

The Use of Injectable Paracetamol as an Adjunct for Postoperative Pain Management After Off-pump Fast-track Coronary Artery Bypass Grafting Surgery

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Objective: In this prospective, double-blind, randomized, placebo-controlled study; was designed to evaluate the analgesic efficacy, safety and morphine-sparing effects of the recently administered injectable paracetamol in off-pump fast-track coronary artery bypass grafting (CABG) surgery.

Methods: Forty adult patients undergoing off-pump fast-track CABG were enrolled in the study. In ICU, patients received morphine 5 mg IV and either paracetamol 1 gm IV every 6 hours (paracetamol group) or IV placebo (control group) and were allowed patient controlled analgesia (PCA) machine with morphine when fully conscious.

Results: Paracetamol coupled to morphine PCA provided better analgesia at 6 and 12 hours (Visual analogue scale was 4.11 ± 0.69 and 4.04 ± 0.74 for paracetamol group vs. 4.6 ± 0.74 and 4.66 ± 0.89 for control group at 6 and 12 hours, respectively) and less sedation at 12 and 18 hours (Ramsay sedation scale > 3 in 64.7% and 47.05% in paracetamol group and 93.4% and 80% in control group at 12 and 18 hours, respectively) than morphine PCA alone. Morphine consumption in the first 24 hours was 27% higher in control group (31.26 ± 5.72 mg) compared to paracetamol group (24.58 ± 3.04 mg). Incidence of nausea (but not vomiting) was statistically higher in control group than paracetamol group (40% vs. 23.5%).

Conclusion: IV paracetamol coupled to morphine PCA provided better analgesia, less sedation and definite morphine-sparing effect when compared to morphine PCA al

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Optimization of pain relief after cardiac surgery has proved to be difficult with no one modality of therapy providing ideal efficacy with an acceptable side effect profile (1). Pain after cardiac surgery is associated with sternotomy, leg vein harvesting, pericardiotomy, and chest tube insertion. Good postoperative pain control is essential to ensure adequate breathing, as well as to reduce the number of ischemic episodes after coronary artery bypass grafting surgery (2).

Postoperative pain management after cardiac surgery has been mainly based on parenteral opioids (3). The main concern for using high doses of opioids in the postoperative period is the risk of sedation and respiratory depression. Opioids have also been associated with other side effects including confusion, nausea, vomiting, ileus, biliary spasm, pruritus and urinary retention (4). In the last 10 years, "fast-track" technique became widely adopted in coronary artery bypass grafting (CABG) surgery, aiming to reduce total cost

of surgery, shorten intensive care and hospital stay, and improve resource use (5, 6).

Fast-tracking of cardiac patients involves rapidly awakening the patients after surgery, with earlier removal of endotracheal tubes and thus spending shorter time in intensive care unit (5). Yet, this technique added more challenge to the management of postoperative pain after cardiac surgical procedures as fast-track patients receive much lower doses of opioids intra- and postoperatively with the consequence that patients are in pain after surgery and a postoperative analgesic that is not a respiratory depressant is advantageous (1).

Non-steroidal anti-inflammatory analgesic drugs (NSAIDs) have been shown to reduce morphine requirements in variety of surgical procedures and are devoid of CNS side effects typical of narcotics (7-9). NSAIDs exert their anti-nociceptive action by blocking the peripheral synthesis of prostaglandins through inhibition of cyclo-oxygenase enzyme (although a central mechanism has recently been proposed). Yet, cyclo-oxygenase enzyme inhibition also causes platelet dysfunction, may cause renal impairment by blood flow redistribution in kidneys and is responsible for gastrointestinal symptoms (10). Therefore, NSAIDs have not been used widely in cardiac surgical patients due to these concerns (2).

Paracetamol, a non-opiate analgesic, was not used routinely in postoperative pain management after adult cardiac surgery because it was only available in oral or rectal form, which is inconvenient for use in unconscious postoperative adult patients. Intravenous paracetamol (Perfalgan®, Bristol-Myers Squibb, France) was launched in April 2004 for the short-term treatment of moderate pain, especially following surgery, and for the short-term treatment of fever in adults, adolescents and children (11). Although no clinical trials were available on the use of IV paracetamol in the postoperative management of pain, especially following cardiac surgery, an injectable pro-drug form of paracetamol (propacetamol) was investigated recently for postoperative pain management (12-15).

This study was designed to evaluate the analgesic efficacy, safety and morphine-sparing effect intravenously administered paracetamol as an adjunct to patient-controlled (PCA) opioid postoperative analgesia after off-pump coronary artery bypass grafting surgery.

Patients and Methods

After the approval of the hospital's ethics committee, this study was conducted on forty adult patients,

scheduled for off-pump coronary artery bypass grafting (CABG) surgery during the period from August 2004 to January 2005. Preoperative exclusion criteria included age above 75 years old, body weight less than 55 kg or more than 100 kg, history of allergy to any of the study drugs, history of drug abuse, renal impairment (creatinine > 130 μ mol/L), liver impairment (Child's classification 2 or more), impaired left ventricular function (EF < 35%), and inability to operate the PCA machine. Intraoperatively, patients whose surgical decision was changed from multi-vessel grafting to one-vessel graft and patients whose surgery necessitated using cardiopulmonary bypass (CPB) either due to major hemodynamic instability or difficulty in positioning the heart during grafting were excluded. Postoperatively, patients who failed to be extubated or failed to regain consciousness within 2 hours after arrival to ICU, patients who needed re-exploration for postoperative bleeding, hemodynamically unstable patients (hypotension, high inotropic support, excessive bleeding), and patients who were in excessive pain or agitation that necessitated the administration of sedative and analgesic drugs other than the two study drugs (paracetamol and morphine) were excluded.

A written informed consent was obtained from each patient. In the preoperative anesthetic visit, patients were taught about the use of patient-controlled analgesia machine and visual analogue scale and the study protocol and design were explained extensively. Midazolam 7.5 – 15 mg was administered orally to all patients at the night of surgery. Morphine 10 mg was administered to all patients by intramuscular injection half-an-hour before sending the patient to operating room (OR) and 5-mL blood sample was obtained for serum cortisol assessment. All patients were sent to OR at 07:20 AM.

Upon arrival to OR, oxygen was supplied to all patients by nasal cannula, ECG electrodes and pulse oximetry probe were attached. Midazolam IV was given in increments of 1 – 2 mg to a maximum dose of 10 mg. A 20-gauge arterial catheter was inserted in the non-dominant arm's radial artery under local anesthetic infiltration unless radial artery was to be harvested for grafting. Baseline readings of heart rate, peripheral oxygen saturation (SpO₂) and invasive arterial blood pressure (systolic, diastolic, and mean) were obtained before induction of anesthesia.

Anesthesia was induced using a combination of fentanyl 1 – 3 μ g/kg and propofol 1.5 – 2 mg/kg. Muscle relaxation was provided with pancuronium 0.15 mg/kg and patient was ventilated with a mixture of O₂ and

N₂O (50% : 50%) and sevoflurane 2 – 3% for 3 minutes and then endotracheal intubation was performed.

After induction of anesthesia, a flow-directed, balloon-tipped pulmonary artery catheter (CritiCath™ Pulmonary Artery Catheter, Becton-Dickinson Critical Care Systems Pte Ltd, Singapore) was inserted and baseline hemodynamic profile (cardiac index, peripheral vascular resistance, pulmonary vascular resistance, pulmonary artery wedge pressure) was obtained.

Anesthesia was maintained with sevoflurane (1 – 3%) in O₂ : N₂O mixture in a ratio of 50% : 50% (Ohmeda Modulus SE Anesthesia Machine, Datex-Ohmeda, Madison, WI, USA). Increments of pancuronium (0.02 – 0.03 mg/kg) were administered every 45 minutes throughout surgery. Fentanyl 0.5 µg/kg boluses were administered on skin incision, sternotomy and hourly thereafter till time of skin closure. Patients were mechanically ventilated using Datex-Ohmeda 7900 anesthesia ventilator (Datex-Ohmeda, Madison, WI, USA) with a tidal volume of 7 – 10 mL/kg and respiratory rate of 12 – 14 / minute to keep EtCO₂ between 35 – 40 mmHg.

All patients were operated through median sternotomy. Conduits for bypass depended on patient characteristics and included left and right internal mammary arteries (LIMA and RIMA), left radial artery, and saphenous vein grafts. After harvesting conduits and making pericardial sling, heparin (150 IU/kg) was administered, and supplemental doses were added, as needed, to maintain activated clotting time (ACT) between 200 – 250 seconds. At first left internal mammary (LIMA) anastomosis to left anterior descending artery (LAD) was done and then the proximal anastomosis followed by distal ones. Each coronary artery was stabilized in turn using the Medtronic Octopus III Tissue Stabilization System (Medtronic Inc., Minneapolis, MN, USA). Starfish Repositioner (Medtronic Inc., Minneapolis, MN, USA) or deep pericardial stitch was used for positioning and exposure of the heart.

Intracoronary shunts (Clearview Arteriotomy Shunts, Medtronic Inc., Minneapolis, MN, USA) were used in all patients to maintain distal coronary perfusion during the distal anastomosis of the grafts and to aid visualization during anastomosis. After completing the anastomoses, the total dose of heparin administered was reversed with protamine in a 1 : 1 ratio. Cell saver (Bret2, Cobe Cardiovascular Inc., Division of Sorin Biomedica, USA) was used from the start of the operation in all the patients. After revascularization, meticulous he-

mostasis, insertion of chest drains, and closer of median sternotomy was done.

Immediately after skin closure, volatile anesthetics were shut off and patients were ventilated with a mixture of oxygen in air, muscle relaxant was reversed with neostigmine 0.05 mg/kg and atropine 0.01 – 0.02 mg/kg when Train-of-Four (TOF) reading was 0.5, and patients were transferred to intensive care unit (ICU) intubated but spontaneously breathing and ventilation was manually assisted by self-inflating Ambu-bag. On arrival to ICU, patients were connected to mechanical ventilator on pressure support mode of 5 – 10 cmH₂O to achieve a tidal volume of at least 7 mL/kg. In ICU, patients were divided randomly into two groups. The first group (paracetamol group) received morphine 5 mg IV bolus and IV paracetamol 1 gm (Perflagan®, 1 gm in 100 mL, Bristol-Myers Squibb, France) over 30 minutes and then 6 hourly for the first 24 hours. The second group (control group) received morphine 5 mg IV bolus and a placebo in the form of 100 mL of normal saline over 30 minutes and 6 hourly thereafter for 24 hours. ICU team was blinded to patient's group. Patients were routinely extubated within the first 2 hours after end of surgery provided that they could breathe adequately (spontaneous tidal volume \geq 7 mL/kg), regained adequate airway protective reflexes and conscious level was suitable for extubation (Glasgow Coma Scale of at least 12).

In ICU, patients were continuously monitored for ECG, pulse oximetry and invasive arterial blood pressure using Datascope Expert monitor (Datascope Corp., Patient Monitoring Division, Paramus, NJ, USA). These data was recorded on arrival to ICU, hourly for the first 4 hours in ICU then 4 hourly for 24 hours. Pulmonary-artery-catheter-derived hemodynamic profile was obtained on arrival to ICU and then 6-hourly for the first 24 hours or more frequently if required by the treating staff.

Patient-controlled analgesia pump (PCA Plus Micro Delivery Device, Abbott Laboratory, Chicago, IL, USA) was provided to all patients as soon as they were fully conscious and was adjusted to deliver 1-mg bolus of morphine per demand with a lock-out interval of 20 minutes without a background infusion. The total dose of morphine delivered to the patient through the PCA machine in the first 24 hours was recorded. Patient's were asked to assess their pain on the previously explained visual analogue scale every 6 hours for first 24 hours half-an-hour after administration of the study drugs (IV paracetamol or placebo). Also, Ramsay sedation scale (table 1) was assessed 6 hourly for 24 hours.

Table (1): Ramsay Scale for assessment of depth of sedation.

Level	Patient Response
1	Anxious, agitated, or restless
2	Cooperative, oriented, tranquil
3	Quite, responds to verbal commands
4	Asleep, brisk response to forehead tap or loud verbal stimulus
5	Asleep, sluggish response to forehead tap or loud verbal stimulus
6	Unresponsive, comatose

Blood samples for serum cortisol assessment were obtained on arrival to ICU and 6 hours and 24 hours after the end-of-surgery. Time to discharge from ICU and hospital as well as overall morbidity and mortality were recorded. Hypotension was defined as systolic arterial blood pressure lower than 100 mmHg or 30% lower than baseline preoperative reading. Hypoxia was defined as peripheral oxygen saturation < 91% on oxygen 4 – 6 L/minute by simple facemask. Arrhythmia was defined as any rhythm other than normal sinus rhythm except for infrequent atrial or ventricular extrasystoles (< 6 / minute). Bleeding was defined as blood loss of more than 200 mL/hr for the first 3 hours or more than 100 mL/hr in any subsequent hour. If bleeding could not be corrected by medical measures and rate of blood loss was still above the normal rates for the subsequent hour, the patient was returned to OR for exploration and was excluded from the study. Patients were asked to report to the attending staff if they experienced nausea or pruritus. Also, vomiting, excessive sedation not necessitating reintubation, or reintubation due to any cause whether hemodynamic or respiratory were reported.

Data were presented as mean \pm standard deviation, median and range, or number and percentage as appropriate. Between-group comparisons were done using unpaired Student's t test for numerical variables and Chi square test for categorical variables. A P value of 0.05 or less was considered statistically significant.

Results

Forty consecutive patients scheduled to undergo multi-vessel off-pump coronary artery bypass grafting and not having any of the preoperative exclusion criteria

were enrolled in this clinical trial. Three of the studied patients were excluded intraoperatively because of the need to employ cardiopulmonary bypass because of hypotension that didn't respond to inotropic medications in two patients, and because of difficulty to position the heart in the third patient because of the distribution of his distal anastomotic sites.

The remaining 37 patients were divided in a double-blind random fashion on arrival to ICU into two groups; paracetamol group (19 patients) and control group (18 patients). After the commencement of administration of the study drug and placebo in the two groups, five more patients were excluded, two in the paracetamol group and three in the control group, either because of failure to extubate or not regaining consciousness within 2 hours from arrival to ICU, hemodynamic instability, or returning the patient to OR for re-exploration. None of the remaining patients had severe pain (VAS \geq 6) not responding to study analgesic drugs or agitation needing the administration of other analgesic or sedative drugs.

The two groups were comparable as regards age (66.29 \pm 4.99 vs. 64.46 \pm 4.10 years) sex (male : female ratio 13 : 4 for paracetamol group vs. 12 : 3 for control group), weight (78.47 \pm 9.67 vs. 80.26 \pm 8.76 kg), height (170.58 \pm 6.67 vs. 171.66 \pm 7.12 cm), operative time (4.38 \pm 0.40 vs. 4.31 \pm 0.33 hours), and number of grafts (3.47 \pm 0.94 vs. 3.4 \pm 0.91) (table 2).

Table (2): Demographic and operative data in the two groups.

Parameter	Paracetamol Group (n = 17)	Control Group (n = 15)	P Value
Sex (M:F)	4 : 13	3 : 12	
Age (years)	66.29 \pm 4.9	64.46 \pm 4.1	0.135
Weight (kg)	78.47 \pm 9.6	80.26 \pm 8.7	0.296
Height (cm)	170.58 \pm 6.6	171.66 \pm 7.1	0.331
Operative time (hrs)*	4.38 \pm 0.4	4.31 \pm 0.3	0.290
No. of Grafts	3.47 \pm 0.9	3.4 \pm 0.9	0.415

Operative time: Time from entering operating room to arrival to ICU.

Table (3): Hemodynamic measurements in the two studied groups.

	Paracetamol Group (n = 17)				Control Group (n = 15)			
	SBP	DBP	HR	SpO ₂	SBP	DBP	HR	SpO ₂
Preop.	136 ± 18.	75 ± 9.	65 ± 9.	97 ± 1.4	130 ± 18.	77 ± 10.	68 ± 9.	97 ± 2.3
Admission to ICU	104 ± 25.	68 ± 12.	108 ± 10.	95 ± 1.2	113 ± 16.3	69 ± 13.	106 ± 8.	96 ± 1.9
1 hr	114 ± 14.	67 ± 11.	92 ± 6.9	96 ± 2.0	115 ± 16.	66 ± 9.	97 ± 9.	97 ± 1.8
2 hr	108 ± 14.	67 ± 11.	94 ± 8.1	96 ± 2.0	107 ± 15.	68 ± 11.	100 ± 11.	96 ± 1.5
3 hr	98 ± 15.	57 ± 10.	83 ± 15.	97 ± 1.9	97 ± 15.	58 ± 10.	78 ± 12.	98 ± 1.3
4 hr	97 ± 15.	48 ± 6.	71 ± 11.	97 ± 2.0	92 ± 14.	44 ± 6.	68 ± 12.	98 ± 1.2
8 hr	114 ± 20.	55 ± 9.	68 ± 8.8	99 ± 2.1	110 ± 19.	47 ± 8.	73 ± 11.	98 ± 1.2
12 hr	111 ± 20.	48 ± 5.	63 ± 11.	98 ± 2.2	108 ± 18.	46 ± 4.	64 ± 11.	97 ± 1.3
16 hr	112 ± 20.	55 ± 8.	62 ± 11.	98 ± 2.1	106 ± 19.	51 ± 8.	66 ± 11.	96 ± 1.4
20 hr	122 ± 18.	52 ± 9.	69 ± 12.	98 ± 2.0	119 ± 18.	53 ± 7.	68 ± 12.	98 ± 1.8
24 hr	108 ± 17.	47 ± 8.	65 ± 11.	97 ± 2.2	106 ± 17.	42 ± 7.	64 ± 11.	98 ± 1.9

SBP = systolic blood pressure (mmHg); DBP = diastolic blood pressure (mmHg); HR = heart rate (beat per minute); SpO₂ = peripheral oxygen saturation (%); Preop. = preoperative; 1, 2, 3, 4, 8, 12, 16, 20, 24 hr = hours from admission to ICU.

*, P < 0.05, significant difference when compared to control group.

Table (4): Pulmonary artery catheter derived measurements in the two studied groups.

	Paracetamol Group (n = 17)				Control Group (n = 15)			
	CI	SVR	PVR	PCWP	CI	SVR	PVR	PCWP
Before Skin Incision	3.50 ± 0.4	1304 ± 24	209 ± 5	11.64 ± 2.2	3.32 ± 0.2	1312 ± 27	215 ± 5	11.29 ± 2.3
Arrival to ICU	3.13 ± 0.3	1289 ± 26	214 ± 5	11.58 ± 2.0	3.10 ± 0.3	1277 ± 27	213 ± 5	11.47 ± 2.4
6 hrs	3.10 ± 0.3	1292 ± 25	216 ± 5	11.12 ± 1.	3.33 ± 0.3	1282 ± 27	207 ± 5	10.76 ± 2.2
12 hrs	3.09 ± 0.3	1316 ± 245	244 ± 80	10.64 ± 1.6	3.06 ± 0.2	1162 ± 271	176 ± 51	10.8 ± 2.4
18 hrs	3.07 ± 0.3	1325 ± 258	247 ± 60	9.41 ± 3.1	2.96 ± 0.3	1228 ± 268	195 ± 54	10.23 ± 2.2
24 hrs	2.72 ± 0.3	1298 ± 24	219 ± 5	8.62 ± 2.8	2.86 ± 0.3	1334 ± 25	222 ± 4	9.43 ± 2.6

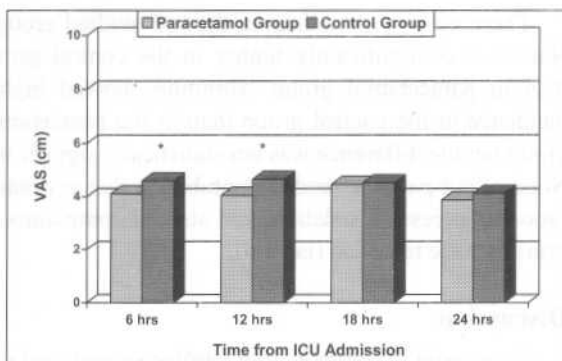


Figure (1): Visual analogue scale in the two studied groups. *, Statistically significant difference when paracetamol group was compared to control group (P < 0.05).

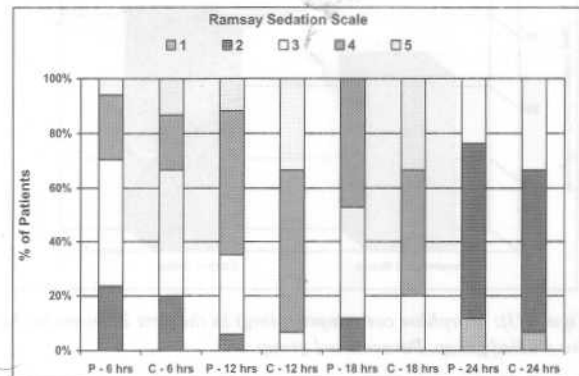


Figure (2): Ramsay scale for sedation in the two studied groups. P, Paracetamol group; C, Control group.

Also, blood pressure and pulse oximetry data were comparable preoperatively and for the first 24 hours after surgery. Heart rate was significantly lower in the paracetamol group at 1, 2, and 8 hours postoperatively but showed comparable readings thereafter (table 3). Pulmonary artery catheter derived hemodynamic data (cardiac index, pulmonary capillary wedge pressure, systemic vascular resistance and pulmonary vascular resistance) were comparable in the two groups, apart from lower systemic vascular resistance and pulmonary vascular resistance at 12- and 18-hour readings in the control group. Systemic vascular resistance and pulmonary vascular resistance were, in general, slightly lower in the control group compared to paracetamol group, but these differences were not statistically significant except at the times mentioned above (table 4).

Visual analogue scale data showed better analgesia in the paracetamol group at 6 hours (4.11 ± 0.69 for paracetamol group vs. 4.6 ± 0.74 for control group, $P = 0.033$) and 12 hours (4.04 ± 0.74 for paracetamol group vs. 4.66 ± 0.89 for control group, $P = 0.023$) and was comparable in the two groups at 18 and 24 hours (figure 1). Ramsay sedation scale showed less sedation in the paracetamol group at 12 hours (patients showing sedation scale > 3 were 11 / 17 patients [64.7%] in paracetamol group vs. 14 / 15 patient [93.4%] in control group) and at 18 hours (8 / 17 patients [47.05%] having sedation scale > 3 in paracetamol group vs. 12 / 15 [80%] in control group) and was comparable in 6- and 24-hour readings (fig 2)

Morphine consumption in the first 24 hours was significantly lower in the paracetamol group (24.58 ± 3.04 an control group (31.26 ± 5.72 mg) (figure 3) .

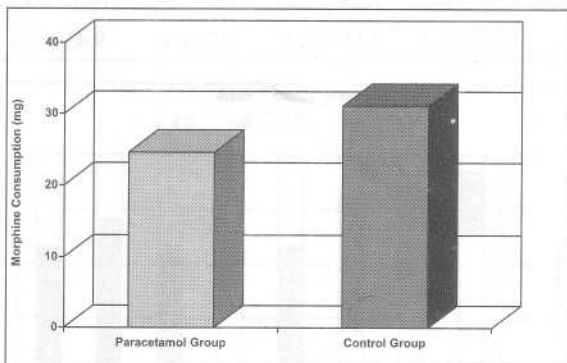


Figure (3): Morphine consumption (mg) in the first 24 hours in the two studied group. Paracetamol group

Morphine dose was 27% higher in control group than in paracetamol group. Time to discharge from ICU

as well as time to discharge from hospital were comparable between the two groups (figure 4).

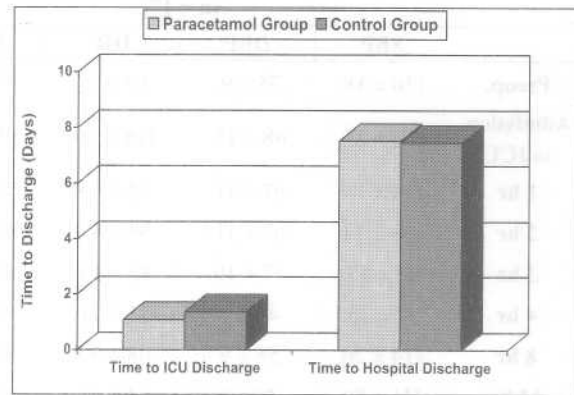


Figure (4): Time to ICU discharge and time to hospital discharge in the two groups of the study. The difference between paracetamol group and control group was statistically non-significant.

Serum cortisol values were also comparable in the two studied groups (figure 5).

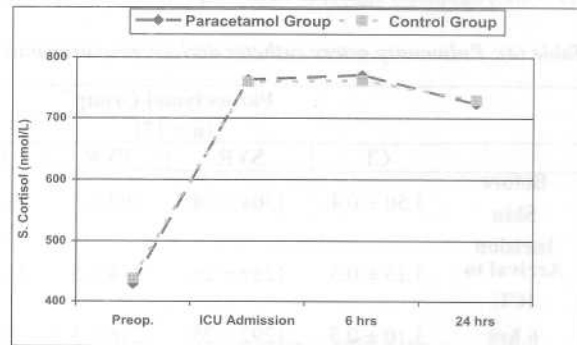


Figure (5): Serum cortisol levels in the two studied groups at different times of the study. There was no statistically significant differences between the two groups

There was no mortalities in the two studied groups. Nausea was significantly higher in the control group than in paracetamol group. Vomiting showed higher incidence in the control group than in the paracetamol group but the difference was not statistically significant. None of our patients needed reintubation due to desaturation or excessive sedation; and also no complaints of pruritus were recorded (table 5).

Discussion

Acute pain is common after cardiac surgery and can keep patients from participating in activities that prevent postoperative complications such as deep breathing exercises and getting out of bed (17).

Table (5): Morbidity and mortality in the two studied groups.

	Paracetamol Group (n = 17)	Control Group (n = 15)
Hypotension	3 / 17 (17.6%)	2 / 15(13.2%)
Hypoxia	2 / 17 (11.7%)	2 / 15(13.2%)
Reintubation	0 / 17 (0%)	0 / 15 (0%)
Arrhythmias	4 / 17 (23.5%)	4 / 15(26.4%)
Bleeding (not necessitating surgical exploration)	3 / 17 (17.6%)	2 / 15(13.2%)
Pruritus	0 / 17 (0%)	0 / 15 (0%)
Nausea	4 / 17 (23.5%) *	6 / 15 (40%)
Vomiting	2 / 17 (11.7%)	2 / 15(13.2%)
Cardiac arrest	0 / 17 (0%)	0 / 15 (0%)
Death	0 / 17 (0%)	0 / 15 (0%)

Data are provided as number of patients (%).

* $P < 0.05$, Statistically significant difference when compared to control group.

The value of multimodal or balanced analgesia in postoperative pain relief, including the use of non-steroidal anti-inflammatory drugs (NSAIDs), is well established in noncardiac surgery (18). Balanced analgesia comprising a combination of opioids, NSAID, and paracetamol may reduce the requirement for opioids postoperatively and potentially benefit the patient by improving the quality of pain relief and decreasing the incidence of opioid-induced side effects (19-21). The rationale behind this therapy is that analgesic drugs acting through different mechanisms result in additive or synergistic analgesia (22).

Paracetamol is widely used to supplement postoperative analgesia after cardiac surgery either by nasogastric or rectal routes (23). Schuitmaker et al. (1999) demonstrated, in a prospective randomized study in cardiac surgical patients, that paracetamol given by nasogastric route was slowly absorbed due to delayed gastric emptying and nasogastric tube losses, where absorption half-life was 1.49 hours and time to maximum concentration was approximately 240 minutes (23). Also, Goldhill et al. reported that the time to reach maximum concentration after oral paracetamol was increased from 14.1 minutes preoperatively to 225.4 minutes postoperatively (24). Rectal paracetamol had an absorption half-life of 2.02 hours in Schuitmaker's study (23). The rectal route of administration is also inconvenient and embarrassing for adult patients, especially when fast-tracking is employed as the patients are fully awake within few hours after surgery.

In this study, we investigated the use of paracetamol through the intravenous route to overcome the delay in absorption and reduced bioavailability of oral and rectal preparations of this drug in the setting of postoperative cardiac surgical procedures.

Intravenous paracetamol was not introduced in the market except very recently. The commercially available product, Perfalgan ® is available in the form of 1 gm paracetamol in 100 mL of aqueous solution. Few clinical trials of IV paracetamol are available till now. The intravenous pro-drug form of paracetamol, propacetamol, have been compared to IV paracetamol. Propacetamol 2 gm is bioequivalent to 1 gm of IV paracetamol for clinical use (11). In this study, we compared our results to other studies where paracetamol was given by nasogastric and/or rectal routes and to studies that investigated IV propacetamol as no studies of IV paracetamol for postoperative analgesia after cardiac surgery, or other major surgeries, were available to us till the end of the study.

The hemodynamic data of the two groups were comparable except for lower heart rate in the paracetamol group at 1, 2 and 8 hours and lower systemic and pulmonary vascular resistance in the control group at 12 and 18 hours. The lower heart rate in patients receiving paracetamol compared to those receiving placebo can't be attributed to better analgesia only as many factors in postoperative cardiac surgical patients besides analgesia determine blood pressure and heart rate, including preoperative medications, cardiac function, volume status of the patient, and active control of hemodynamic parameters using inotropes, vasodilators and beta-blockers. Also, the lower vascular tone in control group patients can't be simply attributed to receiving a higher total dose of morphine, as it is also affected by intravascular volume load, pain, inotropic drug usage, and administration of vasodilators.

Visual analogue scale for pain was significantly lower in patients receiving paracetamol at 6 and 12 hours in ICU. Yet, at 18 and 24 hours, there was no significant difference in VAS between patients receiving placebo and those receiving paracetamol in addition to morphine by PCA. This early better analgesia can be explained by the fact that, in the first few postoperative hours, patients are not yet fully conscious to be able to use PCA machine efficiently, thus few hours would pass before they receive a reasonable analgesic dose of morphine. The dose most patients self-administer in the first six-hour time interval is usually much less than the subsequent intervals. So, analgesia in the early postoperative period is mainly dependent on regularly administered medications, i.e. morphine 5-mg IV bolus given on

arrival to ICU and paracetamol in the paracetamol group only Schug et al. (25) have suggested that a combination of paracetamol and morphine in orthopedic and general surgery results in improved quality of pain relief and patient satisfaction compared to the use of morphine alone. Zhou et al. (26) investigated the use of IV propacetamol, ketorolac, and placebo combined with patient-controlled analgesia for patients undergoing total hip or knee replacement procedures and proved a significantly greater improvement in pain relief than placebo from 45 minutes until 5 hours after its injection. Also, in a randomized controlled clinical trial, Hernandez-Palazon et al. (27) proved that pain scores were significantly lower in patients who received propacetamol with morphine by PCA device after spinal fusion surgery. On the contrary, Lahtinen et al. (3) investigated the efficacy of propacetamol as a complementary analgesic to opioids after cardiac surgery and stated that it didn't enhance opioid-based analgesia in coronary artery bypass grafting patients. Also, Aubru et al. (28), in a study on 550 patients, came to the conclusion that intravenous propacetamol had no benefit as regards pain relief in patients with severe postoperative pain.

In our study, IV paracetamol had a statistically significant morphine-sparing effect. Morphine consumption in the first 24 hours was 21.4% lower in patients who received paracetamol than controls. Similar results came out of Lahtinen's study (3), where cumulative oxycodone consumption was 13% lower in patients receiving IV propacetamol compared to patients receiving placebo after cardiac surgery. In 2004, Fayaz et al. (1) studied the opioid sparing effects of diclofenac and paracetamol administered rectally. Twenty-four-hour morphine consumption was reduced by approximately 40.5% in patients receiving diclofenac, but when diclofenac and propacetamol were used in combination that reduction in morphine administered by PCA was 67.5%. Hernandez-Palazon et al. (27) also proved morphine-sparing effect in patients receiving IV propacetamol in combination with morphine administered by patient-controlled analgesia after spinal fusion surgery. Morphine sparing effect of paracetamol has also been demonstrated after gynecological (29) and orthopedic surgery (30). In Lahtinen et al. (3) study, on the contrary, IV propacetamol did not decrease cumulative morphine consumption when administered in combination with morphine PCA for postoperative pain after cardiac surgery.

Sedation was assessed using Ramsay scale, with a score of "1" indicating anxious, agitated patient and "6" indicating unconscious, comatose patient. Ramsay scale for sedation showed less sedation in the paracetamol group at 12 (patients showing sedation scale > 3 were

11 / 17 patients [64.7%] in paracetamol group vs. 14 / 15 patient [93.4%] in control group) and 18 hours (8 / 17 patients [47.05%] having sedation scale > 3 in paracetamol group vs. 12 / 15 [80%] in control group) and was comparable in 6 and 24 hours readings. Similar results were shown in Fayaz et al. (1) study in which patients who received diclofenac / paracetamol by the rectal route were significantly more awake compared to patients who received diclofenac rectally alone or placebo. Also, when IV propacetamol in combination with morphine administered by PCA was compared to morphine PCA and placebo for postoperative pain management after spinal fusion surgery, most patients in the placebo group obtained a greater degree of sedation on postoperative day 3 (27).

Incidence of nausea was significantly higher in the placebo group (40% vs. 23.5% for the control group and paracetamol group respectively). This may be attributed to the higher dose of morphine used in this group. Yet, incidence of vomiting was comparable in the two groups (11.7% for paracetamol group vs. 13.2% for control group). This may be due to the routine early use of antiemetics on-demand for patients complaining of nausea. In Fayaz et al. (1) study, postoperative nausea and vomiting (PONV) was the most common adverse event, and the incidence of postoperative nausea and vomiting was less in both the diclofenac group and the combined diclofenac and paracetamol group, which used significantly less morphine postoperatively, than in the placebo group. This comes in contradiction with Lahtinen's study (3) on propacetamol as adjunctive treatment for postoperative pain after cardiac surgery, where IV paracetamol failed to reduce any of the opioid adverse effects when given in a dose of 2 gm every six hours for 3 days after surgery and also contradicting with Aubrun's study (28) in 2003, where intravenously administered propacetamol did not change the incidence of morphine-related side effects.

Time to ICU discharge tended to be shorter in the paracetamol group versus control group, but the difference was not statistically significant (26.23 ± 6.84 hours vs. 32.8 ± 9.28 hours for the paracetamol and control groups respectively, $P = 0.0504$). Also, time to hospital discharge was very close in the two groups (7.52 ± 1.12 days for paracetamol group vs. 7.46 ± 0.99 days for control group). The reason may be that both ICU discharge and hospital discharge after CABG surgeries are related to many factors, analgesia not being the most important of which, e.g. hemodynamic stability, postoperative blood loss, overall general condition of the patient, and occurrence of complications.

Serum cortisol level measured preoperatively and on

ICU admission then at 6 and 24 hours showed no significant differences between the two groups. Actually, there is no definite data confirming that serum cortisol or any other stress response indicator can be precisely used to weigh the efficiency of one analgesic regimen over another.

Conclusion

The use of injectable paracetamol (Perfalgan®) combined with morphine PCA for postoperative pain management after off-pump fast-track coronary artery bypass grafting surgery yielded better analgesia, lower morphine consumption and less incidence of opioid-related side effects (nausea, sedation) than when morphine PCA was used alone. There was no significant difference between the paracetamol group and the control group as regards hemodynamic profile and time to ICU and hospital discharge. IV paracetamol may be included in the management of postoperative pain after adult cardiac surgery in combination with opioids. The increase in overall cost is minimal, putting in mind the high overall cost of cardiac surgical procedures.

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