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Intravenous paracetamol as adjunctive treatment for postoperative pain after cardiac surgery: a double blind randomized controlled trial

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Abstract

Background: Nonsteroidal anti-inflammatory drugs and opioids are routinely used after cardiac surgery in order to mitigate postoperative pain; however, these drugs are burdened by side effects. Tramadol and paracetamol are believed to be lacking in such side effects. The aim of this study was to examine the efficacy of intravenous paracetamol as an adjunctive analgesic to a tramadol-based background analgesia after cardiac surgery. **Methods:** A total of 113 patients participated in this single center, placebo-controlled, double-blind, randomized trial. Fifty-six patients were randomized to receive paracetamol and 57 to placebo. Intravenous study drug (1 g) was administered 15 min before the end of surgery and every 6 h for 72 h. Standard analgesia (tramadol) and anti-emetic prophylactic regimen (ondansetron) were available to both patient groups. Postoperative pain was evaluated by visual analog scale, and it was measured at rest and during a deep breath. A rescue dose of 2—5 mg of intravenous morphine was administered whenever the VAS score was greater than 3. **Results:** Baseline characteristics were equivalent between the two groups. At 12, 18, 24 h after the end of operation, patients who received paracetamol had significantly less pain at rest ($p = 0.0041$, 0.0039, 0.0044, respectively); after this time the two groups did not differ. During a deep breath the difference was significant only at 12 h ($p = 0.0040$). Paracetamol group required less cumulative morphine than placebo group (48 mg vs 97 mg) even if the difference did not reach statistical significance ($p = 0.274$). **Conclusions:** In patients undergoing cardiac surgery, intravenous paracetamol in combination with tramadol provides effective pain control.

Keywords: Postoperative pain; Analgesia; Cardiac surgery

1. Introduction

After cardiac operations patients experience incisional pain associated with sternotomy, chest tube insertion, and eventual leg vein incision [1]. Postoperative pain can be the cause of a number of adverse sequelae such as myocardial ischemia [2], respiratory insufficiency [3], and thromboembolic complications [4]. Opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) are administrated parenterally as analgesics in the early postoperative period to alleviate such pain [5]. However, the efficacy of these analgesic drugs is limited by side effects that impede patient rehabilitation after surgical intervention. Opioids, such as morphine, may be associated, with respiratory depression, excessive sedation, biliary spasm, depression of gastrointestinal motility, nausea and vomiting (PONV), and, particularly in older patients, confusion [6]; parenteral NSAIDs, such as ketorolac, may be associated with gastrointestinal lesion ulceration, renal dysfunction, and bleeding caused by platelet inhibition [7].

There is therefore a need for drugs or combinations of drugs not presenting these drawbacks.

Paracetamol (acetaminophen), now also available for intravenous use, is not an NSAID and interferes neither with platelet nor kidney functions, nor does it present the unwanted side effects of NSAIDs. Tramadol is a centrally acting analgesic, which, unlike traditional opioids, does not depress respiration or provoke sedation. In the specific field of cardiac surgery, various studies have been carried out on the use of the intravenous prodrug propacetamol and oral acetaminophen, but so far only two studies — both from the same group of authors — have described intravenous paracetamol use in cardiac surgery [8,9]. Equally, very few studies have been carried out on the use of tramadol in adult cardiac surgery [10—12]. Although the combination of

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paracetamol and tramadol orally administered has been extensively studied, their intravenous combined use has never been reported.

The aim of this study was therefore to examine the efficacy of intravenous paracetamol in a prospective, double-blind, randomized, controlled trial comparing paracetamol administration with placebo as an adjunct to tramadol following cardiac surgery carried out with midline sternotomy.

The primary end-point of the study focused on postoperative pain evaluated using a standard visual analog scale (VAS). We hypothesized that paracetamol reduces postoperative pain following cardiac surgery. We also investigated the morphine consumption and the incidence of PONV.

2. Materials and methods

2.1. Patients

This study was a double-blind, randomized, controlled trial. It was approved by the Ethics Committee of the Healthcare Trust of the Sant'Orsola-Malpighi University Hospital, Bologna, Italy. All the patients were informed and gave written consent. Eligible subjects consisted of patients undergoing non-emergency cardiac operations carried out with a standard midline sternotomy, with harvesting of saphenous vein and internal thoracic artery if indicated.

Preoperative exclusion criteria were the following: age less than 18 years and more than 80 years; body mass index $>$40 kg/m^2; left ventricle ejection fraction $<$35%; serum creatinine $>$2.0 mg/dl; serum bilirubin $>$1.8 mg/dl; aspartate aminotransferase or alanine aminotransferase $>$1.5 of the upper limit of normal; any coagulopathy, recent ($<$7 days) myocardial infarction, uncontrolled diabetes; patients with stroke or transient ischemic attack within 6 months, severe respiratory insufficiency and New York Heart Association class 4.

2.2. Anesthesia

All patients enrolled in the study received a standardized anesthesia regimen. The anesthetic drug doses were calculated according to body weight. Petidine 50—100 mg and atropine 0.5—0.75 mg were given intramuscularly as premedication 45 min before surgery. Anesthesia was induced with propofol 1—1.5 mg kg^{-1}, remifentanil 0.1 μg^{-1} kg^{-1} min^{-1} and cisatracurium 70—100 μg kg^{-1}. Maintenance of anesthesia was achieved with a continuous infusion of propofol 2—4 mg^{-1} kg^{-1} h^{-1}, remifentanil 0.1 μg^{-1} kg^{-1} min^{-1}, and cisatracurium 2—3 μg^{-1} kg^{-1} min^{-1} and inhaled desflurane.

Antegrad intermittent cold crystalloid cardioplegia was used, and the patients were cooled at 34 °C and rewarmed to 37 °C before decannulation. Propofol sedation (2—4 mg^{-1} kg^{-1} h^{-1}) was continued in the Cardiovascular Intensive Care Unit until the patient's skin temperature was 32 °C, after which it was discontinued, and weaning from mechanical ventilation was started.

2.3. Study protocol

Study patients were randomized preoperatively to receive either paracetamol or placebo after surgery. A randomization list was generated using a computer program. The placebo (100 ml of normal saline) and paracetamol (1 g = 100 ml) medications were prepared by the hospital pharmacy and appeared identical. Medication administration and data collection were performed in a double-blind manner, so that neither patients nor healthcare personnel were aware of the medication assignment. The coding remained blinded until the end of the study. All patients received 12 doses of the study drugs at 6 h intervals (i.e., for 72 postoperative hours). The first dose of the drug was given i.v. at the end of intervention, during the skin suture, and before interruption of remifentanil infusion.

In addition to the study medication, a standard analgesic regimen was available to all the patients. This consisted of a loading dose of 200 mg of tramadol administrated i.v. in 30 min just before the administration of the first dose of study drug, followed by a continuous infusion of 300 mg of tramadol during a 24 h period. The tramadol was started at the end of intervention and was continued for 72 h.

Postoperative pain was evaluated using a standard 10 cm visual analog scale (VAS). Patients were familiarized with the scale preoperatively, and postoperative pain was assessed using this scale on days 1—3. When the patients were awake and tracheally extubated, pain was assessed four times daily at rest and during a deep breath.

A rescue dose of 2—5 mg of intravenous morphine was administrated if VAS at rest was greater than 3 (maximum dose per day 10 mg). Even though the infra-additive effect of the combination of tramadol and morphine has been reported [13], we preferred using morphine as the rescue drug rather than an NASID because we judged that the side effects of opioids are more controllable than those of NASIDs. A standard anti-emetic prophylactic regimen (8 mg of intravenous ondansetron every 24 h, the first dose of which at the induction of anesthesia) was available to both the patient groups.

2.4. Statistical analysis

Data were analyzed with SPSS version 13.0 software (SPSS Inc., Chicago, IL) and STATA v. 9. Continuous data are presented as a median and range (min—max) and were compared between groups using a Mann—Whitney test. A Pearson χ^2-test was used for categorical data. VAS score were compared between groups across time intervals using a Mann—Whitney test with Bonferroni correction for multiple comparisons: for each parameter depending on time intervals, the alpha level of each individual test is divided by the number of observation to ensure that the overall type one error remains 0.05. Analyses were conducted on an intention-to-treat basis. All patients who were randomized were included in the analysis.

3. Results

3.1. Patients

One hundred and thirteen patients were randomized (56 paracetamol, 57 placebo). Preoperative characteristics and intraoperative data did not differ significantly

Table 1
Baseline and perioperative data

	Paracetamol	Placebo	p
Weight (kg)	75 (45—109)	75 (51—100)	n.s.
Height (cm)	170 (159—182)	166 (150—186)	n.s.
Age (years)	67 (45—79)	69 (20—84)	n.s.
Gender (m/f)	40/16	41/16	n.s.
Ejection fraction	62 (30—80)	60 (45—70)	n.s.
Cardiopulmonary bypass time (min)	113 (63—342)	115 (68—174)	n.s.
Aortic cross-clamp time (min)	89 (36—148)	88 (41—147)	n.s.
Duration of anesthesia (min)	311 (198—420)	319 (225—438)	n.s.
Extubation time (h)	5.0 (0—18)	5 (0—51)	n.s.

Values are expressed as median (min—max).

between the groups (Table 1). Seven patients from the placebo group and five patients from the paracetamol group were withdrawn from the study prematurely. Within the placebo group, patients were withdrawn for the following reasons: data sampling errors (one patient); insertion of intra-aortic balloon pump (one patient); reoperation because of excessive chest tube output (one patient); need of high doses of inotropes (two patients); and protocol violations (two patients). Within the paracetamol group patients were withdrawn for the following reasons: convulsion (one patient); migraine (one patient); reoperation because of excessive chest tube output (one patient); and protocol violations (two patients). Following were the protocol violations: in two cases the nurse did not evaluate the VAS; in one case the pharmacy did not prepare the sample within a given time; and in one case the flasks fell and six of them were broken.

The type of intervention is listed in Table 2.

3.2. Postoperative pain

Patients who received paracetamol had significantly less pain at the time point of 12 h [1 (0—6) vs 2 (1—10) $p = 0.0041$], 18h [1 (0—5) vs 2 (0—8) $p = 0.0039$], and 24 h [1 (0—5) vs 2 (0—8) $p = 0.0044$]. The pain scores progressively decreased in both groups over the time, and there was no significant difference in pain 30—72 h after operation (Fig. 1). During a deep breath the paracetamol group had significantly less pain than placebo group only 12 h after operation: VAS 2 (1—6) versus 3 (1—10) $p = 0.004$ (Fig. 2).

Table 2
Type of intervention

	Paracetamol	Placebo	Total
Bentall	7	6	13
Bentall + CABG	2	1	3
CABG	15	15	30
Mitral valve repair or replacement	7	10	17
Aortic valve replacement	13	18	31
Aortic valve replacement + CABG	3	5	8
Mitro-aortic replacement	6	—	6
CABG off pump	—	1	1
Mitral valve replacement + CABG	—	1	1
Other	3	—	3
Total	56	57	113

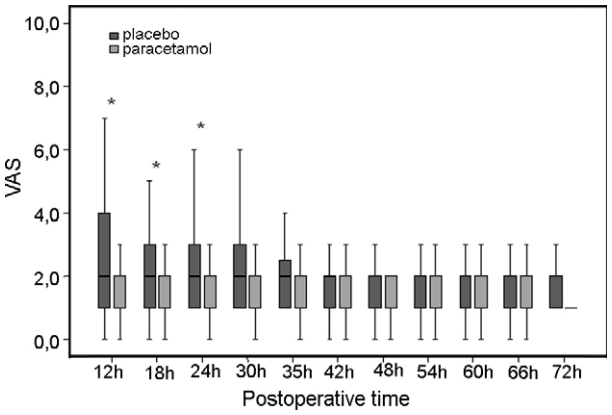

Fig. 1. Time course of visual analog scale (VAS) pain scores at rest. Values are expressed as median. (*) $p < 0.05$.

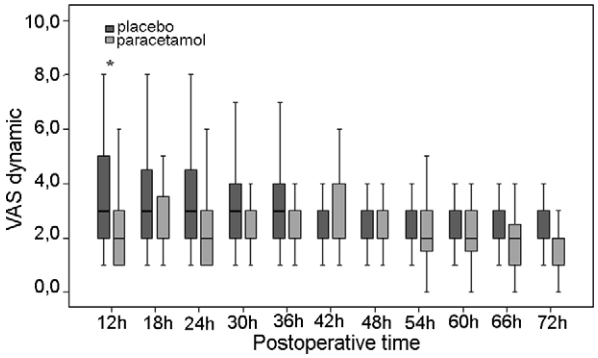

Fig. 2. Time course of visual analog scale (VAS) pain scores during a deep breath. Values are expressed as median. (*) $p < 0.05$.

3.3. Consumption of morphine

Postoperative cumulative morphine consumption was low in both groups. It was less in the paracetamol group than in the placebo group (48 mg vs 97 mg during the first 3 days), but the difference was not significant: median 5 mg (2—10) versus 5 mg (5—15) $p = 0.273$. Patients who received rescue doses of morphine were 8 (14.2%) in the paracetamol group and 14 (24.5%) in the placebo group ($\chi^2 = 1.363$ ($p = 0.254$)).

3.4. PONV

PONV was a very unusual adverse event: it was observed in three patients (6%) of paracetamol group and in one patient (2.12%) of placebo group).

3.5. Cardio-respiratory parameters

Hemogasanalysis, and systolic arterial pressure, did not differ in both groups over the 72-h study (Table 3). Respiratory frequency tended to be higher in the placebo group than in the paracetamol group, but the difference resulted as significant only at 12 h from the end of the intervention ($p = 0.019$) (Fig. 3). Analogously, cardiac frequency resulted as higher for all of the period of the study, but the difference only resulted as significant at 12 h from the intervention ($p = 0.0012$) (Fig. 4).

Table 3
Hemogasanalysis

	PaO_2		$PaCO_2$	
	Paracetamol	Placebo	Paracetamol	Placebo
12 h	238 (85–492)	291 (84–520)	41 (21–50)	41.7 (32–55)
24 h	231 (99–400)	155 (69–329)	43 (35–51)	42.6 (32–55)
48 h	120 (80–311)	119 (68–272)	42 (34–50)	42 (36–52)
72 h	98 (80–190)	100 (52–263)	44 (39–97)	41 (35–55)

Values are expressed as median (min–max).
No statistical significant difference in patient groups over 72 h.

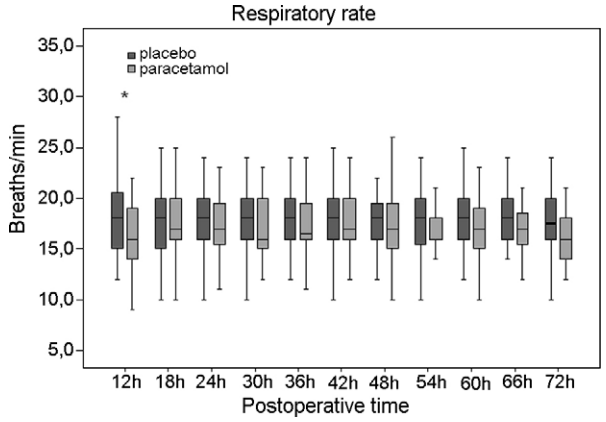

Fig. 3. Time course of respiratory rate. Values are expressed as median. (*) $p < 0.05$.

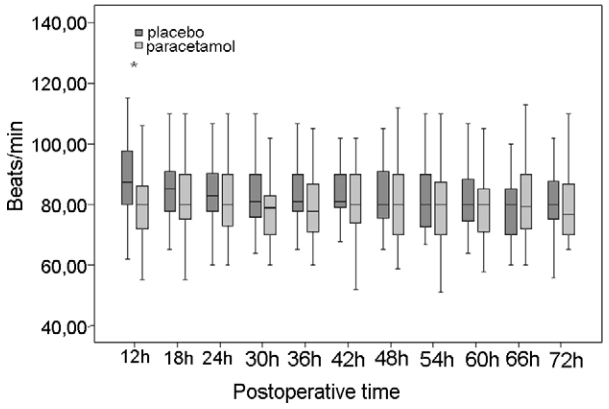

Fig. 4. Time course of heart rate. Values are expressed as median. (*) $p < 0.05$.

4. Discussion

With the advent of fast-track anesthesia techniques, the need for controlling postoperative pain has also become a prime necessity in cardiac surgery, both for the patient's well-being and for avoiding negative consequences provoked by the pain itself. The drugs habitually used toward this are opioids and NSAIDs, both of which have potentially harmful side effects.

Balanced analgesia is a validated concept in the post-operative period and is recommended by guidelines and publications [14,15]. The association of analgesic drugs is expected to improve pain relief and limit the incidence and severity of the side effects of each drug [16].

We studied a combination of drugs, tramadol, and paracetamol, which should present fewer side effects than traditional drugs.

Tramadol is a centrally acting analgesic with a double-action mechanism: one based on the μ-receptor link and the other on serotonin and noradrenalin reuptake inhibition at the central synaptic level [17]. Unlike traditional opioids, it does not interact with either hemodynamic or respiratory function. Furthermore, tramadol does not cause the appearance of tolerance, so it is therefore unnecessary to increase the dosage to maintain the analgesic effect over time [12]. Paracetamol readily prepared in solution has only recently become available, so the literature is still scarce. In any case, a bioequivalence study has shown that 1 g of paracetamol is bioequivalent to 2 g of propacetamol and is safer at the local level [18]. At recommended dosages, paracetamol is not associated with the increased incidence of nausea, vomiting and respiratory depression observed with opioids [19]. Furthermore, paracetamol, due to its different action mechanism, interferes with neither platelet nor kidney function. Paracetamol's analgesic action is not clear although its central-level action has been hypothesized.

The data from our study have highlighted the fact that paracetamol has a good analgesic action: In the first 30 h of the study the at-rest and, to a lesser extent, deep-breath VAS scores are significantly lower in the treatment group as opposed to that of the placebo group. These data are in contrast to those of Lahtinen et al. [6], who found that propacetamol had no analgesic effect. We believe that this could be due to the fact that these authors performed a post hoc analysis only regarding the consumption of oxycodone (which indeed resulted as significantly lower in the treatment group with respect to the placebo in the first 24 h after the intervention) and did not perform the same investigation on the VAS scores, therefore it may not be excluded that the patients, in the first 24 postoperative hours, had less pain than the others. After the first postoperative day the two groups no longer differ: this can be explained by the fact that pain gradually tends to exhaust itself the further one gets from the intervention, and the analgesic supplied by tramadol is enough to soothe the pain. In our patients tramadol showed a good analgesic action to the degree that only 24% of the placebo group patients requested a rescue dose of morphine.

Unlike Petterson et al. [8,9], who reported an incidence of PONV of 41% and Lahtinen et al. [6] of 62%, PONV was a very rare adverse event (4%) in our patients. Our data are also very different from those of Aouad et al. [20], who found no significant difference between placebo, ondansetron, and haloperidol administrated as PONV prophylactics after gynecological interventions. This datum is also surprising for us. It has already been reported that tramadol in continuous infusion, rather than in boluses, has a much lesser prometic effect [12]. The method of tramadol administration, combined with a low morphine consumption and higher doses of ondansetron, may be the reason of such discrepancies. However, further studies are required to confirm, or deny, this datum.

The patients receiving placebos had, 12 h after the intervention, respiratory and cardiac frequencies significantly higher than the group receiving paracetamol. This

could indicate that the patients treated with paracetamol had a better analgesia.

The following are the limitations of this study:

(1) the primary end point was the measurement of pain intensity experienced subjectively by the patient and the nurse, whereas the consumption of opioids administered with patient controlled analgesia is probably a more objective datum. However, had we set the consumption of opioids as the primary end point of the study, we would have needed a much larger sample (approximately 250 patients per group), as in our study morphine was only used as a rescue drug and not as background analgesia;
(2) the VAS scores were taken at fixed times, so the effect before/after paracetamol administration was not investigated nor was the length of the analgesic effect of the paracetamol.

In conclusion, our data suggest that the i.v. paracetamol as adjunctive treatment to tramadol-based background analgesia supplies good analgesic cover after cardiac interventions carried out with a medial sternotomy. The complications that arose and that led to the interruption of treatment do not seem correlated with the use of either of the drugs.

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