Original Article

Effect of timing of intraoperative administration of paracetamol on postoperative shivering: A randomised double-blind controlled trial

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ABSTRACT

Background and Aims: Paracetamol (PCM) has an anti-shivering effect and may also exacerbate intraoperative hypothermia. This study compares the incidence of shivering as the primary outcome and the incidence of perioperative hypothermia (<36°C) and the time to the analgesic requirement as secondary outcomes when PCM was administered after induction of anaesthesia or towards the end of surgery. **Methods:** In this randomised study, 225 adult patients of either gender undergoing elective surgical procedures under general anaesthesia with an expected duration of surgery of 1–4 h were studied. They received intravenous (IV) PCM 15 mg/kg (maximum 1 g) immediately after anaesthesia induction (Early PCM group), 30 min before completion of surgery (Late PCM group) or no PCM (Control group). IV morphine 0.1 mg/kg was administered for analgesia in all three groups. The Chi-square test and repeated measures analysis of variance followed by Tukey's test were used for statistical analysis. **Results:** The incidence of shivering was lower in Late PCM (12%) than in Early PCM (29.3%) ($P = 0.009$) and Control groups (30.6%) ($P = 0.005$). The incidence of postoperative hypothermia was also significantly lower in the Late PCM group than in the Early PCM ($P = 0.002$) and Control groups ($P = 0.016$). Early PCM and Control groups did not significantly differ. The number of patients requiring postoperative analgesia was smaller, and the time to the analgesic requirement was longer in Late PCM compared to other groups. **Conclusion:** Administration of IV PCM 30 min before completion of surgery results in a lower incidence of postoperative shivering and hypothermia when compared to PCM administered after induction of anaesthesia or no PCM.

Key words: Anaesthesia, hypothermia, paracetamol, perioperative, postoperative, shivering, temperature

INTRODUCTION

Postoperative shivering is very common after general anaesthesia (GA) and can lead to many side effects.[1-4] The mechanism may be thermogenic or non-thermogenic.[1-5] The core body temperature set point increases in the postoperative period, and shivering occurs to achieve this set point.[6] Intravenous (IV) paracetamol (PCM) has an anti-shivering effect by centrally mediated prostaglandin inhibition to decrease the hypothalamic temperature set point.[1] As it can decrease body temperature even in the absence of fever, it may be possible to exacerbate perioperative hypothermia in patients whose body temperature is not maintained in the normal range, thus reducing its effectiveness when administered before surgery.[6-8]

An extensive literature search did not reveal any study comparing the effect of different timings of

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IV PCM administration on postoperative shivering. Therefore, the present study was conducted with the primary objective of comparing the incidence of postoperative shivering with varying timings of IV PCM administration.

METHODS

This randomised, double-blind controlled trial was conducted following approval from the Institute Ethics Committee (vide approval number IEC-HR/2019/41/22, dated 16-10-2019) and trial registration at Clinical Trials Registry-India (CTRI/2019/11/022063, www.ctri.nic.in/). Written informed consent was taken from all the patients before inclusion in the study for participation in the study and use of the patient data for research and educational purposes. The patients were recruited from 21-11-2019 to 30-10-2021. This manuscript follows Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. The study was carried out in accordance with the Declaration of Helsinki, 2013 and good clinical practice.

In this study, 225 American Society of Anesthesiologists (ASA) physical status I/II adult patients of either gender undergoing elective surgical procedures performed under GA with expected duration of surgery between 1 and 4 h were studied. Those having body mass index (BMI) >35 kg/cm^2, evidence of liver dysfunction, history of allergy to PCM or body temperature >38°C or <36°C were excluded.

The patients were randomly allocated, using a computer-generated random number table, to one of the three groups of 75 patients each, who received either IV PCM 15 mg/kg (maximum 1 g) over 15 min immediately after anaesthesia induction (Early PCM group) or IV PCM 15 mg/kg (maximum 1 g) for 15 min approximately 30 min before completion of surgery (Late PCM group) or no PCM (Control group). The same volume of normal saline (NS) was infused 30 min before completion of surgery in the Early PCM group, immediately after anaesthesia induction in the Late PCM group, and after anaesthesia induction and before completion of surgery in the control group. Sequentially numbered opaque-sealed envelopes were used for allocation concealment.

The patients were premedicated with oral alprazolam 0.5 mg the night before and on the morning of surgery. In the operating room, routine monitoring included electrocardiography, non-invasive blood pressure and pulse oximetry. An 18-G IV cannula was inserted, and Ringer's lactate infusion started. The IV fluids stored in the operating room were used. Anaesthesia was induced with IV propofol 2 mg/kg, and IV vecuronium bromide 0.1 mg/kg was used to facilitate tracheal intubation. Analgesia was provided with IV morphine 0.1 mg/kg administered at the time of induction of anaesthesia. Anaesthesia was maintained with 70% nitrous oxide in 30% oxygen, minimum alveolar concentration (MAC) isoflurane of 1 and top-up doses of IV vecuronium bromide 0.02 mg/kg when required. Mechanical ventilation was adjusted to maintain end-tidal carbon dioxide levels of 30–40 mmHg.

The test infusions were prepared in a paediatric drip set by a person not involved in the study. The patient and the person observing the patient in the perioperative period were blinded to the group allocation. IV metoclopramide 10 mg was administered before reversal of residual neuromuscular blockade to prevent postoperative nausea and vomiting. Residual neuromuscular blockade was reversed using IV neostigmine 0.05 mg/kg and atropine 0.02 mg/kg, and the trachea was extubated.

The patient's core temperature was monitored using an infrared tympanic membrane thermometer (model 3000A by Kendall, China) before induction, after induction, every 15 min intraoperatively, before reversal of residual neuromuscular blockade, and every 30 min in the recovery room for 4 h. Operating and recovery room temperatures were recorded. All the patients were covered with forced air warmer (WarmTouch, Covidien, Mansfield, MA, USA) intraoperatively and single blanket postoperatively. They were observed for shivering, pain and any other postoperative complications. Shivering was assessed as Grade 0 = no shivering; Grade 1 = piloerection/peripheral vasoconstriction, no visible shivering; Grade 2 = muscular activity in one muscle group; Grade 3 = muscular activity in >1 muscle group, but not generalised; Grade 4 = generalised shivering.[9] Grades 3 and 4 were combined to represent the shivering episodes requiring treatment, and grades 1 and 2 were those not requiring treatment. Grades 3 and 4 were treated with IV tramadol 1 mg/kg; any recurrence was recorded and managed by active warming and extra blankets. Pain was assessed using 0-10 cm visual analogue scale (VAS) scores; VAS ≥4 was treated with slow diclofenac infusion. The study ended after a 4-h observation in the recovery room.

The primary outcome measure was the incidence of shivering, whereas the secondary outcome measures included the incidence of perioperative hypothermia (<36°C), time to analgesic requirement postoperatively and any postoperative complications.

Based on a pilot study conducted in 45 patients, the incidence of postoperative shivering following IV PCM 15 mg/kg administered after induction of anaesthesia was 50% in our patient population. Considering a reduction in the incidence by 50% (25% incidence) following IV PCM administration towards the end of surgery as clinically significant, the sample size required to detect this reduction at a 5% level of significance and 80% power was 73 patients per group. Thus, a total of 225 patients, 75 in each group, were studied. This sample size was obtained using a two-sample proportion formula after adjusting the value of Z to account for Bonferroni correction, as there are three groups. The two-sample proportion formula was applied in the software GPower3.1 (Franz Faul, Universitat Kiel, Germany). Data was analysed using Statistical Package for the Social Sciences (SPSS) statistics software version 20.0 (Armonk, NY: IBM Corp, USA). Incidence of shivering, hypothermia and postoperative complications were analysed using the Chi-square test. Repeated measures analysis of variance followed by Tukey's test was applied for haemodynamic parameters, temperature changes and pain scores. A value of $P < 0.05$ was considered statistically significant.

RESULTS

A total of 242 patients were screened, out of which 17 were excluded [Figure 1]. The demographic parameters, duration of anaesthesia, baseline haemodynamic parameters and temperatures of operating and postoperative rooms were comparable in the three groups [Table 1].

There was no significant difference in the temperature values of the patients in all three groups in intraoperative and postoperative periods [Figures 2 and 3]. The incidence of intraoperative hypothermia was comparable in the three groups [Table 2]. The incidence of postoperative hypothermia was significantly lower in the Late PCM group than in the Early PCM and the Control groups. In contrast, the difference between Early PCM and Control groups was statistically not significant [Table 2]. Similarly, the overall incidence of shivering and shivering requiring treatment was lower in the Late PCM group than in the Early PCM and Control groups [Table 2]. Early PCM and Control groups had no statistically significant difference [Table 2].

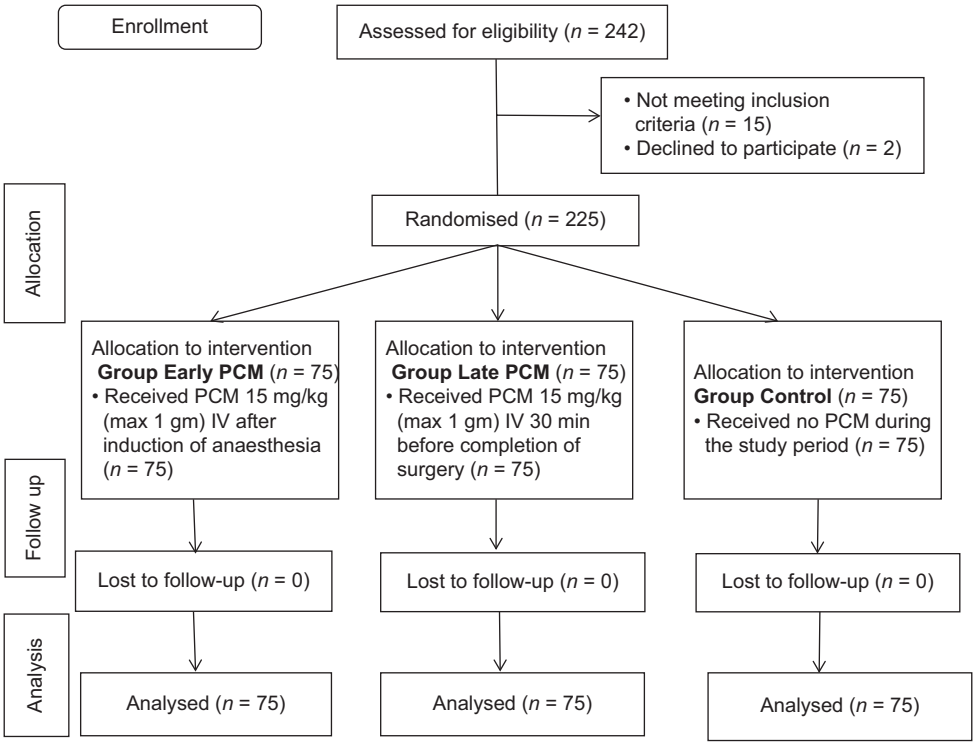

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) flow diagram for patient recruitment. PCM=Paracetamol, IV=Intravenous

Table 1: Patient characteristics

Parameters	Early PCM Group (*n*=75)	Late PCM Group (*n*=75)	Control Group (*n*=75)
Age (years)	36.7 (10.6)	38.8 (12.2)	36.2 (12.5)
Weight (kg)	61.6 (9.8)	61.9 (11.1)	61.9 (9.4)
Gender (male: female)	10:65	15:60	22:53
Duration of anaesthesia (min)	112.7 (32.2)	111.1 (40.4)	117.1 (46.0)
Baseline heart rate (bpm)	81.8 (12.9)	83.8 (12.2)	83.1 (12.6)
Baseline systolic blood pressure (mmHg)	125.9 (16.2)	125.4 (13.0)	124.8 (12.7)
Baseline diastolic blood pressure (mmHg)	77.6 (10.6)	76.6 (6.4)	76.5 (8.3)
Temperature of operating room (°C)	26.1 (2.6)	25.9 (2.5)	25.7 (2.2)
Temperature of postoperative room (°C)	25.7 (2.7)	25.9 (2.7)	25.2 (2.5)

Data are expressed as mean (standard deviation) or numbers. PCM-paracetamol, n=number of patients

Table 2: Incidence of hypothermia and shivering

Parameters	Early PCM Group (*n*=75)	Late PCM Group (*n*=75)	Control Group (*n*=75)	*P*
Intraoperative hypothermia	45 (60%, 48.9–71.1%)	38 (50.6%, 38.9–62.4%)	43 (57.3%, 45.4–68.7%)	0.415
*Postoperative hypothermia	22 (29.3%, 19.4–40.9%)	7 (9.3%, 3.8–18.3%)	18 (24%, 14.9–35.3%)	0.008
†Patients having shivering	22 (29.3%, 19.4–40.9%)	9 (12%, 5.6–21.6%)	23 (30.6%, 20.5–42.4%)	0.012
Patients having shivering grades 1 and 2	2 (2.6%, 0.3–9.3%)	2 (2.6%, 0.3–9.3%)	4 (5.3%, 1.5–13.1%)	0.595
‡Patients having shivering grades 3 and 4	20 (26.6%, 17.1–38.1%)	7 (9.3%, 3.8–18.3%)	19 (25.3%; 16.0–36.7%)	0.013

Values are numbers (%, 95% confidence interval). *Late PCM vs. Early PCM: *P*=0.002; Late PCM vs. Control: *P*=0.016; Early PCM vs. Control: *P*=0.460. †Late PCM vs. Early PCM: *P*=0.009; Late PCM vs. Control: *P*=0.005; Early PCM vs. Control: *P*=0.858. ‡Late PCM vs. Early PCM: *P*=0.005; Late PCM vs. Control: *P*=0.009; Early PCM vs. Control: *P*=0.852, n=number of patients

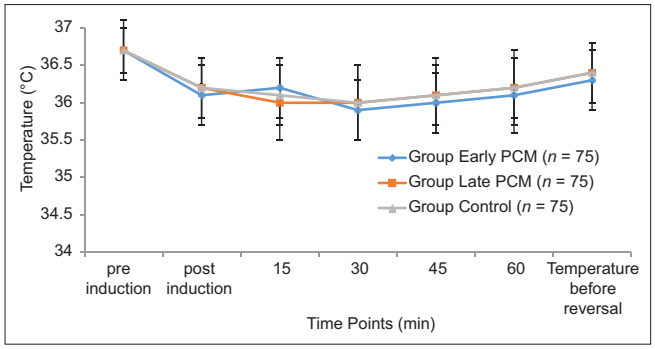

Figure 2: Trends of patient temperatures in three groups in the intraoperative period. *P* > 0.05 at all time intervals. PCM=Paracetamol

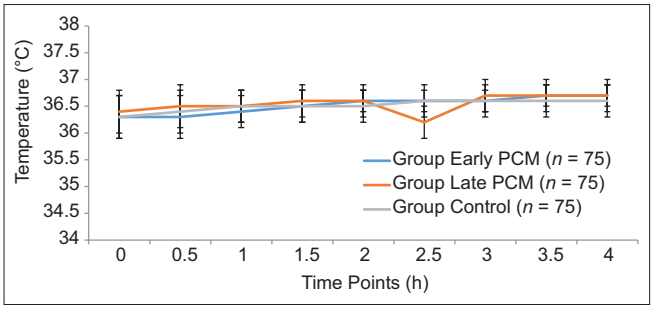

Figure 3: Trends of mean patient temperatures in three groups in the postoperative period. *P* > 0.05 at all time intervals. PCM=Paracetamol

Immediately after shifting to the postoperative room, the heart rate was significantly higher in the control group compared to the Late PCM group ($P = 0.013$). There was no statistically significant difference in intraoperative heart rate, blood pressure and postoperative blood pressure among the three groups at any time. Immediately after shifting the patient to the postoperative area, VAS scores were lower in the Late PCM group than in the other two groups. After that, till 90 min, these were significantly lower in the Late PCM group than in the Control group.

Out of 75 patients, 58, 48 and 62 in Early PCM, Late PCM and Control groups respectively required postoperative analgesia during the 4 h study period ($P = 0.010$). The Late PCM group had a longer time to analgesic requirement (Late vs. Early PCM group, $P = 0.026$; Late PCM vs. Control group, $P = 0.001$). The difference between Early PCM and Control groups did not achieve statistical significance ($P = 0.238$). Seven, five and four patients developed nausea/vomiting in Early PCM, Late PCM and Control groups, respectively ($P = 0.624$).

DISCUSSION

In the present study, the administration of IV PCM 30 min before completion of surgery resulted in the minimum incidence of postoperative shivering, minimum hypothermia, longer time to analgesic requirement and similar incidence of complications, when compared to PCM administration after induction of anaesthesia or no PCM administration. PCM administered immediately after induction of anaesthesia did not have any significant advantage over the control group regarding the incidence of postoperative shivering and hypothermia.

The role of PCM in preventing postoperative shivering is through centrally mediated prostaglandin inhibition to decrease the hypothalamic temperature set point.[1] Surgical stress may increase thermoregulatory set point in the postoperative period,[5,10] associated with increased interleukin (IL)-6 levels.[5] PCM has been shown to reduce post-surgical stress by lowering IL-6 levels[11] and decreasing thermoregulatory set point. The onset of action of its anti-shivering property is similar to that of analgesic property.[12] Regarding the effect on body temperature, the peak reduction in core body temperature has been demonstrated at 120 min after administration of oral PCM 20 mg/kg to normothermic individuals exposed to an environment beneath the thermal neutral zone.[7]

The peak hypothermic action of PCM is about 120 min. Thus, in Early PCM group, although PCM must have exerted an anti-shivering effect, at the same time, its hypothermic action, along with anaesthesia-induced hypothermia and other factors causing a fall in core body temperatures like operating room temperature or surgery-related factors would have added up together and resulted in hypothermia and thus shivering in a large number of patients. In the Late PCM group, where PCM infusion was started 30 min before and finished about 15 min before surgery, its analgesic and anti-shivering effect came into effect without significant hypothermic effect, reducing the incidence of hypothermia and shivering. The PCM-induced hypothermia was not seen in the postoperative period as the intraoperative factors contributing to the reduction in core body temperature, like the anaesthetic agents, were eliminated. In the Control group receiving no PCM, the number of patients who shivered was high as these patients did not receive any drug to prevent shivering.

Administration of PCM towards the end of the surgery has been reported to have an anti-shivering effect in patients undergoing septoplasty[13] and during caesarean section under GA.[14] However, some researchers have also demonstrated PCM's efficacy after anaesthesia induction.[1,15] Kinjo *et al*.[1] administered PCM 15 mg/kg or 0.9% saline IV over 15 min after induction of anaesthesia in 37 women undergoing gynaecological laparotomy. The incidence of severe postoperative shivering was significantly lower in the PCM group. However, the anaesthetic technique used in this study was quite different from ours. The anaesthesia was combined with an epidural. IV fentanyl was given for GA, and inhalational anaesthetic agents were not used. Their study was terminated 2 years after its initiation with a much smaller number of patients studied than the estimated number. Moreover, the test drug was repeated if the duration of surgery was longer than 4 h. The mean duration of surgery in this study was more than 4 h; thus, most of their patients must have received the repeat PCM dose, thus making the comparison of this study with ours difficult. Another study reported a lower incidence of shivering following pre-induction PCM infusion than the control group.[15] However, the core and peripheral body temperatures were lower in the PCM group. Moreover, the intensity of shivering was not mentioned, and the degree of reduction in the mean pethidine requirement for treating shivering did not appear clinically significant.

PCM is administered routinely as part of multimodal analgesia during surgery. The current study supports this practice but presents evidence to administer PCM towards the end of surgery to maximise its benefits by providing an anti-shivering effect and good postoperative analgesia.

The strength of our study is that, to the best of our knowledge, this is the first one to compare the effect of different timings of PCM administration on the prevention of postoperative shivering. However, it has certain limitations also. First, only procedures for 1–4 h were included. Therefore, these results may not apply to procedures lasting longer than 4 h. Second, the ambient operating and postoperative room temperatures should ideally be maintained between 22°C and 24°C; these could not be strictly maintained within this range in some cases due to unavoidable circumstances. However, the mean ambient temperatures were similar in all the groups and were not expected to confound the results.

CONCLUSION

The administration of intravenous paracetamol 30 min before completion of surgery results in a lower incidence of postoperative shivering and hypothermia and provides a better analgesic effect than the administration of paracetamol after induction of anaesthesia or no paracetamol.

Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' institution policy.

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Conflicts of interest
There are no conflicts of interest.

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