Original Article

Effects of Preemptive and Preventive Intravenous Paracetamol on Postoperative Pain and Opioid Consumption in Patients Undergoing Laparoscopic Nephrectomy

Alireza Jafari[1], Mohammadreza Kamranmanesh[1*], Homayoun Aghamohammadi[1], Babak Gharaei[1], Mehranoosh Noori Khorramabadian[1], Behzad Narouie[2], Payam Sarmadi[2], Reza Valipour[3], Abbas Vali[2]

Abstract

Background: Adequate pain control is a goal in postoperative recovery. Although opioids provide good analgesic effects, their side effects such as postoperative nausea and vomiting (PONV) limit their administration. Intravenous Paracetamol as a safe and well-tolerated drug with fewer side effects can be used instead of opioids for pain management. The aim of this study is to compare preemptive or preventive administration of paracetamol with placebo group to investigate its effects on pain control and opioid consumption in patients undergoing laparoscopic nephrectomy.

Materials and Methods: Ninety patients were randomly divided to three groups. Preemptive group received 1 gram Paracetamol in 100 milliliters of 0.9% saline 30 minutes before induction of anesthesia, the preventive group received 1 gram paracetamol in 100 milliliters of 0.9% saline before closure of the skin and placebo group just received 100 milliliters of 0.9% saline. Post-surgical pain was assessed using verbal rating scale (VRS). Pethidine 0.25 mg/kg was administered and repeated each 10 minutes to control pain as needed. Pain scores, total dose of opioid and symptoms like nausea and vomiting were recorded.

Results: Preemptive and preventive groups had lower pain scores than placebo group. Opioid consumption and PONV were significantly higher in placebo group. No significant differences were observed between Preemptive and preventive groups.

Conclusion: Intervenes Paracetamol can provide an adequate pain control with few side effects and may be an effective choice in management of postoperative pain in patients undergoing laparoscopic nephrectomy.

Keywords: Paracetamol, Preemptive analgesia, Preventive analgesia, PONV

Please cite this article as: Jafari AR, Kamranmanesh MR, Aghamohammadi H, Gharaei B, Noori Khorramabadian M, et al. Effects of Preemptive and Preventive intravenous Paracetamol on postoperative pain and opioid consumption in patients undergoing laparoscopic nephrectomy. J Cell Mol Anesth. 2018;3(2):74-80.

1. Anesthesiology Research Center , Department of Anesthesia, Shahid Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Urology and Nephrology Research Center; Department of Urology, Shahid Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Department of Urology, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran

Corresponding Author:
Mohammadreza Kamranmanesh. MD, Anesthesiology Research Center, Department of Anesthesia, Shahid Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Boostan 9th Ave, Pasdaran St, Tehran, Iran; Phone: (+98) 21 225 672 22; Fax: (+98) 21 225 672 82.
Email:
mrz_kamranmanesh@yahoo.com

Introduction

One of the most important issues in postoperative recovery is pain management. Inadequate pain control increases the risk of postoperative complications such as deep vein thrombosis (DVT) and espiratory insufficiency (1). On the other hand, optimal post surgical pain control will lower duration and costs of hospital stay, reduces incidence of postoperative chronic pain and increases patients' outcome (2). For decades, opioids used to be the first line medications in post operative pain management (3). Because of greater analgesic efficacy and higher patient satisfaction, patient-controlled analgesia (PCA) is the method of choice in administration of opioids (4). During opioid PCA, adverse effects such as postoperative nausea and vomiting (PONV), drowsiness, respiratory depression, and gastrointestinal and bladder dysfunction are frequent (5). Methods such as adding non-opioid analgesics like nonsteroidal anti-inflammatory drugs (NSAIDs) (6) or utilizing other additives in the PCA pumps like ketamine (7), other modalities like oral Pregabalin, intravenous corticosteroid, Lidocaine and Nitroglycerine which were reported to decrease postoperative pain (8,10) are used to decrease these side effects.

One of the other approaches to achieve an optimal post surgical pain with minimal side effects is using of preemptive analgesia (11). Preemptive Analgesia is defined as an antinociceptive treatment starting before surgery that prevents establishment of altered central afferent input from injuries; this method was shown to be more effective than preventive Analgesia, which is the administration of intraoperative analgesic agents, in controlling pain-induced sensitization of the central nervous system (11, 12). Paracetamol is a safe, well-tolerated drug with proven efficacy as analgesic that rapidly passes the blood brain barrier (13, 14). Although Paracetamol has peripheral effects but its clinical manifestations arise most likely from central action (13, 14). Intravenous (IV) administration of Paracetamol is used to relief pain (13). Peak analgesic effect of IV Paracetamol is achieved in 1 hour and lasts for 4-6 hours (14). Since it is not sedative and has no major adverse effect like respiratory and circulatory depression, it is an ideal agent for day care procedures with mild to moderate pain (15). Recently, it is suggested to use intravenous Paracetamol in postoperative pain management (11, 13, 16).

The aim of this study was to compare two different protocols of postoperative pain management, using intravenous Paracetamol as preemptive or preventive analgesia in patients undergoing laparoscopic nephrectomy, and to investigate Paracetamol efficacy in reducing the postoperative opioid consumption and its related side effects.

Methods

In this Clinical Trial study, from February 2014 until March 2015, patients between the ages of 20 and 65 years, American society of anesthesiologists (the classification of the ASA) physical status I- II, who were referred for laparoscopic nephrectomy to Labbafinejad Hospital, Tehran, Iran, were included. Written informed consent was obtained from all participating patients and the Helsinki declaration and Labbafinejad ethics committee`s rules were respected all over the study course. Patients with a history of allergy to any of the study medications (opioid, general anesthetic agents or paracetamol), history of opioid or Paracetamol use during the last 48 hours before surgery, hepatic or renal disorders, coagulopathy, pregnancy, cancer, seizure and opioid or alcohol abuse were excluded from the study. Patients with severe hemorrhage (more than 1500 ml) and duration of surgery more than 4 hours were excluded from the study. In case of reoperation before 24 hours, the data was recorded but not included in analysis.

Patients were randomly divided to three groups based on computerized randomization. In preemptive paracetamol group, 1 gram (gr.) Paracetamol (one gr. ampule, authorized by Cobel Darou Co, Iran) in 100 ml 0.9% saline (normal saline) was given to patient 30 minutes before induction of anesthesia; they also received 100 ml of normal saline prior to skin closure during surgery. In preventive Paracetamol group, patients received 100 ml IV normal saline 30 minutes before induction and 1 gr. Paracetamol in 100 ml normal saline before closure of the skin in surgery. Placebo group received 100 ml normal saline 30 minutes before induction and 100 ml normal saline before closure of the skin. All patients received 2

µg/kg Fentanyl (ampule 10 mL, Fentanyl-Janssen™, Belgium) and 0.03 mg/kg Midazolam (ampule 5 mg, MIDAZOLEX®5, Exir-Iran) as premedication. They were oxygenated with 100% oxygen for 3 minutes and then went through induction by Sodium Thiopental (EXIPENTAL 1g, Exir-Iran) 5 mg/kg and Atracurium (ampule 10 mg., Mayne Pharma Plc™, UK) 0.6 mg/kg. After intubation, maintenance of anesthesia was continued by O_2/N_2O 50% and Isoflurane (AErrane; Baxter MFD, Puerto Rico) 1.2%. Patients were continuously monitored for blood pressure, O_2 saturation, heart rate and end-tidal CO_2. The anesthesiologist administered fentanyl (20% of first dose) as needed during the operation. 30 minutes before the end of the operation, Fentanyl was not administered anymore and all the patients received Morphine Sulfate (10 mg. ampule, Darou Pakhsh Co, Iran) 0.05 mg/kg.

Verbal Rating Scale (VRS) was used for assessment of post-surgical pain in all patients 30 minutes, 4, 8 and 24 hours after the operation. In VRS 0 represents "no pain" and 10 represents, "the worst pain possible". Patient`s first request for opioid, total dose of opioid and symptoms like nausea and vomiting were recorded. An anesthesiology resident collected data through provided questionnaire. In patients with scale 3 and higher, Pethidine (ampule 50 mg, Pethedine IPDIC, Caspian Tamin pharmaceutical co. Rasht-Iran) 0.25 mg/kg was administered intravenously and repeated each 10 minutes to control pain. Patients with pain greater than 3 despite two times Pethidine administration were excluded. In patients with history of allergy to Pethidine, Morphine 2.5 mg was administered. In case of vomiting, Metoclopramide (ampule 10 mg, PLADIC®, Caspian Tamin pharmaceutical co. Rasht-Iran) 0.1 mg/kg for the first time and Ondansetron (ampule 4mg, DEMITRON®,Tehran Chemie, Tehran-Iran) 4 mg for the second time were administered. A pilot study of pain reported by patients after nephrectomy revealed that the average VAS score for pain was 3.8 with a standard deviation of 1.5. Considering a power of 0.8, alpha error at 0.05 and maximum allowable difference of 1 in VAS score the sample size of 30 patients in each group was calculated.

Statistical analysis was performed by SPSS software version 19 using ANOVA and FISHER test. $P<0.05$ was considered significant in all tests.

Results

One hundred and four patients were observed for the study. However, ten of them were opioid abusers and four of them had metastatic cancer, they were excluded. Finally, ninety patients (n=30, for each group) met the inclusion criteria. No patients met severe hemorrhage and prolonged duration of surgery. We had no case of reoperation in the first 24 hours (Figure 1). There was no significant difference among the groups regarding patients' characteristics such as age, sex, weight and duration of surgery (Table 1).

Mean values of VRS scores, in recorded intervals show a lower pain severity in preemptive and preventive group in comparison to placebo group. This difference was statically significant. VRS scores

Table 1: Patients' Characteristics.

	Preemptive	Preventive	Placebo
Age(year)	49±10	51±8	50±8
Weight(kg)	73±8	71±4	70±5
Surgery duration(min)	229±14	236±16	233±10
Sex(male/female)	21/9	18/12	24/6
ASA Class(I/II)	18/12	21/9	21/9

ASA: American Societey of Anesthesiologist Class

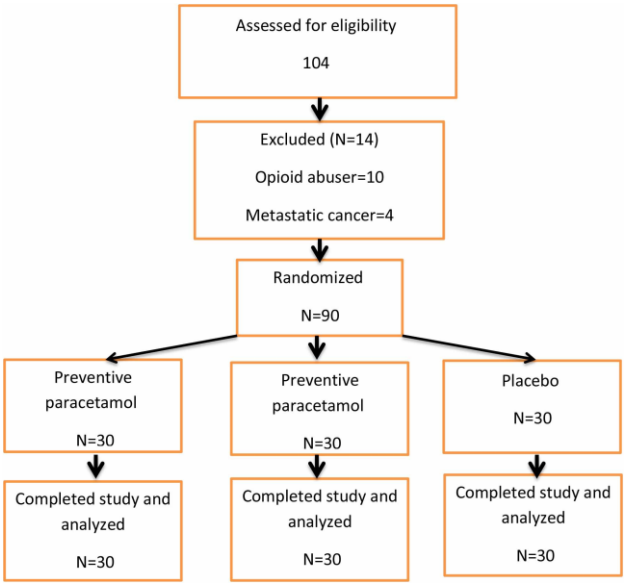

Figure 1. Consort flow diagram.

in preventive group were lower than preemptive group; however, this difference was not statically significant (Table 2). The time of first request for analgesia was also recorded. Due to our results, values of this variable in placebo group were significantly lower than preemptive and preventive group (6±2.0mins, 12±3 mins and 13±4mins respectively) (Table 2).

In all the recorded intervals, opioid consumption in placebo group was significantly higher than groups in which Paracetamol was used (P=0.001). This consumption was almost the same in preemptive and preventive group (Table 2).

Postoperative nausea and vomiting as one of the side effects of opioid, in 4 and 8 hours after operation was significantly lower in groups in which Paracetamol was used (Table 3).

Discussion

In November 2010, intravenous Paracetamol was approved by food and drug administration (FDA) for management of mild to moderate perioperative pain alone; management of moderate to severe pain with adjunctive opioid medication; and reduction of

Table 2: VRS Pain Scores and Opioid consumption in recorded intervals.

	preemptive	preventive	placebo	P-value
VRS 30	5.1±0.9	4.9±0.8	6.7±0.9	<0.0001
VRS 4	3.8±0.4	3.6±0.5	5.2±0.6	<0.0001
VRS 8	3.3±0.6	3.2±0.8	4±1.1	0.001
VRS 24	2.3±1.1	1.9±1.0	3.5±0.7	0.001
First analgesic request (minutes)	12±3	13±4	6±2.0	<0.0001
Recovery opioid consumption	52±14	50±16.0	72.5±18	0.01
Opioid consumption at 4h	40±17	45±15	72.5±14	0.001
Opioid consumption at 8h	32.5±12	27.5±8	50±10	0.001
Opioid consumption at 24h	15±10	17±10	27±8	0.001

Data presented as mean ± SD., VRS = Verbal Rating Scale (0-10)
H: hour

Table 3: The nausea and vomiting rate at 8 and 24 hours postoperative in groups.

		preemptive	preventive	Placebo	
PONV 8	**None**	18	12	9	P=0.02
	Nausea	9	12	8	
	vomiting	3	6	13	
PONV 24	**None**	18	21	17	P=0.04
	Nausea	9	6	3	
	vomiting	3	3	10	

fever. Before that, oral tablets, liquid and rectal suppository of Paracetamol were widely used for more than 4 decades (16). Administration of IV Paracetamol causes a rapid elevation in plasma concentration and higher peak levels when compared with its oral route (17). The mean peak concentration of intravenous rout is 70% higher than an equivalent oral dose. High plasma concentration causes diffusion of Paracetamol across the blood-brain barrier and results in rapid and high levels of drug in the cerebrospinal fluid (18, 19).

Intravenous Paracetamol has been shown to be effective in management of postoperative pains after several surgeries (11, 13, 15, 16). In our study, both preemptive and preventive Paracetamol lowered pain scores. Opioid consumption and side effects related to opioids like PONV were also reduced when Paracetamol was administered. Our results were consistent with Unal et al, who reported that use of preemptive or postoperative paracetamol reduces Fentanyl related nausea-vomiting in patients undergoing open nephrectomy; Although they did not observe significant decrease in total Fentanyl consumption in the early postoperative period (0-4 hours), but Paracetamol reduces total Fentanyl requirements in the first 24 hours postoperatively (13). Majumdar et al, also demonstrated that use of preemptive Paracetamol in palliative head and neck cancer surgery causes in Fentanyl requirements reduction and earlier discharge from hospital (20).

Hassan et al, compared post-surgical analgesic effects of preemptive and preventive Paracetamol in patients after cesarean section. They assessed postoperative pain by visual analog score (VAS). Their results show that preemptive Paracetamol and immediate postoperative opioid analgesia were more effective than preventive paracetamol (11). In our study, however, the differences between analgesic effects of preemptive and preventive were not significant.

Results of Khalili et al, were similar to our results, they compared analgesic effects of Paracetamol in preventive, preemptive and placebo groups on postoperative pain scores in patients undergoing lower extremity surgery. They used verbal rating scale (VRS) 5 minutes before anesthesia, and 6, 12, 18 and 24 hours after surgery. Due to their results, there were no significant differences in pain scores between the preemptive and preventive groups. However, in comparison with placebo group, Paracetamol lowered pain scores and total analgesic consumption (21).

Although paracetamol is a short acting analgesic, previous studies declared its effectiveness on postoperative side effects like PONV during the first 24 hours (22). It is proposed that decreasing the severity of pain during early postoperative period by Paracetamol could enhance its analgesic efficacy and

may end up in opioid sparing until the late postoperative period.

Limitations of our study include a lack of proper method for blinding the investigators and the patients. While this may have a little disturbing effect on Data analysis, further observations with proper method for blinding are recommended.

Conclusion

We demonstrated that IV Paracetamol might be an effective choice in management of postoperative pain in patients undergoing laparoscopic nephrectomy. It lowers pain scores, opioid consumption and reduces side effects of opioid like PONV. Due to this study, there is no significant difference between Preemptive and Preventive protocols for Paracetamol administration.

Acknowledgment

Authors would like to thank members of operation rooms, urology and ICU wards of Labbafinejad hospital for their cooperation.

Conflicts of Interest

The authors declare that they have no conflict of interest.

References

1. Lawrence VA, Hilsenbeck SG, Mulrow CD, Dhanda R, Sapp J, Page CP. Incidence and hospital stay for cardiac and pulmonary complications after abdominal surgery. Journal of general internal medicine. 1995;10(12):671-8.

2. Imani F. Postoperative pain management. Anesth Pain. 2011;1(1):6-7.

3. Gianesello L, Pavoni V, Barboni E, Galeotti I, Nella A. Perioperative pregabalin for postoperative pain control and quality of life after major spinal surgery. Journal of neurosurgical anesthesiology. 2012;24(2):121-6.

4. Ballantyne JC, Carr DB, Chalmers TC, Dear KB, Angelillo IF, Mosteller F. Postoperative patient-controlled analgesia: meta-analyses of initial randomized control trials. Journal of clinical anesthesia. 1993;5(3):182-93.

5. Walder B, Schafer M, Henzi I, Tramer M. Efficacy and safety of patient- controlled opioid analgesia for acute postoperative pain. Acta Anaesthesiologica Scandinavica. 2001;45(7):795-804.

6. Marret E, Kurdi O, Zufferey P, Bonnet F. Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effectsMeta-analysis of randomized controlled trials. The Journal of the American Society of Anesthesiologists. 2005;102(6):1249-60--60.

7. Imani F, Faiz HR, M Sedaghat, Hajiashrafi M. Effects of Adding Ketamine to Fentanyl Plus Acetaminophen on Postoperative Pain by Patient Controlled Analgesia in Abdominal Surgery. Anesth Pain Med. 2014;4(1):e12162.

8. Alimian M, Imani F, Faiz SHR, Pournajafian A, Navadegi SF, Safari S. Effect of Oral Pregabalin Premedication on Post-Operative Pain in Laparoscopic Gastric Bypass Surgery. Anesth Pain Med. 2012;2(1):12-6.

9. Rahimzadeh P, Imani F, Faiz HR, Nikoubakht N, Sayarifard A. Effects of Intravenous Methylprenisolone on Pain after Intertrochanteric Femoral Fracture Surgery. J Clin Diagn Res. 2014;8(4):GC01-4.

10. Gharaei H, Imani F. Beneficial effect of intravenous nitroglycerin and lidocaine in severe pain due to acute arterial occlusion. Indian J Pain. 2014;28(1):42-3.

11. Hassan HIEA. Perioperative analgesic effects of intravenous paracetamol: Preemptive versus preventive analgesia in elective cesarean section. Anesthesia, Essays and Researches. 2014;8(3):339.

12. Shen X, Wang F, Xu S, Ma L, Liu Y, Feng S, et al. Comparison of the analgesic efficacy of preemptive and preventive tramadol after lumpectomy. Pharmacological Reports. 2008;60(3):415.

13. Unal S, Aksoy M, Ahiskalioglu A, Erdem A, Adanur S. The effect of intravenous preemptive paracetamol on postoperative fentanyl consumption in patients undergoing open nephrectomy: A prospective randomized study. Nigerian journal of clinical practice. 2015;18(1):68-74.

14. Arici S, Gurbet A, Türker G, Yavaşcaoğlu B, Sahin S. Preemptive analgesic effects of intravenous paracetamol in total abdominal hysterectomy. Agri. 2009;21(2):54-61.

15. Ali MA, Shamim F, Chughtai S. Comparison between intravenous paracetamol and fentanyl for intraoperative and postoperative pain relief in dilatation and evacuation: Prospective, randomized interventional trial. Journal of anaesthesiology, clinical pharmacology. 2015;31(1):54.

16. Lachiewicz PF. The role of intravenous acetaminophen in multimodal pain protocols for perioperative orthopedic patients. Orthopedics. 2013;36(2):15-9.

17. Schutz R, Fong L, Chang Y, Royal M, editors. Open-label, 4-period, randomized crossover study to determine the comparative pharmacokinetics of oral and intravenous acetaminophen administration in healthy male volunteers. Poster presentation at the 32nd Annual Meeting and Workshops American Society of Regional Anesthesia and Pain (ASRA); 2007.

18. Singla NK, Parulan C, Samson R, Hutchinson J, Bushnell R, Beja EG, et al. Plasma and cerebrospinal fluid pharmacokinetic parameters after single- dose administration of intravenous, oral, or rectal acetaminophen. Pain Practice. 2012;12(7):523-32.

19. Jensen L, Handberg G, Brøsen K, Schmedes A, Ørding H. Paracetamol concentrations in plasma and cerebrospinal fluid: A-785. European Journal of Anaesthesiology (EJA). 2004;21:193.

20. Majumdar S, Das A, Kundu R, Mukherjee D, Hazra B, Mitra T. Intravenous paracetamol infusion: Superior pain management and earlier discharge from hospital in patients undergoing palliative head-neck cancer surgery. Perspectives in clinical research. 2014;5(4):172.

21. Khalili G, Janghorbani M, Saryazdi H, Emaminejad A. Effect of

preemptive and preventive acetaminophen on postoperative pain score: a randomized, double-blind trial of patients undergoing lower extremity surgery. Journal of clinical anesthesia. 2013;25(3):188-92.
22. Cok OY, Eker HE, Pelit A, Canturk S, Akin S, Aribogan A, et al. The effect of paracetamol on postoperative nausea and vomiting during the first 24 h after strabismus surgery: A prospective, randomised, double- blind study. Eur J Anaesthesiol. 2011;28:836-41.