COMPARISON OF INTRAVENOUS PARACETAMOL AND TRAMADOL AS PRE-EMPTIVE ANALGESIC FOR LOWER ABDOMINAL SURGERIES IN CHILDREN- A PROSPECTIVE RANDOMISED DOUBLE-BLIND STUDY

Seham Syeda¹, Jyothi B², Pratishruti Singh³, Safiya I. Shaikh⁴

¹Senior Resident, Department of Anaesthesiology, NIMHANS, Bengaluru, Karnataka, India.

²Associate Professor, Department of Anaesthesiology, KIMS, Hubballi, Karnataka, India.

³Postgraduate Student, Department of Anaesthesiology, KIMS, Hubballi, Karnataka, India.

⁴Professor and HOD, Department of Anaesthesiology, KIMS, Hubballi, Karnataka, India.

ABSTRACT

BACKGROUND

Pre-emptive analgesia is administration of an analgesic before a painful stimulus, so as to prevent central sensitisation. Intravenous (IV) formulation of paracetamol has been introduced and its safety and pharmacokinetic properties have been established for children providing excellent analgesia and avoiding side effects associated with opioids and non-steroidal anti-inflammatory drugs. Present study was done to compare the analgesic effects of pre-emptive I.V. paracetamol and tramadol in children undergoing lower abdominal surgeries.

MATERIALS AND METHODS

Sixty-four children of ASA physical status I and II, aged 2 to 12 years scheduled for elective lower abdominal surgeries under general anaesthesia were recruited for a prospective, randomized controlled, double blinded study, into group P and group T. Following induction, group P received 15 mg/kg I.V. paracetamol and group T 1 mg/kg tramadol in 75 ml of normal saline over 15 minutes before surgical stimulus. Postoperative modified objective pain scale (OPS), time to first rescue analgesia (FRA), Aldrete score, time to reach Aldrete score > 9, sedation scores, parent satisfaction scores and PONV were recorded for 24 hours.

RESULTS

Mean pain scores by OPS in group P and T were similar and statistically insignificant. Time to FRA being 320 ± 20 min in group P as compared to group T 340 ± 30 min. 12.5% patients had PONV in group P as compared to 81.5% in group T ($p \leq 0.05$). Mean duration to reach Aldrete score of 9 was 11 ± 1.5 min and 16.7 ± 3 min in group P and T respectively ($p \leq 0.05$).

CONCLUSION

Pre-emptive I.V. paracetamol is as efficacious as I.V. tramadol for postoperative analgesia with early recovery and lower incidence of PONV in paracetamol group.

KEYWORDS

Paediatric, Postoperative Pain, Paracetamol, Tramadol.

HOW TO CITE THIS ARTICLE: Syeda S, Jyothi B, Singh P, et al. Comparison of intravenous paracetamol and tramadol as pre-emptive analgesic for lower abdominal surgeries in children- a prospective randomised double-blind study. J. Evolution Med. Dent. Sci. 2019;8(09):599-603, DOI: 10.14260/jemds/2019/133

BACKGROUND

Children can have most displeasing experience due to acute pain secondary to injury, illness or surgical intervention.¹ Pre-emptive analgesia is regional or systemic analgesics administered prior to painful stimulus thereby preventing central sensitisation and subsequently reducing the analgesic requirement.^{2,3} The practice of multimodal analgesia is preferred for acute pain management in children with combination of drugs (NSAIDs, opioids, paracetamol etc.) and regional anaesthesia. Opioids provide satisfactory analgesia and better emergence, but prolonged sedation and other undesirable side effects such as post-operative nausea and

vomiting (PONV), respiratory depression, pruritus and urinary retention prolongs the recovery time and delayed discharge from the hospital⁴. NSAIDs are effective in reducing postoperative pain with a lower risk of PONV, however they introduce the possibility of increased bleeding due to its anti-platelet action.^{5,6}

Tramadol is a synthetic analogue of codeine which binds to opioid receptors and inhibits norepinephrine and serotonin uptake. Tramadol is efficacious in pain relief with its negligible effect on respiration when compared to traditional opioids.⁶ Paracetamol is a non-opioid analgesic which is devoid of risks associated with opioid and NSAIDs⁷. Its analgesic action is mediated by central inhibition of cyclooxygenase 2 (COX2), inhibition of nitric oxide generation via blockade of N-methyl D aspartate receptors and activation of descending serotonergic pathways. Although, enteral formulations of paracetamol are the most commonly used, they are weak analgesic. Intravenous (I.V) paracetamol has been approved by FDA in 2011 for children more than 2 years of age. The target plasma concentration is achieved rapidly with reduced variability via intravenous compared to enteral route.

'Financial or Other Competing Interest': None.

Submission 15-06-2018, Peer Review 16-02-2019,

Acceptance 22-02-2019, Published 04-03-2019.

Corresponding Author:

Dr. Jyothi B,

Associate Professor,

Department of Anaesthesiology,

KIMS, Hubballi,

Karnataka, India.

E-mail: dr.jyothib1@gmail.com

DOI: 10.14260/jemds/2019/133

A prospective randomized controlled, double blind study was conducted to evaluate the efficacy of pre-emptive I.V. paracetamol on postoperative analgesia and its effect on quality of recovery as compared to I.V. tramadol in children undergoing elective lower abdominal surgeries under general anaesthesia. The primary outcome of our study was to determine the duration of postoperative analgesia and the secondary outcome was to evaluate the quality of recovery, frequency of PONV and satisfaction scores among parents.

MATERIALS AND METHODS

A randomized controlled, double blind clinical study protocol was approved by institutional ethical committee. Based on previous article a minimum sample size of 26 in each group was obtained for detecting a difference of 8 min for time to FRA and population SD of 10 min with alpha of 5% and power of 80%. A final total sample of 64 with 32 in each group was taken to avoid losses to follow-up. Written informed consent was obtained from patient's parents. Sixty-four patients of American Society of Anaesthesiologists (ASA) I and II, aged between 2-12 years undergoing elective lower abdominal surgeries were included in the study protocol. Children who were allergic to the study drugs, those who had taken NSAIDs or any analgesic prior to 12 hours of surgery, acute renal and hepatic impairment were excluded from study. All children in the study were assessed by a preanesthetic evaluation a day prior to surgery and were fasted from solid food for 6 hours and clear fluids were permitted 2 hours prior to surgery.

Oral midazolam 0.5 mg/kg was given to children as a premedicant 30 minutes prior to surgery. Monitors like non-invasive blood pressure (NIBP), electrocardiography (ECG), pulse oximetry (SpO₂) and end tidal carbon dioxide (ETCO₂) monitors were connected. Children were pre-oxygenated with oxygen for 3 minutes. All children were induced by standard general anaesthesia with intravenous fentanyl 2 µg/kg, thiopentone sodium 5 mg/kg and 0.1 mg/kg vecuronium bromide. After endotracheal intubation, anaesthesia was maintained with 60% N₂O in oxygen, sevoflurane to a MAC of 0.7 and intermittent boluses of vecuronium.

The study drug was then prepared by an anaesthesiologist who is not involved in anaesthetizing the patient. The medications were diluted with normal saline to a total volume of 75ml. The anaesthesiologists who were administering the anaesthesia and assessing the parameters were blinded to the study drug being administered.

Randomisation and allocation were done by computer generated random number table through sequentially numbered, sealed, opaque envelopes which was opened just after induction of anaesthesia. Following induction and prior to skin incision, children were allocated to one of the two groups with 32 patients in each group. Patients in Group P (Paracetamol) received 15 mg/kg of I.V. paracetamol and group T (Tramadol) received 1 mg/kg of I.V. tramadol over 15 minutes (min).

Additional opioids were not administered intraoperatively. Intravenous fluid managed with ringer lactate solution, according to body weight fluid deficit and maintenance was calculated and replaced. At the end of the procedure neuromuscular blockade was reversed with I.V. neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg, and

extubated when respiration was adequate and regular. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and end tidal carbon-dioxide (ETCO₂) were continuously monitored throughout the procedure.

Postoperative observational pain scores (OPS) described by Hannallah et al,⁸ Aldrete score,⁹ time to reach modified Aldrete score (MAS) of 10, HR and mean arterial blood pressure (MAP) were recorded for one hour in post-anaesthetic care unit (PACU). Patients were then transferred to the ward. Postoperative pain was assessed using OPS at 2, 4, 6, 8, 10, 12 and 24 hours. This scale has been validated in infants and children between 2-13 years of age with scores ranging from 0 to 10.¹⁰

During first six hours OPS of 4 or more received rescue analgesic with I.V. meperidine 0.5 mg/kg and after 6 hours oral paracetamol 20 mg/kg was administered every 6 hourly. In the postoperative care unit hemodynamic parameters and scores were assessed by the same anaesthesiologist who was unaware of the patient group assignment. Adverse effects such as postoperative nausea and vomiting (PONV), sedation scores were recorded.

Nausea was defined as unpleasant feeling associated with intention to vomit and vomiting was defined as forceful ejection of gastric contents through mouth. Assessment of sedation was done by using a four-point scale where 0 - fully awake, 1 - awake but drowsy, 2 - sleeping but arousable by light touch or speech 3 - sleeping, not arousable. At the end of the study parents were asked to assess the quality of postoperative analgesia using parent satisfaction scores which were as follows: - 1 - bad, 2 - poor, 3 - good and 4 - excellent.

All statistical analysis was performed using SPSS for Windows, version 11 (SPSS Chicago IC). Continuous data was summarized as Mean & SD and analysed using t test. Categorical data was summarized as frequency &/or percentage and was analysed using Chi square or Fischer exact test. Kaplan Meir survival curves were constructed for time to discharge (time to achieve MAS of 10) for two groups and analysed using log rank test. P value less than 0.05 was considered significant for all statistical analysis.

RESULTS

Demographic data concerning patient's age, sex, weight, duration of surgery and anaesthesia and surgery were similar and comparable in the study groups (Table 1). Postoperative pain score by OPS at different time intervals (Graph 1 and Table 2) were statistically insignificant between two groups. Highest pain scores in both groups was noted at 6 hours postoperatively which decreased following administration of rescue analgesia. Time to first rescue analgesia (FRA) being 340±23.6 min in group P and 320±20.3 in group T which was significant (p =0.0006, Table 3) Number of patients with MAS of 10 was 71.8% and 56.25% in group P and group T respectively, time taken to reach MAS of 10 as 11.03±1.18 in group P and 16.72±3.37 in group T, with the difference between two being statistically significant (p <0.05) as shown in table 4. Kaplan—Meier survival curves showed that Paracetamol group patients reached Aldrete score of 10 faster than patients in Tramadol group (P < 0.001). Time to discharge was shorter with paracetamol. (Graph 2 and Table 5) Parent satisfaction scores weren't statistically different in both groups.

Patients in group T had higher frequency of PONV when compared to group P (Table 6). Sedation scores was higher in group T when compared to group P with mean value being 0.80, 0.56, 0.41, 0.41, 0.19 and 0.19 at 0, 2, 4, 6, 8, 10, 12 and 24 hours respectively and statistically significant. (Table 7)

Variable	Group	n	Mean	SD	Independent t Test	
					t Value	p Value
Age (Years)	P Group	32	8.09	2.48	0.0482	0.9617
	T Group	32	8.06	2.70		
Weight (Kg)	P Group	32	23.38	5.64	1.205	0.2327
	T Group	32	21.69	5.56		
Duration of Surgery (Min)	P Group	32	45.41	15.59	0.315	0.7533
	T Group	32	44.16	16.08		

Table 1. Distribution of Study Groups with Respect to Age, Weight and Duration of Surgery

Time	Group	N	Mean	SD	Independent t test	
					t-value	P-value
0 hrs.	P Group	32	2.81	0.54	-0.825	0.412
	T Group	32	2.94	0.67		
2 hrs.	P Group	32	2.38	0.49	-0.502	0.612
	T Group	32	2.44	0.50		
4 hrs.	P Group	32	2.22	0.42	-0.569	0.570
	T Group	32	2.28	0.46		
6 hrs.	P Group	32	4.44	0.88	0.505	0.615
	T Group	32	4.31	1.09		
8 hrs.	P Group	32	3.75	0.72	0.167	0.867
	T Group	32	3.72	0.77		
10 hrs.	P Group	32	3.19	0.59	-1.002	0.320
	T Group	32	3.34	0.65		
12 hrs.	P Group	32	2.06	0.25	0.000	1.000
	T Group	32	2.06	0.25		
24 hrs.	P Group	32	2.03	0.18	0.000	1.000
	T Group	32	2.03	0.18		

Table 2. Comparison of Ops Between Group P and Group T at Different Time Points

Group	Mean	SD	Independent t Test	
			t Value	p Value
P group	340	23.6	3.634	0.0006*
T group	320	20.3		

Table 3. Comparison Group of P and T with Respect to Time for First Rescue Analgesic in Min

Group	Mean	SD	Independent t Test	
			t Value	p Value
P group	11.03	1.18	9.015	0.0001*
T group	16.72	3.37		

Table 4. Comparison of Group P and T with Respect to Time Taken to Reach MAS of 10 in Min

*p<0.05

	Mean			Median			Log Rank Test
	Estimate	95 % CI		Estimate	95 % CI		
		Lower	Upper		Lower	Upper	
Paracetamol	11.41	10.94	11.88	12	11.29	12.72	P <0.001
Tramadol	17.88	16.45	19.32	18	16.83	19.17	
Overall	15.34	14.13	16.55	15	13.13	16.87	
Table 5. Time to Reach Modified Aldrete Score of 10							

Table 5. Time to Reach Modified Aldrete Score of 10

Time	P group (n=32)	T group (n=32)	Total (n=64)	Fischer Exact Test
0 hrs.	0 (0)	26 (81.25)	26 (40.63)	P < 0.001*
2 hrs.	2 (6.25)	15 (46.88)	17 (26.56)	P < 0.001*
4 hrs.	2 (6.25)	13 (40.63)	15 (23.44)	P = 0.002*
6 hrs.	0 (0)	13 (40.63)	13 (20.31)	P < 0.001*
8 hrs.	0 (0)	13 (40.63)	13 (20.31)	P < 0.001*
10 hrs.	0 (0)	6 (18.75)	6 (9.38)	P = 0.024*
12 hrs.	0 (0)	6 (18.75)	6 (9.38)	P = 0.024*
24 hrs.	0 (0)	4 (12.5)	4 (6.25)	P = 0.113

Table 6. Comparison of Group P and T with Respect to PONV At Different Time Points

*Significant

Time	Group	n	Mean	SD	Z value	P-value
0 hrs.	P Group	32	0.00	0.00	-5.5857	0.00001*
	T Group	32	0.81	0.40		
2 hrs.	P Group	32	0.06	0.25	-2.7928	0.0052*
	T Group	32	0.47	0.51		
4 hrs.	P Group	32	0.06	0.25	-2.3632	0.0181*
	T Group	32	0.41	0.50		
6 hrs.	P Group	32	0.00	0.00	-2.7928	0.0052*
	T Group	32	0.41	0.50		
8 hrs.	P Group	32	0.00	0.00	-2.7928	0.0052*
	T Group	32	0.41	0.50		
10 hrs.	P Group	32	0.00	0.00	-1.2890	0.1974
	T Group	32	0.19	0.40		
12 hrs.	P Group	32	0.00	0.00	-1.2890	0.1974
	T Group	32	0.19	0.40		
24 hrs.	P Group	32	0.00	0.00	-0.8593	0.3902
	T Group	32	0.13	0.34		
Table 7. Comparison of Sedation Scores in Group P and Group T at Different Time Points						
*p<0.05						

DISCUSSION

Optimal treatment of post-operative pain is of paramount importance in order to reduce the morbidity and mortality associated with surgery. Most commonly used drugs are opioids and NSAIDs. Previously, oral/rectal paracetamol has been used as a sole analgesic or in combination with other analgesics. An IV formulation of paracetamol, soluble in water, being available and intravenous route being preferred in the peri-operative period to administer rapid analgesia, we decided to conduct a study comparing the analgesic efficacy of I.V. paracetamol 15 mg/kg and tramadol 1 mg/kg in children undergoing lower abdominal surgeries.

No statistical difference in the OPS was noted between both the groups. The highest pain scores by OPS were recorded six hours postoperatively. Also, the need of rescue analgesia was first noted after 6 hours and not before, in both the groups. This could be attributable to the comparable duration and equi-potency of the drugs in our study. Our research is in harmony with the study conducted by H.Y. Uysal et al,¹¹ who noted that there was no difference in post-operative pain scores in children between I.V. paracetamol and I.V. tramadol groups. However, they conducted this study in patients undergoing adenotonsillectomy.

Evaluation of recovery characteristics, requirement of rescue analgesic and side effects associated with drugs in study group were our secondary objectives. Despite a need for higher rescue analgesics in both groups, pain scores remained on lower scale during study period.

Our study noted the time to reach MAS of 10 was slightly faster with paracetamol compared to tramadol which wasn't statistically significant yet worth mentioning. Also, paracetamol recipients had earlier discharge compared to tramadol. Authors believe that higher rates of PONV and sedation with tramadol are the main culprits for the above findings. Tracheal intubation, opioids and use of nitrous oxide would have acted synergistically with tramadol.^{12,13,14} However the parents were satisfied equally with the both the drugs.

Our study was in conflict with the study by Pendeville et al¹⁵ where I.V. paracetamol resulted in higher postoperative pain scores than did I.V. tramadol given before surgical incision. This could be due to the variable and high

drug doses used in their study. We advocate further study to evaluate and compare different doses of paracetamol i.e. 15 mg/kg and 30 mg/kg to study the minimum requirement for effective analgesia.

The choice of a control group is a paramount importance when one conducts a study. Here we selected tramadol as a control group as it is our routine practice to use it as an intraoperative analgesic. Our study was in disagreement with the results of Alhashemi and Daghistani¹⁶ who used meperidine as an analgesic. Meperidine being a better and stronger analgesic will definitely outperform paracetamol. Hence a larger study comparing the potency and side effect profile of different analgesics with different doses by i.v route used routinely should be studied.

CONCLUSION

Intravenous paracetamol with its early recovery profile and lower incidence of PONV is as efficacious as intravenous tramadol for postoperative analgesia in children undergoing lower abdominal surgeries.

REFERENCES

- [1] Kraemer WF. Treatment of acute pediatric pain. *Semin Pediatr Neurol* 2010;17(4):268-74.
- [2] Grape S, Tramèr MR. Do we need preemptive analgesia for the treatment of postoperative pain? *Best Pract Res Clin Anaesthesiol* 2007;21(1):51-63.
- [3] Caliskan E, Sener M, Kocum A, et al. The efficacy of intravenous paracetamol versus dipyron for postoperative analgesia after day-case lower abdominal surgery in children with spinal anesthesia: a prospective randomized double-blind placebo-controlled study. *BMC Anesthesiology* 2013;13(1):34.
- [4] Viitanen H, Annala P. Analgesic efficacy of tramadol 2 mg kg (-1) for paediatric day-case adenoidectomy. *Br J Anaesth* 2001;86(4):572-5.
- [5] Marret E, Flahault A, Samama CM, et al. Effects of postoperative, nonsteroidal, antiinflammatory drugs on bleeding risk after tonsillectomy: meta-analysis of randomized, controlled trials. *Anesthesiology* 2003;98(6):1497-502.
- [6] Lundeborg S, Lönnqvist PA. Update on systemic postoperative analgesia in children. *Paediatric Anaesthesia* 2004;14(5):394-7.
- [7] Pickering G, Lorient MA, Libert F, et al. Analgesic effect of acetaminophen in humans: first evidence of a central serotonergic mechanism. *Clin Pharmacol Ther* 2006;79(4):371-8.
- [8] Hannallah RS, Broadman LM, Belman AB, et al. Comparison of caudal and ilioinguinal/iliohypogastric nerve blocks for control of post orchiopexy pain in pediatric ambulatory surgery. *Anesthesiology* 1987;66(6):832-4.
- [9] Aldrete JA. The post-anesthesia recovery score revisited. *J Clin Anesth* 1995;7(1):89-91.
- [10] Aspinall RL, Mayor A. A prospective randomized controlled study of the efficacy of ketamine for postoperative pain relief in children after adenotonsillectomy. *Paediatric Anaesthesia* 2001;11(3):333-6.

- [11] Uysal HY, Takmaz SA, Yaman F, et al. The efficacy of intravenous paracetamol versus tramadol for postoperative analgesia after adenotonsillectomy in children. *J Clin Anesth* 2011;23(1):53-7.
- [12] Ewah BN, Robb PJ, Raw M. Postoperative pain, nausea and vomiting following paediatric day-case tonsillectomy. *Anaesthesia* 2006;61(2):116-22.
- [13] Van den Berg AA, Halliday E, Lule EK, et al. The effects of tramadol on postoperative nausea, vomiting and headache after ENT surgery. A placebo controlled comparison with equipotent doses of nalbuphine and pethidine. *Acta Anaesthesiol Scand* 1999;43(1):28-33.
- [14] Pang WW, Mok MS, Huang S, et al. Intraoperative loading attenuates nausea and vomiting of tramadol patient-controlled analgesia. *Can J Anaesth* 2000;47(10):968-73.
- [15] Pendeville PE, Von Montigny S, Dort JP, et al. Double blind randomized study of tramadol vs. paracetamol in analgesia after day-case tonsillectomy in children. *Eur J Anaesthesiology* 2000;17(9):576-82.
- [16] Alhashemi JA, Daghisthani MF. Effects of intraoperative I.V. acetaminophen vs i.m. meperidine on post-tonsillectomy pain in children. *Br J Anaesth* 2006;96(6):790-5.