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Intravenous paracetamol infusion and tramadol as agents for post operative pain relief in urosurgical patient: A randomized control trial

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***Abstract*---**Analgesia is one of the most important consideration in perioperative setting as it determines the recovery and discharge of a patient. Among the drugs used for analgesia, non steroidal anti-inflammatory drugs and opioids are the most commonly used ones in the current scenario. The aim of this study was to compare the efficacy of intravenous (IV) paracetamol and IV tramadol in alienating pain postoperatively. 100 adult patients of ASA grade I & II in the age group of 25-55 years were randomized into two groups of 50 patients, scheduled for elective urosurgical procedures and were administered IV paracetamol and IV tramadol 30 minutes before the completion of

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surgery for postoperative analgesia and assessment was done with visual analog scale (VAS) score. In the present study, both the drugs showed effective pain relief. The onset of analgesia is faster in tramadol group. In paracetamol group, the onset of analgesia was slightly delayed but pain scores significantly decreased after 60 min, and this was observed up to 6 h with a statistically significant decrease in post operative nausea vomiting (PONV)with paracetamol group . IV paracetamol is a better and safer alternative to tramadol with better VAS scores and lesser PONV postoperatively. Hence, it contributes to lesser time of stay in the hospital and earlier discharge.

***Keywords*---**paracetamol, tramadol, postoperative pain.

Introduction

Ten to 50% of patients with post surgical pain develop chronic pain and good analgesia post operatively lowers the days of hospitalization ,complications and provides better patient satisfaction.[1] Paracetamol inhibits prostaglandins and neither interferes with platelet function nor is nephrotoxic whereas chances of adverse reactions are less than 1/10,000 individuals.[6] Tramadol belongs to aminocyclohexanol group acting selectively on mu receptors.It also inhibits synaptic noradrenaline reuptake and induces release of intrasynaptic serotonin by acting on neuroamine transmission. Since both IV paracetamol and tramadol have minimal effects on renal system, we selected these two drugs for comparison in urosurgical patients.[3],[8]

Materials and Methods

The present study was carried out in 100 adult patients of ASA grade I & II, between the age group of 25-55 years. Patients were randomized into two groups of 50 patients each, scheduled to undergo elective urosurgical procedures under general anaesthesia with controlled ventilation. The study was carried out in Department of Anaesthesiology of our hospital over a period of 2 years. The Study Protocol was approved from Institute Ethics Committee IEC Number 1201, and included the patients scheduled to undergo elective urosurgical procedures. An informed consent was taken from all the patients. One hundred patients of ASA I and II weighing 40-70 kg of either sex, and undergoing urosurgical procedures who gave consent for study were included and divided into two groups of 50 each using numbers generated by computer randomly. In the paracetamol group (Group P), patients received 1gm in 100 ml of intravenous paracetamol infusion, infused over 15 min half an hour before the completion of surgery and then was repeated 6 hours after surgery completion. In the tramadol group (Group T), patients received 2 mg/kg intravenous tramadol slowly half an hour before the completion of surgery and was repeated 8 hours after surgery completion.

Drugs preparation and labeling by random number generated by computer was done by anaesthetists not involved in the procedure and data collection. We excluded patients with hepatic, renal, cardio-respiratory diseases, neuropathies, hypertensive, diabetics, pregnant and lactating patients. A post hoc power

analysis was conducted using the software package, G*Power version 3.1.9.2 (Franz Faul, university kiel, Germany). The alpha level used for this analysis was $p<0.05$ and beta was 0.20. If the post hoc analysis reveals the statistical power of 0.40, it detects a small effect size, whereas if the power exceeds 0.80 it detects moderate to large effect size. By using the parameter VAS at T1, which was the primary outcome of this study, power of the study has been calculated to be 0.94 and with an effect size of 0.65 with 10% chance of error for total sample size 100 i.e. 50each.

A thorough pre- anaesthetic evaluation was done a day prior to the surgery and all the necessary routine investigations carried out. Before the surgery, patients would be explained about the VAS 0–10 of pain. The Visual Analogue Scale (VAS) consists of a straight line with the endpoints defining extremes like no pain and pain as severe as it could be. The patient is asked to mark his pain level on the line between the two endpoints. The distance between 'no pain at all' and the mark then defines the subject's pain. All patients was kept fasting overnight and given alprazolam tablet 0.25 mg and tablet ranitidine 150 mg orally on the night before and on the day of surgery respectively. After obtaining written informed consent from the patient, an intravenous line was secured with 18G cannula and normal saline 500 ml infusion was started. Baseline parameters like SpO_2, heart rate, systolic, diastolic and mean BP were noted.

On the operation table, all routine monitors such as noninvasive blood pressure, pulse oximetry, and electrocardiogram were attached and above mentioned vitals were again noted.4mg Ondansetron i.v was given as a premedication. After 5 minutes of pre-oxygenation with 100% oxygen, patient was intubated after induction with 2 mg/kg propofol IV and 2mg/kg succinylcholine IV. Bilateral air entry was checked. Anaesthesia was maintained on oxygen: nitrous oxide (50:50) and isoflurane (MAC 1). Thereafter, neuromuscular blockade was achieved with 0.1mg/kg vecuronium i.v and controlled ventilation was carried out. At the end of procedure the neuromuscular blockade was reversed with Neostigmine and glycopyrrolate. The postoperative pain score was evaluated using Visual analogue score (VAS score) and graded as 0 (no pains) and 10 (maximum pain). VAS was studied at different time intervals of 0 min, 15 min, 30 min, 1 h, 3 h, 6 h, 12 h, and 24 h. The hemodynamic parameters including heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, saturation partial pressure of oxygen (Spo_2)were noted. The postoperative complications like nausea, vomiting, dry mouth were noted.

Statistical analysis

Data was collected and analyzed using SPSS for windows version 21.0[SPSS Inc,Chicago, USA].Continuous variables were expressed as the mean ± SD and categorical values as a percentage. Chi-square tests were used to examine the association between qualitative variables. A probability value (p-value) less than 0.05 was considered statistically significant.

Results

Table 1
Demographic data

Patient characteristic	Group P(30)	Group T(30)	p value
Age	42.86±8.56	42.76± 8.45	0.953
Sex	12:38	14:36	0.648
Weight(kg)	74.96±9.56	74.70±10.06	0.895
Mallampati Grade I/II	27/23	23/27	0.424
ASA Status I/II	31/19	37/13	0.198
Duration of surgery(mins)	144± 52.2	120± 46.2	0.143

In the present study,both the groups were comparable in the demographic data with respect to age,gender,weight ,Mallampati grade and ASA grade. The duration of surgery was also comparable in both the groups.

Table 2
VAS score after application post-operative period in Paracetamol Group vs. Tramadol Group

VAS	Paracetamol Group	Tramadol Group	p-value
VAS Baseline	9.48±0.50	9.44±0.50	0.692
VAS 15mins	1.46±0.65	1.48±0.61	0.874
VAS 30 mins	0.92±0.75	0.64±0.56	0.038
VAS After 1hr	0.42±0.50	0.64±0.48	0.028
VAS After 3hr	1.16±0.74	2.38±0.60	0.000
VAS After 6hr	2.00±0.61	3.16±0.68	0.000
VAS After 12hr	2.70±0.68	3.24±0.74	0.000
VAS After 24hr	2.48±0.54	2.84±0.82	0.011

At baseline mean VAS score in Paracetamol group and tramadol group was 9.48±0.50 vs. 9.44±0.50. (p=0.692). The onset of analgesia is faster in tramadol group. There was a significant decrease in VAS score from 15 min onward, and this was observed up to 3 h. In paracetamol group, the onset of analgesia was slightly delayed. Pain scores significantly decreased after 60 min, and this was observed up to 6 h and pain scores increased thereafter. At 15 min, mean VAS score in Paracetamol Group and Tramadol Group was 1.46±0.65 vs 1.48±0.61 respectively, there was no significant difference in between groups. However, at 3 hour, mean VAS score in Paracetamol Group was 1.16±0.74 and 2.38±0.60 in tramadol group. There was significant difference in between the group ($p<0.0001$). At 6 hour, mean VAS score in Paracetamol Group was 2.00±0.61 and 3.16±0.68 in tramadol group. There was significant difference in between the group (p=0.0000). At all the other time intervals, Paracetamol group had mean VAS scores lower than Tramadol Group, and significant statistically at 12 hour and 24 hour intervals.

Table 3
Mean Arterial Pressure after application post op period Paracetamol Group vs. Tramadol Group

MAP	Paracetamol Group	Tramadol Group	T	p-value	95% Confidence Interval of the Difference	
	Mean±SD	Mean±SD			Lower	Upper
Baseline	86.69±4.91	85.72±4.77	1.005	0.317	-0.95	2.89
After 1hr	85.29±5.40	85.81±5.86	-0.461	0.646	-2.76	1.72
After 3hr	85.13±5.18	84.19±5.45	0.884	0.379	-1.17	3.05
After 6hr	86.63±5.03	85.25±5.03	1.371	0.174	-0.62	3.38
After 12hr	88.27±5.01	88.95±5.10	-0.673	0.503	-2.69	1.33

The Mean Arterial Pressure at baseline in Paracetamol Group was 88.27±5.01 and in Tramadol Group was 88.95±5.10.There was no significant difference in the Mean Arterial Pressure at any time till 12 hours after surgery.

Table 4
Comparison of SPO2 in between the groups

SPO2	Paracetamol	Tramadol	T	p-value	95% Confidence Interval of the Difference	
	Mean±SD	Mean±SD			Lower	Upper
Baseline	98.92±0.90	98.92±0.85	0.000	1.000	-0.35	0.35
After 1hr	98.80±0.83	99.02±0.84	-1.311	0.193	-0.55	0.11
After 3hr	98.88±0.87	98.82±0.83	0.353	0.725	-0.28	0.40
After 6hr	98.80±0.90	99.08±0.88	-1.572	0.119	-0.63	0.07
After 12hr	99.10±0.84	98.96±0.86	0.826	0.411	-0.20	0.48

The mean of SPO2 in Paracetamol Group was 98.90±0.90 and 98.90±0.85 at baseline. There was no significant difference in the sPO_2at any time till 12 hours after surgery in this Group.

Table 5
Comparison of nausea/ vomiting in between the groups

		Paracetamol Group		Tramadol Group		Total	Chi-square value	p-value
		Number	Percentage	Number	Percentage			
Nausea/Vomiting	No	48	96.0%	42	84.0%	90	4.000	0.046
	Ye	2	4.0%	4	16.0%	10		

	s							
Total		50	100.0%	50	100.0%	100		

There were 4.0% patients who experienced nausea/vomiting in Paracetamol group and 16.0% who experienced nausea/vomiting in tramadol Group. The difference ($p<0.05$) in the two groups was statistically significant.

Table 6
Comparison of dry mouth in between the groups

		Paracetamol Group		Tramadol Group		Total	Chi-square value	p-value
		Number	Percentage	Number	Percentage			
Dry mouth	No	46	92.0%	48	96.0%	96	0.709	0.400
	Yes	4	8.0%	2	4.0%	6		
Total		50	100.0%	50	100.0%	100		

There were 4.0% patients who experienced dry mouth in tramadol group and 8.0% who experienced dry mouth in Paracetamol Group. There was no significant difference in between groups.

Discussion

The management of Post-operative pain is a critical domain for postoperative recovery. Postoperative pain contributes significantly to patient morbidity and mortality, moreover it has been estimated that 80% of the patients experienced pain despite of their pain management.Pain management itself has emerged as an element for better patient outcome following surgical intervention be it a major or a minor one. Moreover inadequate pain control results in increased hospital stay and bad experience for the patient. Apart from this, increased risk of morbidity and mortality in the patients due to complications like hypertension, delayed healing of wound, myocardial infarction, atelectasis, pneumonia may occur. Choy CY et al emphasised the role of anaesthetist in ensuring early recovery post operatively and inhibit the transit to chronic from acute pain by optimal intra operative anesthesia and also adequate analgesia post operatively.[9]

Opioids and nonsteroidal antiinflammatory drugs (NSAIDs) are the commonly administrated parenteral analgesics in the early postoperative period to alleviate pain.[10] However, their adverse effects such as nausea, vomiting, itching, and respiratory depression are of concern. Opioid free anaesthesia is a technique where the administration of opioids is avoided intraoperatively either intravenously, neuraxially or intracavitary. In current times a number of case reports and studies have demonstrated the benefits of opioid free anaesthesia. With these findings in background lots of non opiod adjuvants like low dose

ketamine,magnesium, paracetamol, local and regional techniques are being used to decrease postoperative pain scores. Paracetamol acts by inhibiting the release of prostaglandin E and antagonizing the effect of endogenous fever inducing mediators in the hypothalamic thermoregulatory centres. Tramadol acts on μ-receptor agonist and is a serotonin and norepinephrine reuptake inhibitor.[12] Various analgesic agents available are opioids, NSAIDS like diclofenac, ketamine, paracetamol.. Scare of serious side effects especially respiratory depression, and haemodynamic changes limits the use of opioids. However absence of chest rigidity, bradycardia/ tachycardia, organ toxicity or abuse tendency makes tramadol a preferable agent among opioids. Tramadol iv in dose of 1 to 2 mg/kg IV devoid of any respiratory adverse effect. [13] NSAIDs on the other hand may cause peptic ulceration, interfere with kidney function .Paracetamol does not cause gastric irritation, erosion or bleeding like other NSAIDS.[14] Many a trial have been conducted under different circumstance concerning the relative advantage of one drug over the other. Since there is scarcity of literature regarding intravenous paracetamol infusion, we decided to undertake the present study comparing intravenous paracetamol and intravenous tramadol. There are no studies comparing the efficacy of these drugs for postoperative analgesia for urosurgeries and hence we decided to do one. We found IV paracetamol and tramadol tends to offer adequate postoperative analgesia and IV paracetamol is a safer alternative to tramadol with less PONV in the postoperative period. We have taken paracetamol intravenous infusion of 1g in 100 ml solution as analgesic dose as was taken by Bandey S et al.[11] The dose of tramadol intravenous infusion of 2mg/kg as an analgesic as was taken by Gunes Y et al.[12]

Aghamir et al. compared paracetamol and tramadol in open urologic surgeries and found paracetamol to be useful, but for cases of severe pain it was inadequate,[20] whereas in a study done by Akcali et al compared the efficacy of paracetamol, tramadol and lornoxicam in extracorporeal shockwave lithotripsy and found that there is similar efficacy among all three.[21] Interestingly, in our study, both the drugs showed effective pain control relief but the onset of analgesia was faster in tramadol group. However there was a significant decrease in VAS score from 15 min onward, and this was observed up to 3 h. In paracetamol group, the onset of analgesia was slightly delayed, pain scores significantly decreased after 60 min, and this was observed up to 6 h and pain scores increased thereafter. At 15 min, mean VAS score in Paracetamol Group and Tramadol Group was (1.46±0.65 and 1.48±0.61 respectively) which was not a significant difference in between groups (p=0.874). However, at 3 hour, there was significant difference between the mean VAS score in Paracetamol Group and tramadol group which was found to be 1.16±0.74 and 2.38±0.60 respectively. At 6 hour, mean VAS score in Paracetamol Group vs tramadol group was 2.00±0.61 vs. 3.16±0.68 which means the paracetamol group subjects required rescue analgesia later than that of tramadol group.At all the other time intervals, Paracetamol group had mean VAS scores lower than Tramadol Group, and significant statistically at 12 hour and 24 hour intervals (p=0.000).

Our study has similar results as Manne et al who found that the onset of pain relief was quick in tramadol group.[3] with a significant decrease in VAS score from 15 min. In the paracetamol group, analgesic effect of paracetamol appeared a bit later than tramadol. However tramadol give quick action than paracetamol in the

study. Similar results was found by Bandey S et al they concluded that both the drugs showed effective control on pain scores.[11] Paracetamol Group was shown to be better in pain management as compared to tramadol group. Paracetamol significantly reduce the in term of VAS score in patients after surgery as compared to tramadol at different time interval. They concluded that paracetamol as a better safe analgesic than tramadol.[11]

In our study, there were non-significant changes in mean SBP and diastolic blood pressures and hence mean arterial pressures after surgery. Similar results was found in study by Manne et al and Shahid M et al.[3],[5] Lee et al. found paracetamol can be used as an alternative to ketorolac for pain management after mild to moderate painful surgery in situations where the use of NSAIDs is unsuitable.[16] In our study, there were 4.0% patients who experienced nausea vomiting in Paracetamol group and 16.0% who experienced PONV in tramadol Group. There was significant difference in between groups. Our results are similar to the study done by Shahid et al.[5] In our study, there were very few patient who experienced adverse effect and there were non-significant difference in between group which was similar to what Vadivelu N et al found .[19] On the basis of our study we conclude that paracetamol is safe and quite effective in pain management as it has prolonged effect lasting upto 6 hours with less incidence of post operative nausea vomitting and can be used for postoperative pain in patient undergoing urosurgical procedures. However for patients requiring acute pain management it cannot be the agent of choice for its onset of action is not quick.

Conclusion

Both paracetamol and tramadol are safe for postoperative analgesia in urosurgical patients. IV paracetamol is a better and safer alternative to tramadol with better VAS cores and lesser PONV postoperatively. Hence, it contributes to lesser time of stay in the hospital, earlier discharge and can be used as an alternative to opioids in postoperative pain management.

Limitations

Limitation of our study was small sample size and lack of placebo group.

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