Original Article

Comparison between Infusion Pumps: Fentanyl/Ketamine and Fentanyl/Paracetamol in Pain control Following Tight and Leg Surgeries

Behnam Mahmoodiyeh[1], Mohamad khalili[1], Maryam Panahi[1], Esmaeel Moshiri[1], Sayed Mehran Marashian[2], Alireza Jahangiri-Fard[3*]

Abstract

Background: Adjuvants such as ketamine, promethazine, and paracetamol could bring up patients satisfaction and control harmful effects of opioids besides lessening their needed doses, as seen by fentanyl/paracetamol and fentanyl/ketamine combination before. The current study headed to compare paracetamol and ketamine, in addition to fentanyl applied by infusion pumps in order to pain relief following major surgery.

Materials and Methods: Through a double blinded, randomized clinical trial, patients between18 and 65 with elective surgery for tight or leg fractures with ASA Class 1 and 2 referring to a university hospital in Arak, a town in the central region of Iran, were recruited and used infusion pump for their postoperative pain control. The participants were divided into cases and controls regarding using ketamine/fentanyl (KF) or paracetamol/fentanyl (PF) infusion pumps.

Results: The mean pain score was totally 3.87 with the highest value in KF (5.06) and the lowest in PF (4.50) immediately after finishing the surgery and getting conscious when started using infusion pump. There was no statistical difference between the groups in this regard. Concerning the side effects of the applied medications, blood pressure and heart rate had no differences comparing the groups.

Conclusion: This study showed that paracetamol used in infusion pump can be brilliant in pain control after major surgeries like what done in lower extremities and joint replacement while lessens opioid use. Although paracetamol was more effective than ketamine in the current trial, more qualified studies at bigger size and in other fields of surgery beside orthopedic ones would be useful to support the effects if applicable.

Keywords: Infusion pump, Ketamine, Paracetamol, Fentanyl, Postoperative pain

1. Anesthesiology and Critical Care Department, Arak University of Medical Sciences, Tehran, Iran
2. Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Lung Transplantation Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

Corresponding Author:
Alireza Jahangiri-Fard MD; Lung Transplantation Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
Email: omidjahangiri_55@yahoo.com; alirezajahangiri@sbmu.ac.ir

Received: July 23, 2016
Accepted: September 7, 2016

Please cite this article as: Mahmoodiyeh B, khalili M, Panahi M, Moshiri E, Marashian S M, Jahangiri-Fard A. Comparison between Infusion Pumps: Fentanyl/Ketamine and Fentanyl/Paracetamol in Pain control Following Tight and Leg Surgeries. J Cell Mol Anesth. 2016;1(4):168-74.

Introduction

Continuous pain following surgeries not only make patients unsatisfied and the hospital stay longer, but also raises some annoying problems such as tachycardia, tachypnea, higher risks of cardiovascular diseases, immunosuppression and anti-inflammatory reactions, as well as leukocytosis and hypercoagulation (1). Pain killers are the most traditional agents to control postoperative pain while local and epidural blocking are useful too and recently, intravenous and neuroaxial infusion pumps have been also introduced in this regard (1).

Infusion pumps are usually and perfectly used in moderate to severe pain where oral analgesics fail to control pain. They are advised by many of the health providers worldwide even immediately after surgery to get the optimal effects. A vast number of drugs and adjuvants are used in infusion pumps which ensure enough on time pain killer received by patients. Morphine, fentanyl, paracetamol, in addition to combinations of opioids and several drugs like ketamine, diclofenac Na and others are commonly used by pumps (2). Adjuvants such as ketamine, promethazine, and paracetamol could bring up patients satisfaction and control harmful effects of opioids besides lessening their needed doses, as seen by fentanyl/paracetamol and fentanyl/ketamine combination (2-4).

Ketamine belongs to an intravenous anesthetic group which induce dissociative anesthesia affecting on "N-methyl-D-aspartate" (NMDA) receptors and make obvious anesthesia without cardiovascular or respiratory depression. It affects perfectly and separately on the sympathetic nervous network while having some side effects like increased ICP and intraocular pressure (IOP) as well as increased O_2 consumption by myocardial tissues (5) which can limit its use in ischemic diseases.

Paracetamol may cause rashes; hepatotoxicity and nephropathy in long-term use besides tachycardia and hypertension in lower than 15% of prescribed people (6) but seems safer than ketamine. This is why the current study headed to compare above adjuvants namely paracetamol and ketamine in addition to fentanyl applied by infusion pumps in order to pain relief following major surgery. However, paracetamol may be safer if has at least the same effect as ketamine has in pain control.

Methods

Through a double blinded , randomized clinical trial, patients between 18 and 65 years with elective surgery for tight or leg fractures with ASA Class 1 and 2 referring to a university hospital in Arak, a town in the central region of Iran, were recruited and used infusion pump for their postoperative pain control.

The study had two groups, including cases and controls 30 patients in each. Participants were all cases of fractures in lower limbs like DHS and multiple fractures needed to repair surgeries using prosthesis, elizarof, and knee replacement and so on in Vali-e-Asr hospital in Arak. All the patients used standard general anesthesia (taking 0.04 mg/kg midazolam in addition to 2-3 mg/kg fentanyl as premedication followed by 2 mg/kg propofol and 0.5 mg/kg atracurium as induction before using 50% N_2O and 1MAC isoflurane and repeatable atracumiun doses as maintenance after intubation).

Following the surgery, patients transferred to PACU after normalizing their respiration and during this stage, participants were divided into cases and controls regarding using ketamine/fentanyl (KF) or paracetamol/fentanyl (PF) infusion pumps.

Controls (KF group) used 12 mg/kg fentanyl and 3.6 mg/kg ketamine in addition to 4mg ondansetron in 100CC normal saline. The other group was given 12 mg/kg fentanyl and 10mg/kg paracetamol plus 4mg ondansetron in the same amount of normal saline. The injection speed was 4cc/hour for infusion pump in both groups. Patients, physicians, and nurses did not know the containing of pumps for each patient. Nurses were trained for recovery activation for patients and pain severity was assessed using 10-score visual analog score (VAS). Pain, respiratory rate, heart rate, blood pressure, consciousness level, postoperative pethidine consumption, chilling severity, nausea and vomiting were checked and recorded in recovery and 2, 6, 12 and 24 hours later in the general ward.

Sever pain (VAS≥5) needed 25mg IV pethidine and patients who gave>100mg pethidine

excluded the study. Plasil (10 mg/dose metoclopramide) was prescribed in nausea/vomiting. Vertigo, visual disorders, respiratory disorders, illusions and other similar signs to show critical conditions could exclude participants from the study. Patients' consciousness was also assessed in a 5-score system in which "0" means complete alertness and "4" means the patient cannot open his/her eyes even when called loudly or touched strictly while is in deep sleep. Score 1 shows drowsiness and 2 and 3 show sleepy people who the former wakes up with the voice and the latter with painful stimulation.

People who needed ICU care, or reacted to medications, had uncorrectable hypotension (SBP<60mmHg), O_2 saturation < 85%, history of respiratory disease, history of sleep apnea, allergy to the used drugs, BMI>35, who used antidepressants and antipsychotics, and who were cases of drug abuse, a history of chronic renal or hepatic problems and diabetes mellitus were excluded as well.

Statistics

Considering confidence interval of 95% and type one error (0.05) and a proportion of 0.23, the sample size for each group was calculated 30 by the following formula:

Data entered SPSS 20 for windows. Central tendency values were analyzed using t-test and the frequencies were reported by chi-square. Comparisons were done by t-test in parametric data.

Ethics

This study used well-known medications with defined effects and side effects and there was no challenge to introduce them because of several clinical trials and other descriptive studies on them by several authors. Participants were perfectly explained for the aims, process and outcome of the trial before getting their vocal informed consent. No extra costs were imposed on patients and they could quit the study any time they decided. All the data were secured by the investigators.

Results

After applying inclusion and exclusion criteria, 57 patients between 18 and 59 years old enrolled this study with major surgeries in tight and leg due to fractures. Males were 44 (77%) and females 13 (23%) totally among them the 24 men (82.8%) and 5 women (17.2%) were in KF and 20 men (71.4%) and 8 women (28.6%) made up PF group. The mean age was 38.9±12.3 years in KF and 33.85±12.6 in PF which was not different. Sex distribution was not significantly different as well (Table 1). ASA class I owned 45 (78.9%) of all patients and the rest were in ASA class II (21.1%).

Table 1: Age and sex distribution in studied groups.

Group	Male (%)	Female (%)	Mean age±SD
KF	24 (82.8)	5 (17.2)	38.9±12.3
PF	20 (71.4)	8 (28.6)	33.85±12.6
Total	44 (77.2)	13 (22.8)	36.42±12.6

Table 2: The mean of pain score throughout the study in both groups.

Group	0 time	Ward	2 hrs	6 hrs	12 hrs	24 hrs
KF	5.07	7.17	5.44	4.34	3.79	3.38
PF	4.5	6.28	5.17	4.1	3.46	2.71
Sig	0.5	0.1	0.4	0.6	0.27	0.048

The mean pain score was totally 3.87 with higher value in KF (5.06) and lower in PF (4.5) immediately after finishing the surgery and getting conscious when started using infusion pump. There was no statistical difference between the groups in this regard.

Table 2 and diagram in figure 1 shows pain scores at studied times in both groups which were statistically different only in the first 24 hours (p value=0.048). Concerning the side effects of the applied medications, blood pressure and heart rate had no differences comparing the groups as can be seen in

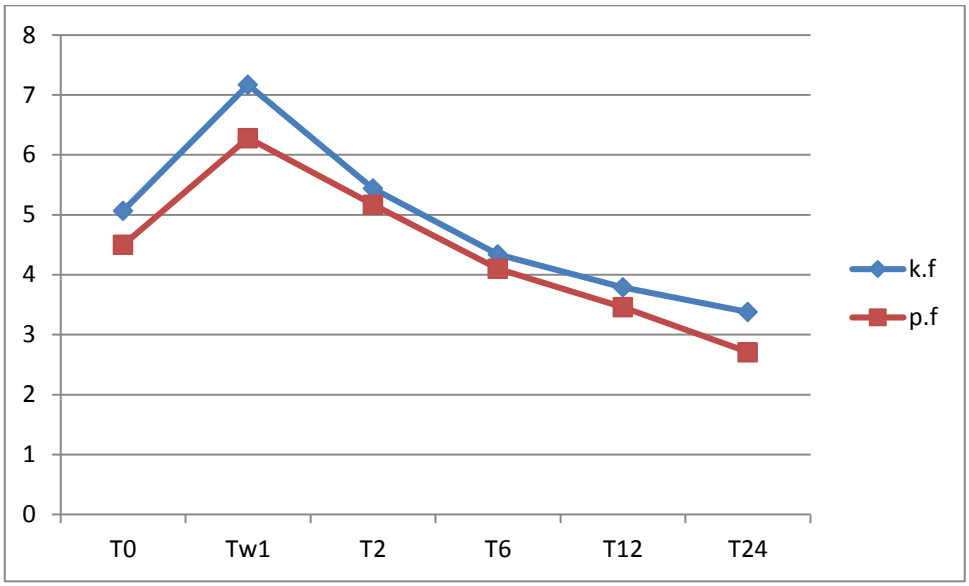

Fig. 1. A diagram showing the mean score of pain from starting time of using infusion pumps in both studied groups to 24 hours after transferring to ward.

table 3 and figure 2. The PF group had always little lower heart rates when compared with the other group, but this difference was not significant. Interestingly, respiratory rate was significantly higher in the PF group only in recovery and at the time of transferring to the general ward (p value=0.004 and 0.03, respectively) (Table 3). Patients' consciousness was checked and showed a significant difference in pump starting time between the groups, indicating lower consciousness in the PF group (p value=0.006)

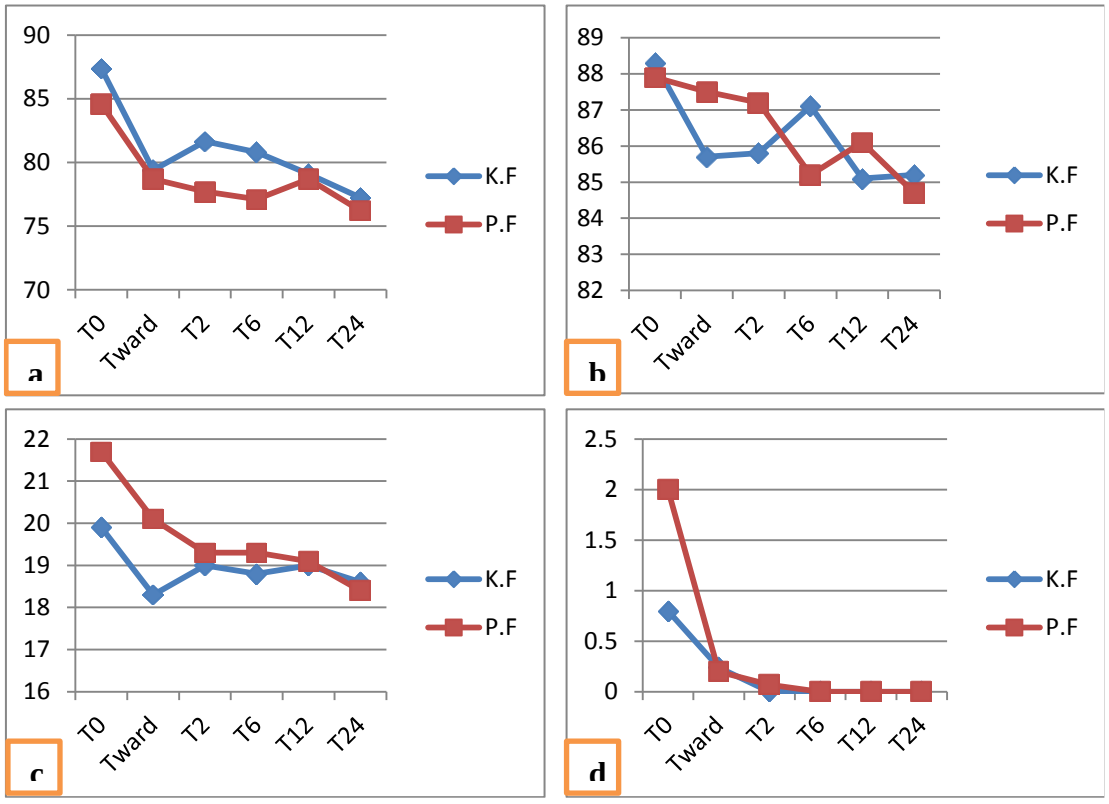

Fig. 2. Hemodynamic and consciousness of patients in both groups. a- Blood pressure; b- Heart rate; c- Respiratory rate; d- Consciousness.

Table 3: The mean of hemodynamic values in both groups at check points.

Hemodynamics		KF	PF	Sig
Blood pressure	0	88.3	87.9	0.83
	W	85.7	87.5	0.8
	2 hrs	85.8	87.2	0.3
	6 hrs	87.1	85.2	0.75
	12 hrs	85.1	86.1	0.5
	24 hrs	85.2	84.7	0.84
Heart rate	0	87.37	84.6	0.49
	W	79.4	78.7	0.8
	2 hrs	80.8	77.1	0.16
	6 hrs	81.65	77.7	0.23
	12 hrs	79.1	77.5	0.48
	24 hrs	77.24	76.21	0.65
Respiratory rate	0	19.9	21.7	0.004
	W	18.3	20.1	0.03
	2 hrs	19	19.3	0.6
	6 hrs	18.8	19.3	0.4
	12 hrs	19	19.1	0.9

	24 hrs	18.6	18.4	0.5
	0	0.8	2	0.006
	W	0.24	0.2	0.9
	2 hrs	0	0.07	0.3
Consciousness	6 hrs	0	0	-
	12 hrs	0	0	-
	24 hrs	0	0	-

although almost all the patients became alert after 2 hours of their surgery as can be observed in table 3 and figure 2. The study groups had statistically the same times and amounts of pethidine consumption after surgery. Two-third of patients in both groups did not need pethidine. No other important side effects occurred.

Discussion

The current study determined the same ability of pain control for paracetamol and ketamine when combined with fentanyl in applying infusion pump among patients who suffered elective major surgeries due to lower limb fractures or knee replacement procedure. Paracetamol presented more pain relief than ketamine although no statistical difference found. Furthermore, both patients and physicians were subjectively more satisfied by the combination of fentanyl and paracetamol compared to the other group. The pain control was better in PF group all the time, but mostly 24 hours after surgery at which showed significantly lower pain.

Using adjuvants like paracetamol and ketamine has been shown to decrease fentanyl contents and is very important in decreasing fentanyl-derived side effects such as nausea, vomiting and itching as Liang and Cha concluded through their trial (2-4). Similarly, Wong, Hahn and Rahimzadeh got better pain relief after postoperative paracetamol prescription comparing with ketamine following abdominal open hysterectomy (7-9).

Arici et al. were other group to assess the effect of paracetamol in surgical pain and got enough results to support this medication and its adjusting role for postoperative morphine consumption (10). Paracetamol showed similar effects on opioid decreased consumption through our study and had better accuracy than ketamine although no significant finding presented. Cobby et al. in 1999 explained better effects with diclofenac Na than rectal acetaminophen and placebo (11). After 24 hours of surgery, paracetamol may show stronger effects in earlier usage. In this matter, Gilbert Morell identified that IV ketamine less than 0.15 mg/kg had no analgesic effect (12). Paracetamol could also present predominant effects in combination with tramadol as Kilicaslan et al. showed in Turkey (13). They found perfect pain control with the combination compared with tramadol alone after cesarean section. Paracetamol has been given superiority to tramadol in renal pain with lower side effects too (14).

Studies have compared paracetamol with opioids and raised it as a medication to compete with opioids in neurosurgery as well as minor and dental surgeries. (15-18). Rawal et al. believed that paracetamol can replace morphine in pain control after surgeries with moderate pain, especially in the long term. They determined longer analgesic effects

of paracetamol than morphine although its late-onset effect (19).

The current study observed no side effects like nausea, vomiting and vertigo by the used pain killers like what happened in the trial by Dahl and Sen and colleagues (20). Almost all studies on paracetamol recorded lower side effects mainly due to decreased opioid prescription. Our study used very low dose of fentanyl (12 mg/kg) beside ondansetron and no side effects appear. Hemodynamic situation was also stable throughout the current trial with no statistical difference.

Conclusion

This study showed that paracetamol used in infusion pump can be brilliant in pain control after major surgeries like what is done in lower extremities and joint replacement while lessens opioid use. Although paracetamol was more effective than ketamine in the current trial, more qualified studies at bigger size and in other fields of surgery beside orthopedic ones would be useful to support the effects if applicable.

Acknowledgment

The Authors would like to acknowledge the kind efforts of the personnel of Anesthesiology and Critical Care Department, Arak University of Medical Sciences and Chronic Respiratory Diseases Research Center and Lung Transplantation Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

Conflicts of Interest

The authors declare that there are no conflicts of interest.

References

1. John Feiner. Clinical cardiac and pulmonary physiology. In: M. Sdrales L, D. Miller R. Miller's Anesthesia Review. 2nd edition, Philadelphia, Saunders, 2013; pp: 2757.

2. Liang SW, Chen YM, Lin CS. Low-dose ketamine combined with fentanyl for intravenous postoperative analgesia in elderly patients. Nan Fang Yi Ke Da Xue Xue Bao. 2006;26(11):1663-4. [Article in Chinese]

3. Cha MH, Eom JH, Lee YS, Kim WY, Park YC, Min SH, et al. Beneficial effects of adding ketamine to intravenous patient-controlled analgesia with fentanyl after the Nuss procedure in pediatric patients. Yonsei Med J. 2012;53(2):427-32.

4. Kim SH, Kim SI, Ok SY, Park SY, Kim MG, Lee SJ, et al. Opioid sparing effect of low dose ketamine in patients with intravenous patient-controlled analgesia using fentanyl after lumbar spinal fusion surgery. Korean J Anesthesiol. 2013;64(6):524-8.

5. Miller RD, Eriksson LI, Fleisher L, et al. Miller's Anesthesia. 8th edition 2014, Philadelphia, Elsevier.

6. Roberts E, Nunes VD, Buckner S, et al. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. Ann Rheum Dis doi:10.1136/annrheumdis-2014-206914.

7. Hahn TW, Mogensen T, Lund C, Jacobsen LS, Hjortsoe NC, Rasmussen SN, et al. Analgesic effect of IV paracetamol: possible ceiling effect of paracetamol in postoperative pain. Acta Anaesthesiol Scand. 2003;47(2):138-45.

8. Wong I, St John-Green C, Walker SM. Opioid-sparing effects of perioperative paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) in children. Paediatr Anaesth 2013;23(6):475-95.

9. Rahimzadeh P, Imani F, Alimian M, Behzadi M, Faiz HR. Comparison between ketamine and acetaminophen administered at the end of anesthesia for pain management after hysterectomy. Journal of Anesthesiology and Pain official Journal of ISRAPM 2013;14(1):15-24.

10. Arici S, Gurbet A, Turker G, Yacaoglu B, Sahin S. Preemptive analgesic effects of intravenous paracetamol in total abdominal hysterectomy. AĞRI. 2009;21(2):54-61.

11. Cobby T, Crighton I, Kyriakides K, Hobbs G. Rectal parasetamol has a significant morphine-sparing effect after hysterectomy. Br Jo Anes. 1999;83(2):253-6.

12. Gilabert Morell A, Sánchez Pérez C. Effect of low-dose intravenous ketamine in postoperative analgesia for hysterectomy and adnexectomy. Rev Esp Anestesiol Reanim. 2002;49(5):247-53.

13. Kiliçaslan A, Tuncer S, Yüceaktaş A, Uyar M Reisli R.The effects of intravenous paracetamol on postoperative analgesia and tramadol consumption in cesarean operation. AĞRI. 2010;22(1):7-12

14. Emir E, Serin S, Erbay RH, Sungurtekin H, Tomatir E. Tramadol versus low dose tramadol-paracetamol for patient controlled analgesia during spinal vertebral surgery. Kaohsiung J Med Sci. 2010;26(6):308-15.

15. 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. 26(6):475-9.

16. Cattabriga I, Pacini D, Lamazza G, Talarico F Di Bartolomeo R, Grillone G, et al, Intravenous paracetamol as adjunctive treatment for postoperative pain after cardiac surgery: a double blind randomized controlled trial. Eur J Cardiothorac Surg. 2007;32(3):527-31.

17. Van Aken H, Thys L, Veekman L, Buerkle H. Assessing analgesia in singe and repeated administrations of proparacetamol for postoperative; pain: comparison with morphine after dental surgery. Anesth Analg. 2004;98(1):159-65.

18. Maiachkin RB, Nikoda VV. Study of analgesic efficacy of

propacetamol in the postoperative period using a double blind placebo controlled method. Anestesiol reanimatol. 2002;4:26-9.
19. Rawal N, Allvin R, Amilon A, Ohlsson T, Hallén J Postoperative analgesia at home after ambulatory ,hand surgery: a controlled comparison of tramodol ;metamizol and paracetamol. Anesth Analg. 2001;92(2):347-51
20 Mofidi M, Shaker H, Ghafouri H. Comparison of Analgesia effect Between Intravenous Propacetamol and Tramadol. J Mazandaran Univ. Med Sci. 2007;17(61):81-87. [Persian].