Comparison of Intravenous Infusion of Tramadol Alone with Combination of Tramadol and Paracetamol for Postoperative Pain after Major Abdominal Surgery in Children

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Abstract

Background: Pain is a common complaint after surgery and seems to be difficult to manage in children because of fear of complications of pain treatment or misconception that infants and small children do not feel pain at all or feel less pain. A survey reported that 40% of pediatric surgical patients experienced moderate or severe postoperative pain and that more than 75% had insufficient analgesia. Our study was carried out to provide continuous infusion of intravenous (i.v.) tramadol alone using a dedicated infusion device Graseby 2100 syringe pump and compared it to a combination of i.v. tramadol infusion and per rectal paracetamol. Subjects and Methods: A total of 124 children aged 1–8 years selected for the study were randomized into two groups using a table of random numbers. Power calculation had suggested a sample size of 62 in each group with a power of 80% and significance level of 5%. Group A comprising 62 children, received i.v. infusion of tramadol in a dose of 0.25 mg/kg/h for 24 h postoperatively. Group B comprising 62 children, received i.v. infusion of tramadol in a dose of 0.25 mg/kg/h for 24 h postoperatively in addition to per rectal suppository of paracetamol in a dose of 90 mg/kg in 24 h (30 mg/kg as first dose followed by 20 mg/kg every 6 hourly for the next 18 h). Postoperatively, patients were observed for 24 h. Results: A statistically significant difference (P ≤ 0.001) in Face, Legs, Activity, Cry, Consolability pain scores was seen between two groups at 4, 6, and 8 h. Pain scores being less in Group B patients who had received infusion of tramadol and per rectal suppositories of paracetamol compared to Group A patients who received only infusion of tramadol. A statistically significant difference (P < 0.05) was found in mean analgesic consumption during the first 24 h between the groups. Consumption was more in Group A as compared to Group B. In Group A, 13 patients (21%) required rescue analgesia as compared to only 4 patients (6.5%) in Group B. Conclusion: We recommend use of an infusion of tramadol in a dose of 0.25 mg/kg/h in the first 24 h after surgery, in combination with a regular per rectal paracetamol in a daily dose of 90 mg/kg/day in four divided doses for children after major abdominal surgery. However, a close nursing supervision is essential to increase the safety profile.

Keywords: Infusion, paracetamol, suppository, tramadol

John Bonica tirelessly pioneered the development of multidisciplinary concept of pain research and treatment from the Second World War until his death in 1994.1

A major problem in treating pain in children is associated with difficulty in assessment.2 Generally, two types of assessment...
tools are used in children, i.e., self-report and observation of behavior. Although visual analog scale is most commonly used to measure pain intensity in adults,\(^{[31]}\) Face, Legs, Activity, Cry, Consolability (FLACC) scale is a common measurement tool to assess pain in children between 2 months and 8 years and also in patients not able to communicate.\(^{[4]}\) Pain after surgery is inevitable, and one of the fundamental responsibilities of perioperative team is to relieve this pain. Pain after surgery can adversely affect both physical and physiological functions. Fear or anticipation of pain may inhibit coughing, necessary to clear the airways of pulmonary secretions.\(^{[5]}\) A survey reported that 40% of pediatric surgical patients experienced moderate or severe postoperative pain and that more than 75% had insufficient analgesia.\(^{[6]}\) We need to respond to this challenge and develop methodologies that allow us to provide several days of effective and safe relief of moderate to severe pain. Superior postoperative pain control may result in improved cost effectiveness, more efficient use of resources, and ultimately improved patient satisfaction.\(^{[7]}\)

Opioids are well-established and most reliable analgesics in all age groups. However, their use in extreme age groups needs strict monitoring and a robust pain service to ensure safety. Audit of control of postoperative pain in children in our institution revealed a very varied and unfortunately ineffective practice to treat pain in pediatric and plastic surgical wards. We also found that in our pediatric surgical ward, tramadol in the dosage of 1 mg/kg is added to 4 hourly fluid requirements and infused through a burette set with a poor control of infusion rate without proper monitoring of effectiveness and any side effects thereof. Since this pain management therapy has not been properly investigated and pain assessment has not been carried out, our study was carried to provide continuous infusion of intravenous (i.v.) tramadol alone using a dedicated infusion device Graseby 2100 syringe pump and compare it to a combination of i.v. tramadol infusion and per rectal paracetamol.

**Subjects and Methods**

This prospective, randomized, double-blind study was conducted in the Department of Anesthesiology and Critical Care and Department of Pediatric Surgery, after approval from the Institutional Ethical Committee in the pediatric age group of 1–8 years during 2014–2016. The study aimed to compare the analgesic effect of i.v. infusion of tramadol alone and in combination with per rectal paracetamol on postoperative pain in pediatric patients undergoing abdominal surgery. After obtaining informed consent from parents, we recruited a total of 124 children, 1–8 years old belonging to American Society of Anesthesiologist (ASA) Classes I and II, posted for routine major abdominal surgery. Children with hypersensitivity to tramadol, preexisting neurological disease, coagulopathy, spinal deformity, and infection in the sacral area or with known seizure disorder were excluded from the study. Main investigator was blinded to the group distribution of children, i.e., was not knowing which of these children have received per rectal paracetamol.

The patients selected for the study were kept fasting on solids and milk for 6 h, and clear liquids were allowed for up to 2 h preoperatively. The standard monitoring included electrocardiography, heart rate, pulse oximetry, noninvasive blood pressure, end-tidal carbon dioxide, temperature and vapor concentration at induction and during the operative procedure. No premedication was used. Patients were induced with 2–4 mg/kg of propofol or with inhaled sevoflurane in oxygen and nitrous oxide as inhalational agents if i.v. access was not available. Injection fentanyl (2 µg/kg) and atracurium (0.5 mg/kg) were injected to facilitate endotracheal intubation. Injection dexamethasone 0.15 mg i.v. was given to all the children as prophylactic antiemetic. The caudal block was performed with 1.5 ml/kg of 0.2% ropivacaine in all the children. Anesthesia was maintained with oxygen, nitrous oxide, and isoflurane through circle absorber using low flows with continuous monitoring of age-adjusted vapor and minimum alveolar concentration (MAC), keeping it between 1.2 and 1.3 (i.e., MAC 95). Intraoperative analgesia was supplemented by intermittent boluses of 2 µg/kg of fentanyl whenever necessary during surgery. Ondansetron in a dose 0.1 mg/kg was given as additional antiemetic before extubation. Patients were reversed and extubated awake and transferred to postanesthesia care unit (PACU) for monitoring and pain assessment and management.

Once fully awake, pain free, and stable in PACU, i.v. infusion of tramadol was started in the PACU so that there was no break in the analgesia provided in these 24 h of the study period. The patients selected for the study were randomized into two groups using a table of random numbers. Power calculation had suggested a sample size of 62 in each group with a power of 80% and significance level of 5%.

- **Group A:** comprising 62 patients, received i.v. infusion of tramadol in a dose of 0.25 mg/kg/h for 24 h postoperatively
- **Group B:** comprising 62 patients, received i.v. infusion of tramadol in a dose of 0.25 mg/kg/hr for 24 h postoperatively in addition to per rectal suppository of paracetamol in a dose of 90 mg/kg in 24 h (30 mg/kg as first dose followed by 20 mg/kg every 6 hourly for the next 18 h). Postoperatively, patients were observed for 24 h, and following parameters were observed and analyzed.

Age, weight, ASA class, type of surgery, duration of surgery, FLACC pain scores at 1, 2, 3, 4, 6, 8, 12, 16, 20, 24 h postoperatively. The frequency of rescue analgesia used with episodes of nausea and vomiting were noted.

Descriptive statistics of data including the mean and standard deviation for numerical variables and the percentages of different categories were obtained. Student’s \( t \)-test was employed for parametric data. Chi-square or Fischer Exact test whichever appropriate was used for nonparametric data. \( P < 0.05 \) was considered statistically significant.
Table 1: Comparison of age, weight and duration of surgery between two groups

| Group | Age (years) | Weight (kg) | Duration of Surgery (minutes) |
|-------|-------------|-------------|------------------------------|
|       | Mean | SD | Range | P | Mean | SD | Range | P | Mean | SD | Range | P |
| A     | 4.9  | 2.24 | 1-8 | 0.098 | 18.6 | 7.03 | 7-33 | 0.449 | 105.8 | 38.98 | 45-165 | 0.513 |
| B     | 4.3  | 1.77 | 1-8 |           | 17.7 | 6.68 | 7-34 |           | 101.6 | 32.41 | 65-170 |           |

**RESULTS**

The two groups were comparable with reference to age, weight, ASA physical status classes, and duration of surgery [Tables 1 and 2]. No statistically significant difference was found to be present in FLACC scores between the two groups at 1, 2, and 3 h postoperatively [Table 3]. However, there was a statistically significant difference ($P < 0.001$) in FLACC pain scores between two groups at 4, 6, and 8 h, pain scores being less in Group B patients who had received infusion of tramadol and per rectal suppositories of paracetamol compared to Group A patients who received only infusion of tramadol [Table 4].

Mean analgesic consumption during the first 24 h was more ($137.3 \pm 42.84$) in Group A as compared to Group B ($106.1 \pm 41.70$) [Table 5]. In Group A, 13 patients (21%) required rescue analgesia at mean time of $5.8 \pm 0.98$ h as compared to only 4 patients (6.5%) in Group B at mean time of $6.5 \pm 1.01$ h, respectively. The difference was found to be statistically significant ($P < 0.05$) [Table 6]. More patients in Group A had side effects, but the difference was statistically insignificant [Table 7].

**DISCUSSION**

“Acute postoperative pain is a complex physiological reaction to tissue injury, visceral distention, or disease. It is a manifestation of autonomic, psychological, and behavioral responses that result in patient-specific unpleasant, unwanted sensory, and emotional experience.” [8]

Multimodal analgesia is a rational approach to pain management and is more effective. The aim of multimodal analgesia combination is to reduce postoperative pain and to minimize or prevent the side effects of drugs used. The aim of our study was to compare the duration and analgesic efficacy of i.v. infusion of tramadol alone and when used in combination with per rectal paracetamol in children aged 1–8 years in the postoperative period after major abdominal surgery. Demographic data, ASA physical status classes, and mean duration of surgery were comparable in both groups.

The observations in our study clearly demonstrated lower FLACC pain scores in both the groups for the 24-h study period, during which i.v. infusion of tramadol was used [Figure 1]. However, there was a statistically significant difference ($P \leq 0.001$) in FLACC pain scores between the two groups at 4, 6, and 8 h, pain scores being less in Group B patients who had received infusion of tramadol and per rectal suppositories of paracetamol compared to Group A patients who received only infusion of tramadol. This could be attributed to the use of paracetamol suppository in Group B patients in addition to the tramadol infusion. However, we cannot explain why the statistically significant difference was achieved only at 4, 6, and 8 h after starting the infusion postoperatively when Group B patients received per rectal paracetamol suppositories on a regular basis after every 6 h irrespective of the FLACC pain scores. It is very important to note that with this regime of tramadol infusion, patients in both groups were more or less comfortable during the infusion period [Table 8].

The results of our study go in agreement with Fricke et al.,[9] who found the superiority of tramadol-paracetamol combination over tramadol alone in the treatment of acute pain following oral surgery. Ali and Khan[10] conducted a study to compare the analgesic efficacy of tramadol alone using a higher dose (1.5 mg/kg) with tramadol (1 mg/kg) and paracetamol combination in day-care laparoscopic adult female patients. They also demonstrated clear efficacy of the multimodal analgesic combination in reducing the mean pain scores and at the same time reducing the side effects. Another study which is in agreement with our results comes from Emir et al.,[11] who compared the effectiveness of tramadol versus low dose tramadol and paracetamol on postoperative pain using numeric rating pain scale in spine vertebral surgery and found that pain scores were significantly lower in the group that received low dose tramadol and paracetamol combination than that in the group that received tramadol alone. Kiliçaslan et al.,[12] in their study compared the effects of i.v. paracetamol combined with patient-controlled i.v. analgesia using tramadol versus tramadol alone in elective cesarean operations for postoperative pain control. They concluded that paracetamol is a safe and effective treatment option in postcesarean pain for combination with tramadol, as it produces effective analgesia and reduces tramadol consumption and side effects. Rawal et al.,[13] found that following ambulatory hand surgery under regional i.v. anesthesia, postoperative pain management was comparable but with a better safety profile in patients using a combination of tramadol and paracetamol as opposed to using a higher dose.

Table 2: ASA distribution

| ASA | Group A | Group B | P  |
|-----|---------|---------|----|
| No. | Percent | No.     | Percent |
| ASA I | 55 | 88.7 | 52 | 83.9 | 0.433 |
| ASA II | 7 | 11.3 | 10 | 16.1 |
| Total | 62 | 100 | 62 | 100 |
of tramadol alone, again confirming a better pain management with multimodal regimes.

Our study observations are also in agreement with the study of Spagnoli et al., who compared the efficacy between an analgesic combination of tramadol and paracetamol to paracetamol alone for acute postoperative pain after hand and foot surgery. They found that the pain score after surgery was significantly lower in the group that received tramadol and paracetamol combination. Alfano et al., compared in their study, the analgesic efficacy of two fixed combinations of tramadol and paracetamol and codeine and paracetamol, and they found tramadol-paracetamol combination was superior to codeine paracetamol as far as analgesic efficacy was concerned.

In our study, mean analgesic consumption during the first 24 h was more (137.3 ± 42.84) in Group A compared to Group B (106.1 ± 41.70). In Group A, 13 patients (21%) required rescue analgesia at mean time of 5.8 (±0.98) hours as compared to only 4 patients (6.5%) in Group B at mean time of 6.5 (±1.01) hours, respectively. The difference was found to be significant ($P < 0.05$). As far as overall analgesic consumption in our study is concerned, various other authors have also observed similar findings. Emir et al. found that additional analgesic requirement and the total dose of tramadol were lower in Group P (tramadol-paracetamol) than in Group T (tramadol). Kiliçaslan et al. also reported that the cumulative tramadol consumption was lower in the paracetamol-tramadol group than the control group that received tramadol only. Spagnoli et al. also found that analgesic requirement was significantly lower in tramadol-paracetamol group. Alfano et al. reported that less patients required rescue medications, 5.5%
from tramadol-paracetamol group compared to 18.2% from codeine-paracetamol group.

In our study, seven patients in Group A had nausea and four patients had vomiting, while in Group B, four patients had nausea and two patients had vomiting [Table 7]. More patients had side effects in Group A compared to Group B but the difference was statistically insignificant ($P > 0.05$). As far as the side effect profile is concerned, various authors also reported either a decrease in side effect profile with tramadol-paracetamol combination or no difference at all. Fricke et al.\cite{9} found that nausea, dizziness, and vomiting occurred more frequently in the tramadol group than in the tramadol-paracetamol group.

Kiliçaslan et al.\cite{12} found no significant difference in nausea and vomiting between the groups ($P > 0.05$). Rawal et al.\cite{13} reported that tramadol-paracetamol treatment showed a better safety profile than tramadol alone, and overall incidence of nausea, vomiting, and sedation scores was markedly lower in the combination group. Alfano et al.\cite{11} also reported decreased incidence of side effects in tramadol-paracetamol group than in codeine-paracetamol group, and they had a statistically significant difference with a $P < 0.01$ in favor of tramadol-paracetamol group. The lower incidence of nausea, vomiting, or both in our study could be attributed to use of ondansetron in a dose of 0.1 mg/kg every 6 hourly during the infusion period.

One of the limitations of our study is that we started the infusion of tramadol without giving a bolus dose, which could have resulted in poor analgesia in the postoperative period. This was done to avoid sedation as a result of use of a combination of tramadol and an opioid such as fentanyl, which was used intraoperatively to provide analgesia. If children would have been in any sort of discomfort as a result of pain, they had to be given tramadol bolus before the infusion would be commenced as children who complained of pain postoperatively were given tramadol as rescue analgesia. Another limitation is the use of continuous monitoring of children for respiratory depression and sedation. Children had to be monitored for seizure activity though rare.

**Conclusion**

We recommend the use of an infusion of tramadol in a dose of 0.25 mg/kg/h in the first 24 h after surgery, in combination with a regular per rectal paracetamol in a daily dose of 90 mg/kg/day in four divided doses for children after major abdominal surgery if facilities for continuous infusion of epidural analgesia are not available. However, a close nursing supervision is essential to increase the safety profile.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Bonica JJ. The Management of Pain. 2nd ed., Vol. 1. Philadelphia: Lea and Febiger; 1990. p. 18-27.
2. Keuren KV, Eland JA. Perioperative pain management in children. Nurs Clin North Am 1997;32:31-44.
3. Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper D, Hauser SL, et al. In: Harrison’s Principles of Internal Medicine. 14th ed., Ch. 12. New York: McGraw-Hill; 1997.
4. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: A behavioral scale for scoring postoperative pain in young children. Pediatr Nurs 1997;23:293-7.
5. Kotiniemi LH, Ryhänen PT, Moilanen IK. Behavioural changes in children following day-case surgery: A 4-week follow-up of 551 children. Anaesth Analg 1997;52:970-6.
6. Goregaonkar A, Maroli S, Mehta S, Pawar D. Post op pain relief for ambulatory surgery. Indian Med Gaz 2003;138-50.
7. Mather L, Mackie J. The incidence of postoperative pain in children. Pain 1983;15:271-82.
8. Asokumar B, Lubenow TR, Kroin JS. Postoperative pain and its management. In: Wall & Melzack’s Textbook of Pain. 6th ed., Ch. 46. Philadelphia: Elsevier Health Sciences; 2013. p. 629.
9. Fricke JR Jr., Hewitt DJ, Jordan DM, Fisher A, Rosenthal NR. A double-blind placebo-controlled comparison of tramadol/acetaminophen and tramadol in patients with postoperative dental pain. Pain 2004;109:250-7.
10. Ali M, Khan FA. Comparison of analgesic effect of tramadol alone and a combination of tramadol and paracetamol in day-care laparoscopic surgery. Eur J Anaesthesiol 2009;26:475-9.
11. Emir E, Serin S, Erbey RH, Sungurtek H, Tomatir E. Tramadol versus low dose tramadol-paracetamol for patient controlled analgesia during spinal vertebral surgery. Kaohsiung J Med Sci 2010;26:308-15.
12. Kiliçaslan A, Tuncer S, Yüceaktas A, Uyar M, Reisi R. The effects of intravenous paracetamol on postoperative analgesia and tramadol consumption in cesarean operations. Agri 2010;22:7-12.
13. 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.
14. Spagnoli AM, Rizzo MI, Palmieri A, Sorvillo V, Quadrini L, Scuderio N. A single blind controlled comparison of tramadol/paracetamol combination and paracetamol in hand and foot surgery. A prospective study. In Vivo 2011;25:291-5.
15. Alfano G, Grieco M, Forino A, Meglio G, Pace MC, Iannotti M. Analgesia with paracetamol/tramadol vs. paracetamol/codeine in one day-surgery: A randomized open study. Eur Rev Med Pharmacol Sci 2011;15:205-10.