravenous paracetamol could have a significant analgesic effect, reduce the required meperidine after surgery. This result was obtained through measurement of postoperative pain in patients using VAS and the amount of post-cesarean meperidine administrations.

In the present study, paracetamol was administered as preemptive. The purpose of this method was to block pain receptors before painful stimulation. In Ong et al. and Arici et al. studies, paracetamol was administered in the same manner (9, 11).

Most studies have emphasized the analgesic effects of paracetamol. Kiliçaslan et al. compared the patients' post-cesarean pain score in two groups (n=25), one receiving intravenous paracetamol plus tramadol and one receiving tramadol alone. They concluded that pain score was lower in paracetamol group (19). Inal conducted a study on 50 patients under cesarean surgery and compared the analgesic effect of paracetamol and meperidine. They found that paracetamol led to reduction of pain score in the patients (20). Faize and colleagues were compared intravenous paracetamol and ketamine injection to control pain after abdominal hysterectomy. Pain score (VAS) was significantly lower in the paracetamol group, the highest difference being seen at 6 hours after surgery (21). This result is in agreement with the results of the present study. In another study, Ali and Khan compared the analgesic impact of tramadol plus paracetamol and tramadol alone on 60 patients undergoing laparoscopic surgery and they obtained the same results as presented above (22). Cattabriga et al. investigated the analgesic effect of paracetamol on postoperative pain in patients undergoing cardiac surgery and reported that intravenous paracetamol could induce appropriate analgesic effect in the patients (23). In all studies cited above, the frequency of administration and total dose of narcotic analgesic were reduced when paracetamol was administered. In our study, although the difference between the two groups was not statistically significant for meperidine intake, but clinically, meperidine administration was lower in the paracetamol group.

Vuilleumier et al. conducted a study in Switzerland in 1998 and compared the postoperative analgesic effect of paracetamol and morphine. They found that paracetamol could be used as a substitute to morphine to induce postoperative analgesia in moderate pain. They reported that morphine had a better short-term analgesic effect, but finally paracetamol had a longer analgesic effect (24). Nikoda et al. carried out a study in Russia in 2002 and examined the postoperative analgesic effects of Paracetamol on 30 patients. They concluded that paracetamol reduce the severity of postoperative pain (25). In another study, Emir et al. compared the analgesic effect of tramadol plus paracetamol and tramadol alone on the spinal surgery and reported a higher efficacy of paracetamol (26). Mofidi et al. also conducted a study on 80 patients with renal pain and found that intravenous paracetamol to be a safe and effective drug with no remarkable side effects in relieving pain in renal patients. Further, they reported paracetamol had a higher efficacy and fewer complications than tramadol in relieving the patients' renal pain (27).

In the present study, paracetamol was administered preoperatively and, although peak efficacy was 1 hour and duration of effect was 4 to 6 hours, pain score was significantly reduced at 6 and 24 hours postoperatively. In Arici et al. study, the effect of preoperative and end-of-operation injections of paracetamol was compared with the control group in abdominal hysterectomy. There was a significant difference between the pain scores of the two intervention groups and the control group. Although the difference of pain score was not significant in the two intervention groups, it was clinically lower in the

preemptive group than in the other group, and this effect remained for up to 24 hours. Morphine consumption was lower in the intervention groups than in the control group. The difference between the two intervention groups was statistically significant, Preoperative use was lower than the end-operative group (11). In this study, as our study, the analgesic effect of paracetamol was longer than the drug effect duration. Maybe these results caused by pain receptors blocking before painful stimulations. In addition, cutting off pain signals can prevent central nerves from becoming sensitive.

However, some studies have shown no significant difference between the analgesic effect of paracetamol and narcotic analgesics, such as the study of Van Aken et al. that compared the analgesic effects of paracetamol and morphine in dental surgery (28) and that of Rawal et al. which compared the analgesic effect of oral tramadol and intravenous paracetamol in outpatient surgeries (29). The differences between the results of these two studies with our and other results appear to be due to differences in the extent of surgery. However, in both of these articles, paracetamol had no weaker effect than the other two drugs.

In our study, the side effects such as nausea and chills were reported in both groups. Previous studies have mostly reported significantly fewer side effects in paracetamol group, due to reduced total dose of narcotic drug (30, 31).

Pain had a descending trend in both groups during the study period, which is in agreement with patient's gradual improvement and reduction of neural damages. Generally, pain level was different in both groups; pain reduction was greater in paracetamol group, this difference is statistically significant at 6 and 24 Hours after operation . This result is similar to some studies, such as Sinatra et al. study (2005) that investigated the effect and safety of single and repeated administration of 1g intravenous paracetamol for pain management following large orthopedic surgery (32), study of Olonisakin et al. (2012) on the saving effect of intravenous paracetamol on using morphine for postoperative pain control in women (31) and study of Iqbal (2009) on the analgesic level and quality of postoperative intravenous administration of paracetamol and reduction of narcotic requirement (33).

However, some studies like that of Uysal et al. (2011) on comparative analysis of efficacy of intravenous paracetamol versus tramadol for postoperative analgesia in pediatric adenotonsillectomy (34), study of Kiliçaslan et al. (2010) on the effect of intravenous paracetamol on postoperative analgesia and tramadol on cesarean section (19) and that of Lee et al. (2010) on the effect of paracetamol, ketorolac and paracetamol plus morphine on pain control after thyroidectomy showed no significant difference between the two groups in terms of pain reduction, the only advantage being quicker rehabilitation (35).

The present study found nausea and chills in both paracetamol and control groups although no significant difference was observed. Sanjar Mousavi and Khalili reported dizziness, nausea, headache, vomiting, sleepiness and immobility in both groups receiving paracetamol and opioid for postoperative pain relief, but no significant difference was observed between groups (36).

The findings of the present study indicated no significant difference between the two groups in systolic blood pressure in different measurement stages, during and after cesarean, but diastolic blood pressure 15 minutes after start of cesarean section was significantly lower in paracetamol group than control group. Further, diastolic blood pressure 45 minutes after starting of cesarean, was significantly lower in paracetamol group than control group. In a systematic review by Turtle et al. (2012), it was shown that in many studies paracetamol increased blood pressure, but in two studies, no effect was observed, and in one study, hypotension with paracetamol was observed. Therefore, they concluded that the effect of paracetamol on blood pressure was unclear (37). Based on the results of Beyzaee et al., systolic blood pressure changes in both groups underwent significant changes over time, reducing three hours after surgery and then rising again, but no significant difference was found between paracetamol and control groups with respect to systolic blood pressure. Similarly, their results showed significant changes in diastolic blood pressure over time in both groups, but the difference between two groups was not statistically significant (38). According to the results of the present study and the above mentioned studies, further studies on the effect of paracetamol on blood pressure seems to be needed.

Since the effects of a drug have been studied in this study and the drugs have specific pharmacogenetic effects, so the results of this study can be extended to other races and communities.

Conclusion

This study showed that preemptive intravenous administration of paracetamol induced great analgesic effects on post-cesarean pain and reduced the frequency and total dose of meperidine despite statistically insignificant difference. If future studies confirm this result, intravenous paracetamol can be used extensively as an adjuvant medication or even a substitute to opioids in cesarean.

List Of Abbreviations

BMI: Body Mass Index

VAS: Visual Analogue Scale

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

IRCT: Iranian Registry of Clinical Trial

NPO: Nil Per Os

MAP: Mean Arterial Pressure

Declarations

1. **Ethic approval and consent of participate**

The proposal of this study approved by the ethics committee of Rafsanjan University of Medical Sciences, with code IR.RUMS.REC.1395.115 on 2016-11-08.

2. **Consent for publication**

Not applicable

3. **Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

4. **Competing interests**

The authors declare that they have no competing interests.

5. **Funding**

Rafsanjan University of Medical Sciences funded this article. Funding was used to procure equipment, purchase medicines, reproduce questionnaires, and data analysis.

6. **Authors' contribution**

SHPM designed the study in the field of anesthesia and drug administration, MP was involved in selecting patients, describing research steps to patients, and assisting in writing articles, RG preformed statistical analysis, TMK was involved in completing the questionnaires, AR designed the questionnaire, SA also involved in completing the questionnaires and SMK designed the study in midwifery part and was write the articles. All authors have read and approved the manuscript.

Acknowledgment: The authors thank the Rafsanjan University of Medical Sciences for funding this research (proposal No. 841). Anesthesiology and maternity nursing staff helped us in this study, and we appreciate them for their cooperation. We also thank Doctor Foad Iranmanesh; assistant professor of Rafsanjan University of Medical Sciences for his help in the writing, editing and submitting the article.

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Tables

Table 1. Comparison of age, weight, height and BMI between paracetamol and control groups

P-Value	Total	Control	Paracetamol	Variable
	Mean±SD	Mean±SD	Mean±SD	
0.310	31.10±6.96	30.64±6.72	31.55±7.13	Age (year)
0.787	79.82±13.77	79.57±14.90	80.06±12.61	Weight (kg)
0.118	159.60±8.08	160.43±5.87	158.73±9.83	Height (m)
0.290	31.19±5.42	30.81±5.74	31.58±5.06	BMI

Table 2. Frequency of post-cesarean chills and nausea in pregnant women in paracetamol and control groups

P-Value	Total		Control		Paracetamol			Variable
	Percentage	Number	Percentage	Number	Percentage	Number	Index	
0.315	14.1	33	15.7	18	12.6	15	Yes	Chills
	85.9	201	84.3	97	87.4	104	No	
0.198	17.5	42	15	18	20	24	Yes	Nausea
	82.5	198	85	102	80	96	No	

Table 3. Mean and standard deviation of pain scores at different hours after surgery in paracetamol and control groups

24 hours	12 hours	6 hours	4 hours	2 hours	1 hour	Group
26±1.85	2.94±1.78	4.01±2.22	4.58±2.58	3.38±2.43	0.82±1.83	Paracetamol
67±1.80	3.37±1.92	4.83±2.35	5.13±2.36	3.87±2.45	0.72±1.48	Control
0.038	0.072	0.008	0.082	0.108	0.573	P-Value

Table 4. Mean consumption of pethidine 24 hours after surgery in paracetamol and control groups

Pethidine (mg) Mean±SD	Group
34.78±12.47	**Paracetamol**
40.53±58.12	**Control**
0.245	**P-Value**

Table 5. Mean and standard deviation of pulse rate at different hours after start of surgery in paracetamol and control groups

60 minutes	45 minutes	30 minutes	15 minutes	Group
95.40±12.66	93.78±14.00	96.62±17.75	91.21±19.87	Paracetamol
97.84±16.63	96.81±14.83	94.75±17.47	94.31±19.46	Control
0.499	0.094	0.428	0.397	P-Value

Table 6. Mean and standard deviation of systolic blood pressure at different hours after start of surgery in paracetamol and control groups

60 minutes	45 minutes	30 minutes	15 minutes	Group
106.81±14.18	103.17±14.38	99.83±20.66	107.67±20.36	Paracetamol
109.39±13.33	107.48±15.36	104.42±19.35	107.17±19.70	Control
0.228	0,053	0.273	0.786	P-Value

Table 7. Mean and standard deviation of diastolic blood pressure at different hours after start of surgery in paracetamol and control groups

60 minutes	45 minutes	30 minutes	15 minutes	Group
57.93±13.09	54.50±12.08	55.67±14.07	60.67±12.88	Paracetamol
58.20±13.17	57.63±13.31	57.81±14.74	63.42±12.73	Control
0.885	0.042	0.255	0.046	P-Value

Figures

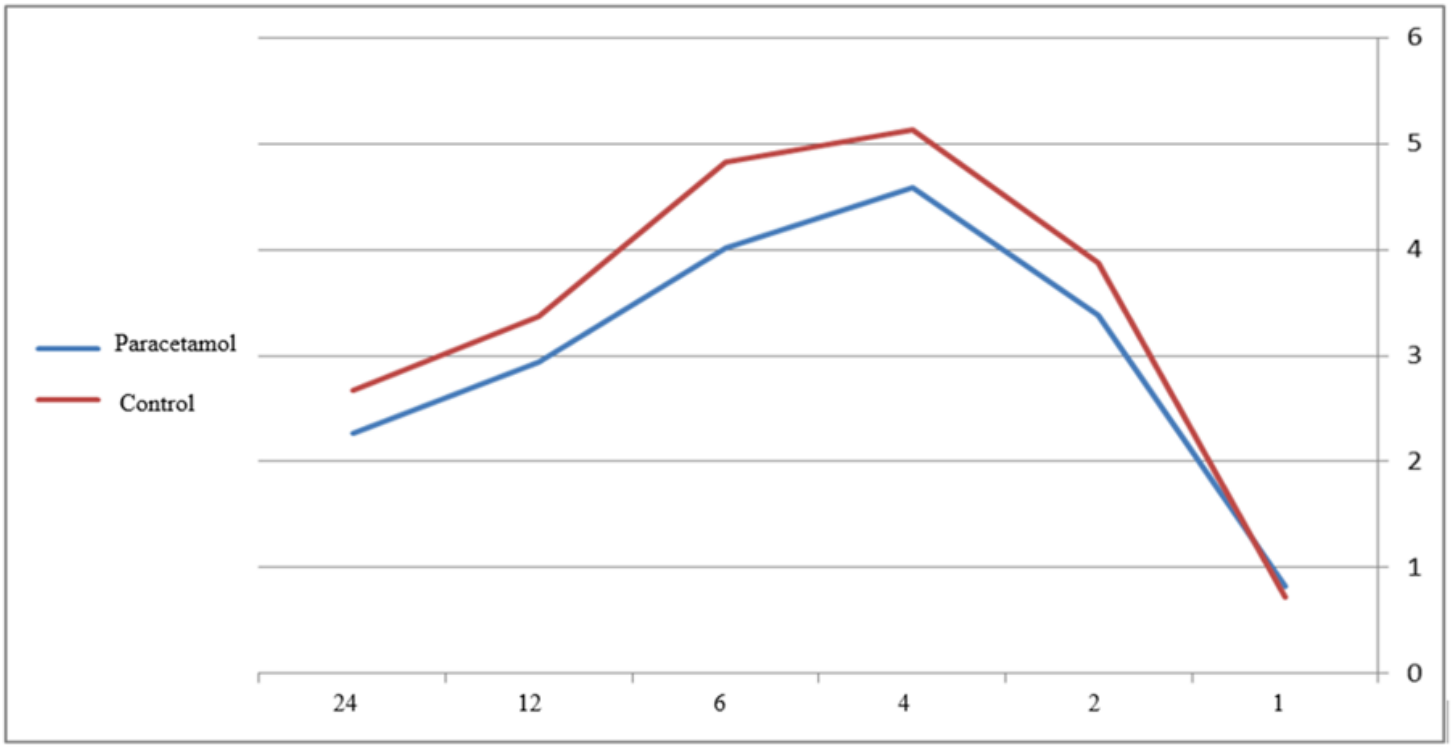

Figure 1

Mean of pain scores over time in paracetamol and control groups

Supplementary Files

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

- CONSORT2010Checklist.doc
- CONSORTFlowdiagram.docx