

The effect of preoperative intravenous paracetamol administration on postoperative fever in pediatric cardiac surgery

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ABSTRACT

Background: Post-operative fever is a common complication of cardiac operations, which is known to be correlated with a greater degree of cognitive dysfunction 6 weeks after cardiac surgery. The aim of the present study was to examine efficacy and safety of single dose intravenous Paracetamol in treatment of post-operative fever in children undergoing cardiac surgery. **Materials and Methods:** In this randomised, double-blind, placebo-controlled clinical trial, 80 children, aged 1-12 years, presenting for open heart surgery were entered in the trial and randomly allocated into two groups: Placebo and Paracetamol. After induction of anaesthesia, 15 mg/kg intravenous Paracetamol solution was infused during 1 h in the Paracetamol group. Patients in placebo group received 15 mg/kg normal saline infusion during the same time. Since the end of operation until next 24 h in intensive care unit, axillary temperature of the two group patients was recorded in 4-h intervals. Any fever that occurred during this period had been treated with Paracetamol suppository (125 mg) and the amount of antipyretic drug consumption for each patient had been recorded. In order to examine the safety of Paracetamol, patients were evaluated for drug complication at the same time. **Results:** Mean axillary temperature during first 24 h after operation was significantly lower in Paracetamol group compared with placebo group ($P = 0.001$). Overall fever incidence during 24 h after operation was higher in placebo group compared with Paracetamol group ($P = 0.012$). Of Paracetamol group patients, 42.5% compared with 15% of placebo group participants had no consumption of antipyretic agent (Paracetamol suppository) during 24 h after operation ($P = 0.001$). **Conclusion:** This study suggests that single dose administration of intravenous Paracetamol before paediatric cardiac surgeries using cardiopulmonary bypass; reduce mean body temperature in the first 24 h after operation.

Key words: Cardiac surgery, paracetamol, paediatric, post-operative fever

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INTRODUCTION

Post-operative fever is a common complication of cardiac operations using cardiopulmonary bypass (CPB). Frequency of post-operative fever in cardiovascular

surgery varies from 12% to 73% in studies of adults and children. In cardiovascular surgery, this type of fever has generally been related with the use of CPB and the post-perfusion syndrome, as well as infections, blood transfusions, dehydration and atelectasis.^{1,2} Post-operative fever is known to be correlated with a greater degree of cognitive dysfunction 6 weeks after cardiac surgery.^{3,4}

Induced hypothermia is the only reliable method of neuroprotection from injuries related to cerebral ischemia from any cause.⁵ However, several studies have failed to confirm the putative protective effect of hypothermia during cardiac surgeries.^{5,6} Possible explanations for this may be due to the well-known inflammatory response

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to CPB and damage occurring during the re-warming process.^{6,7}

Post-operative fever reflect an inflammatory response initiated either in response to the surgical trauma itself or to the interaction of blood with the foreign surfaces of the CPB circuit.⁸ In cardiac surgery, cytokines such as TNF- α , IL-1 β and IL-6 are also known to be elevated both during and after surgery in a manner consistent with other markers of cellular injury and inflammatory stimuli.^{9,10} Alternatively, fever may be a marker of cerebral injury with altered function of the thermoregulatory centre in the hypothalamus.^{11,12}

Paracetamol is a synthetic, non-opioid, centrally acting analgesic and antipyretic agent. Its effectiveness as an antipyretic agent has been attributed to its effect on the hypothalamic heat regulating centre. It has a well-established efficacy profile, a well understood risk/benefit ratio and a very low potential for harmful drug interactions. In recommended doses, Paracetamol is considered safe for all age strata, from infants to the elderly.¹³ Several studies have examined intravenous Paracetamol effect on pain^{14,15} and lately a systematic review of the analgesic effect of Paracetamol has confirmed its efficacy and safety as an analgesic agent in post-operative pain treatment.¹⁶ However, evidences regarding Paracetamol antipyretic effect, especially on post-operative fever are not sufficient.

The aim of the present randomised, double-blind, placebo-controlled clinical study was to examine the efficacy and safety of single dose of intravenous Paracetamol in treatment of post-operative fever in children undergoing cardiac surgery.

MATERIALS AND METHODS

During the present double-blind randomised, placebo-controlled clinical trial (IRCT201207215506N6), which was performed in Educational-Medical centres of Tabriz University of Medical Sciences (Tabriz, Iran) between September 2010 and September 2012, 80 children, aged 1-12 years, presenting for open cardiac surgery were entered in the trial after written informed parental consent and verbal child assent had been obtained. Using a computer-generated random table, a hospital nurse allocated children into two groups: Placebo and Paracetamol. Both the patients and investigators were blinded to the study group assignment. Exclusion criteria were history of previous sensitivity to Paracetamol, liver and kidney disease.

Demographic characteristics consisted of vital signs and axillary temperature of the participants were measured and recorded exactly before the anaesthesia induction. After induction of anaesthesia, 15 mg/kg intravenous Paracetamol solution was infused during 1 h in the Paracetamol group. Patients in placebo group received 15

mg/kg normal saline infusion during the same time. Since the end of operation until next 24 h in intensive care unit (ICU), axillary temperature of the two group patients was recorded in 4-h intervals. The fever was defined based on axillary temperature more than 37.2°C. Any fever occurred during this period had been treated with Paracetamol suppository (125 mg) and the amount of antipyretic drug consumption for each patient had been recorded. In order to examine the safety of Paracetamol, patients were evaluated for drug complication (systolic blood pressure (SBG) below 90 mmHg, dyspnoea, skin rash, anaphylactic shock and thrombocytopenia) at the same time.

Induction of anaesthesia was done by fentanyl 10 μ g/kg, intravenously, and in children with haemodynamic stability thiopental 4 mg/kg, intravenously, followed by pancuronium 0.1 mg/kg intravenously. Sevoflurane inhalation for children without intravenous access with 7% concentration and after intravenous access was used. According to pre-operative status and response to induction of anaesthesia and tolerance of individual patient, maintenance of anaesthesia was done. Maintenance of anaesthesia was achieved by sevoflurane and fentanyl 2 μ g/kg/h intravenous bolus. After induction of anaesthesia and securing of the airway, arterial and central venous lines are placed. Standard monitoring includes electrocardiogram (ECG), pulse oxymetry, capnography, blood pressure (BP), central venous pressure, temperature, urine out-put and airway volume and pressure. During CBP, anaesthesia was maintained with intravenous narcotic, muscle relaxant and benzodiazepine. After successful weaning from CBP, maintenance anaesthesia was preferred to with fentanyl and a small amount of sevoflurane because the minimal myocardial depression was associated with these agents. In most children with uncomplicated defects, endotracheal extubation was performed early in the ICU.

The primary outcome variables were incidence of fever and mean temperature increase during the first 24 h post-operatively. Secondary outcome variables were need for antipyretic consumption and incidence of complications (dyspnoea and thrombocytopenia, decrease in SBG, anaphylactic shock and skin rash) in the first 24 h post-operatively. The data were collected by the ICU nurses and subsequently validated by the review of clinical notes.

Statistical analysis was performed by SPSS software package version 16.0 for Windows (SPSS Inc., Chicago, USA). Quantitative data were presented as mean \pm standard deviation (SD), while qualitative data were demonstrated as frequency and percent (%). For statistical analysis, collected data were studied using descriptive statistical methods, the mean difference test for independent groups, chi-square test or Fisher's exact test. One way analysis of variance (ANOVA) test was used to compare groups. However, repeated measurements of ANOVA were used to compare post-operative axillary temperature levels in both

groups. *P* value less than 0.05 was statistically considered significant in all steps. The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences (TUMS), which was in compliance with Helsinki Declaration.

RESULTS

Eighty children recruited based on inclusion criteria and divided randomly in two groups of Paracetamol (*N* = 40) and placebo (*N* = 40). The patients and surgical characteristics were comparable across the groups [Table 1]. There were no significant differences in pre-operative vital signs including heart rate (HR), respiratory rate (RR), axillary temperature, SBP and diastolic blood pressure (DBP) between two groups [Table 1].

Mean axillary temperature during first 24 h after operation was significantly lower in Paracetamol group compared with placebo group (37.57 ± 0.53 Vs. 37.80 ± 0.60, respectively, *P* = 0.001) [Figure 1 and Table 2].

Overall fever (axillary temperature more than 37.2°C) incidence during 24 h after operation was higher in placebo group compared with Paracetamol group and this difference was significant in mean temperature measured 4 h after surgery (*P* = 0.012) [Table 3].

Seventeen (42.5%) patients of Paracetamol group compared with six (15.0%) of placebo group participants had no consumption of antipyretic agent (Paracetamol suppository) during 24 h after operation (*P* = 0.001).

None of the patients in both groups had dyspnoea, skin rash, anaphylactic shock and thrombocytopenia in 24 h

Table 1: Patient characteristics and pre-operative vital signs of study groups

Study groups Characteristics	Paracetamol group (N = 40)	Placebo group (N = 40)	P
Age (year)	5.80±3.78	5.87±4.07	0.93
Sex (male: female)	24:16	27:13	0.23
Operation duration (h)	2.51±0.51	2.52±0.43	0.86
RR	15.90±3.82	14.05±1.50	0.45
HR	121.57±18.84	124.50±13.07	0.78
Axillary temperature (°C)	36.62±0.23	36.62±0.29	0.99
SBP (mmHg)	91.25±14.10	93.90±27.88	0.63
DBP (mmHg)	79.12±18.62	63.52±20.41	0.17

*Data was shown as Mean ± Standard Deviation; RR – Respiratory rate; HR – Heart rate; SBP – Invasive systolic blood pressure; DBP – Invasive diastolic blood pressure

Table 2: Post-operative mean axillary temperature in study groups

Temperature study groups	T ICU	T4	T8	T12	T16	T20	T24	To-24
Paracetamol group	36.63±0.50	37.43±0.71	37.54±0.49	37.68±0.50	37.59±0.52	37.60±0.49	37.59±0.50	37.57±0.53
Placebo group	36.90±0.81	37.64±0.82	38.00±0.69	37.75±0.47	37.86±0.51	37.77±0.65	37.81±0.51	37.80±0.60
<i>P</i>	0.07	0.22	<0.001	0.52	0.02	0.19	0.06	<0.001

*Data was shown as Mean ± Standard Deviation; T ICU – Temperature immediately after operation; T4 to T24 – Temperatures recorded every 4 h after operation; To-24 – Mean temperature during 24 h after operation

after operation. Similarly two of the children in each group had SBP below normal range, based on their age in 24 h after operation, but none of them need further intervention.

DISCUSSION

This trial attempted to study the antipyretic effect of intravenous Paracetamol on post-operative fever in paediatric cardiac surgery and compare it with placebo in a randomised manner. Our data showed that mean axillary temperature during first 24 h after operation was significantly lower in Paracetamol group compared with placebo group. Despite this, there was no significant difference, overall fever incidence in the same time was higher in placebo group compared with Paracetamol group. In contrast, compared with the placebo group, patients receiving Paracetamol had fewer post-operative fever rate and body temperature rise. The present study assumes that Paracetamol reduces body temperature by two possible mechanisms; blocking production of inflammatory chemicals and lowering the hypothalamic set-point in the thermoregulatory centre of brain.

Duhamel *et al.*, in a study on 67 fevered 1-month-old to 12-year-old children, compared antipyretic effect of 15 mg/kg intravenous Paracetamol and 30 mg/kg intravenous Paracetamol and finally stated that while any of two drugs had dominance on the other one in terms of fever decrease but prescribing Paracetamol was safer for this age group.¹⁷

In a study comparing antipyretic effect of 15 mg/kg Paracetamol and 10 mg/kg Ibuprofen on 3-month-old

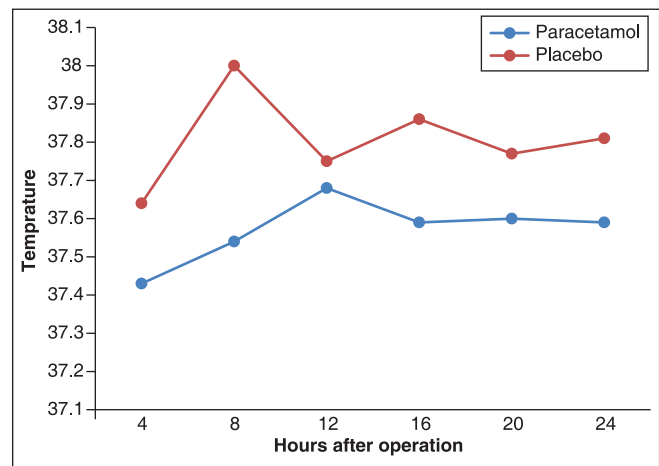


Figure 1: Post-operative mean axillary temperature in study groups

Table 3: Fever incidence during 24 h after operation in study groups

Study groups fever incidence	Paracetamol group N (%)	Placebo group N (%)	P
F ICU 0	0 (0.0)	3 (7.5)	0.07
F ICU 4	9 (22.5)	19 (47.5)	0.01
F ICU 8	16 (40.0)	24 (60.0)	0.07
F ICU 12	16 (40.0)	22 (55.0)	0.17
F ICU 16	19 (47.5)	27 (67.5)	0.07
F ICU 20	20 (50.0)	21 (52.5)	0.83
F ICU 24	18 (45.0)	26 (65.0)	0.07

F ICU 0 – Fever incidence immediately after operation; F ICU 4-24 – Fever incidence 4-24, h after operation

to 12-year-old children with fever of unknown origin, Ibuprofen was more successful in decreasing fever.¹⁸

Schuitmaker *et al.*, in a study compared the effect of rectal 15 mg/kg Paracetamol and nasogastric in decreasing post-operative fever in 9-day-old to 7-year-old children who had undergone heart surgery, and finally no significant difference between two methods was observed.¹⁹

There are numerous studies examining antipyretic effects of Paracetamol in different clinical settings in literature, for example Kett *et al.*, evaluated the antipyretic effect and safety of intravenous Paracetamol using an endotoxin-induced fever model, which shows that intravenous Paracetamol in a single 1000-mg dose, is safe and effective in reducing fever.¹³

In another study on 210 febrile children (6 months to 6 years) with uncomplicated respiratory tract infection received oral Paracetamol (15 mg/kg) or placebo, Paracetamol achieves effective antipyretic and provides early symptomatic improvement in children with febrile illness without prolongation of fever duration or excessive adverse effects.²⁰ These studies similarly suggest Paracetamol as an effective and safe antipyretic medication and not only are the same as our findings but also could be supportive of our assumption.^{20,21}

Various studies have assessed Paracetamol in clinical surgical conditions as an analgesic agent for post-operative pain²²⁻²⁴ but as far as we know, studies regarding antipyretic effect of Paracetamol on post-operative fever are not sufficient, especially in paediatric cardiac surgery, thus our study could be one of the first randomised clinical trials evaluating Paracetamol effect in paediatrics cardiac operation.

There was potential limitation for this study due to axillary measuring of temperature. Axillary temperature is not a reliable representative of body core temperature and is technique dependent or can vary by peripheral body circulation alterations. Therefore it could be suggested to design a study by use of rectal or nasal temperature. Another limitation was that, surgery duration was different in each individual, which could affect post-operative body temperature alterations. In order to minimise these

limitations, all the temperature measurements were done just by one specific nurse and different types of surgeries were randomly and equally distributed in both Paracetamol and placebo groups.

CONCLUSION

In conclusion, this study suggests that single dose administration of intravenous Paracetamol before paediatric cardiac surgeries using CBP; limits mean body temperature rise in the first 24 h after operation.

REFERENCES

- Kane JM, Friedman M, Mitchell JB, Wang D, Huang Z, Backer CL. Association between postoperative Fever and atelectasis in pediatric patients. *World J Pediatr Congenit Heart Surg* 2011;2:359-63.
- Villasis-Keevser MA, Zapata-Arenas DM, Penagos-Paniagua MJ. Frequency of postoperative fever in children with congenital heart disease undergoing cardiovascular surgery and associated risk factors. *Rev Esp Cardiol* 2002;55:1063-9.
- Nussmeier NA. Cardiovascular anesthesiology: Management of Temperature During and After Cardiac Surgery. *Texas heart institute journal/from the texas heart institute of st luke's episcopal hospital, texas children's hospital* 2005;32:472.
- Naghavi-Behzad M, Alizadeh M, Azami S, Foroughifar S, Ghasempour-Dabbaghi K, Karzad N, *et al.* Risk factors of congenital heart diseases: A case-control study in Northwest Iran. *J Cardiovasc Thorac Res* 2013;5:5-9.
- Thong WY, Strickler AG, Li S, Stewart EE, Collier CL, Vaughn WK, *et al.* Hyperthermia in the forty-eight hours after cardiopulmonary bypass. *Anesth Analg* 2002;95:1489-95.
- Bar-Yosef S, Mathew JP, Newman MF, Landolfo KP, Grocott HP. Neurological Outcome Research Group; C A R E Investigators of the Duke Heart Center. Prevention of cerebral hyperthermia during cardiac surgery by limiting on-bypass rewarming in combination with post-bypass body surface warming: A feasibility study. *Anesth Analg* 2004;99:641-6.
- Yaghoubi A, Tabrizi JS, Mirinazhad MM, Azami S, Naghavi-Behzad M, Ghojzadeh M. Quality of life in cardiovascular patients in Iran and factors affecting it: A systematic review. *J Cardiovasc Thorac Res* 2012;4:95-101.
- Hindman BJ. Emboli, inflammation, and CNS impairment: An overview. *Heart Surg Forum* 2002;5:249-53.
- Mitchell JD, Grocott HP, Phillips-Bute B, Mathew JP, Newman MF, Bar-Yosef S. Cytokine secretion after cardiac surgery and its relationship to postoperative fever. *Cytokine* 2007;38:37-42.
- Sharma M, Ganguly NK, Chaturvedi G, Thingnam SK, Majumdar S, Suri RK. Release of pro-inflammatory mediators during myocardial ischemia/reperfusion in coronary artery bypass graft surgery. *Mol Cell Biochem* 2003;247:23-30.
- Beamer NB, Coull BM, Clark WM, Hazel JS, Silberger JR. Interleukin-6 and interleukin-1 receptor antagonist in acute stroke. *Ann Neurol* 1995;37:800-5.
- Grocott HP, Mackensen GB, Grigore AM, Mathew J, Reves JG, Phillips-Bute B, *et al.* Neurologic Outcome Research Group (NORG), Cardiothoracic Anesthesiology Research Endeavors (CARE) Investigators' of the Duke Heart Center. Postoperative hyperthermia is associated with cognitive dysfunction after coronary artery bypass graft surgery. *Stroke* 2002;33:537-41.
- Kett DH, Breitmeyer JB, Ang R, Royal MA. A randomized study of the efficacy and safety of intravenous acetaminophen vs. intravenous placebo for the treatment of fever. *Clin*

- Pharmacol Ther 2011;90:32-9.
14. Memis D, Inal MT, Kavalci G, Sezer A, Sut N. Intravenous paracetamol reduced the use of opioids, extubation time, and opioid-related adverse effects after major surgery in intensive care unit. *J Crit Care* 2010;25:458-62.
 15. Rawal N, Macquaire V, Catalá E, Berti M, Costa R, Wietlisbach M. Tramadol/paracetamol combination tablet for postoperative pain following ambulatory hand surgery: A double-blind, double-dummy, randomized, parallel-group trial. *J Pain Res* 2011;4:103-10.
 16. Macario A, Royal MA. A literature review of randomized clinical trials of intravenous acetaminophen (paracetamol) for acute postoperative pain. *Pain Pract* 2011;11:290-6.
 17. Duhamel JF, Le Gall E, Dalphin ML, Payen-Champenois C. Antipyretic efficacy and safety of a single intravenous administration of 15 mg/kg paracetamol versus 30 mg/kg propacetamol in children with acute fever due to infection. *Int J Clin Pharmacol Ther* 2007;45:221-9.
 18. Autret-Leca E, Gibb IA, Goulder MA. Ibuprofen versus paracetamol in pediatric fever: Objective and subjective findings from a randomized, blinded study. *Curr Med Res Opin* 2007;23:2205-11.
 19. Schuitmaker M, Anderson BJ, Holford NH, Woollard GA. Pharmacokinetics of paracetamol in adults after cardiac surgery. *Anaesth Intensive Care* 1999;27:615-22.
 20. Gupta H, Shah D, Gupta P, Sharma KK. Role of paracetamol in treatment of childhood Fever: A double-blind randomized placebo controlled trial. *Indian Pediatr* 2007;44:903-11.
 21. Vijarnsorn C, Winijkul G, Laohaprasitiporn D, Chungsomprasong P, Chanthong P, Durongpisitkul K, *et al.* Postoperative fever and major infections after pediatric cardiac surgery. *J Med Assoc Thai* 2012;95:761-70.
 22. Duggan ST, Scott LJ. Intravenous paracetamol (acetaminophen). *Drugs* 2009;69:101-13.
 23. Gibb IA, Anderson BJ. Paracetamol (acetaminophen) pharmacodynamics: Interpreting the plasma concentration. *Arch Dis Child* 2008;93:241-7.
 24. Ghojazadeh M, Azami-Aghdash S, Mohammadi M, Vosoogh S, Mohammadi S, Naghavi-Behzad M. Prognostic risk factors for early diagnosing of Preeclampsia in Nulliparas. *Niger Med J* 2013;54:344-8.

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