

# Efficacy of Intravenous Paracetamol Versus Intravenous Morphine in Acute Limb Trauma

Mohammad Jalili,<sup>1,\*</sup> Ali Mozaffarpour Noori,<sup>2</sup> Mojtaba Sedaghat,<sup>3</sup> and Arash Safaie<sup>1</sup>

<sup>1</sup>Department of Emergency Medicine, Tehran University of Medical Sciences, Tehran, IR Iran

<sup>2</sup>Department of Emergency Medicine, Zahedan University of Medical Sciences, Zahedan, IR Iran

<sup>3</sup>Department of Community Medicine, Tehran University of Medical Sciences, Tehran, IR Iran

\*Corresponding author: Mohammad Jalili, Department of Emergency Medicine, Imam Hospital, Keshavarz Boulevard, Tehran University of Medical Sciences, Tehran, IR Iran. Tel: +98-9125483998, Fax: +98-2166904848, E-mail: mjalili@tums.ac.ir

Received 2014 April 27; Revised 2014 July 23; Accepted 2014 August 23.

## Abstract

**Background:** Efficient pain management is one of the most important components of care in the field of emergency medicine.

**Objectives:** This study was conducted to compare intravenous paracetamol and intravenous morphine sulfate for acute pain reduction in patients with limb trauma.

**Patients and Methods:** In a randomized double-blinded clinical trial, all patients (aged 18 years and older) with acute limb trauma and a pain score of greater than 3/10 in the emergency department were recruited; they received either 1 g intravenous paracetamol or 0.1 mg/kg intravenous morphine sulfate over 15 minutes. The primary outcome was the pain score measured on a numerical rating scale at 0, 15 and 30 minutes after commencing drug administration. The requirement for rescue analgesia and the frequency of adverse reactions were also recorded.

**Results:** Sixty patients randomly received either IV paracetamol (n = 30) or IV morphine (n = 30). The mean reduction in numerical rating scale pain intensity scores at 30 minutes was 3.86 ( $\pm$  1.61) for paracetamol, and 2.16 ( $\pm$  1.39) for morphine. However, pain relief was significantly higher in the paracetamol group compared to the morphine group ( $P < 0.001$ ). Four patients in the paracetamol group and 15 patients in the morphine group needed rescue analgesia and the difference was significant ( $P = 0.05$ ).

**Conclusions:** Intravenous paracetamol appears to provide better analgesia than intravenous morphine in acute limb trauma. Further larger studies are required.

**Keywords:** Analgesics, Acute Pain, Acetaminophen, Morphine, Acetaminophen

## 1. Background

Efficient pain management is one of the most important components of care in the field of emergency medicine. Many patients, however, suffer from inadequate or delayed pain relief while in the emergency department (ED) (1, 2). Acute pain management has been the subject of numerous studies over the past decades and various modalities have been recommended for this purpose. The ideal analgesic for the treatment of acute pain in ED setting should relieve pain rapidly and effectively, while maintaining a low incidence of adverse effects (1, 3). The choice of analgesic should not have significant interaction with other drugs commonly used in the ED.

Morphine has classically been the agent of choice for treatment of moderate to severe pain in patients with isolated limb trauma (4). However, this potent analgesic is associated with several dose-dependent undesirable effects including sedation, nausea, respiratory depression, and even confusion (4). Besides, morphine is a controlled drug and may not be available in all settings and even when available, its administration may be delayed

due to the formalities of the process of accessing it. These side effects and administration constraints necessitate a search for a safe and effective alternative drug.

Paracetamol (acetaminophen) is a centrally acting inhibitor of cyclooxygenases which has commonly been reported as a safe and effective analgesia in the ED (5-7). It is associated with fewer untoward effects than either opioids or non-steroidal anti-inflammatory drugs (NSAIDs) and has few contraindications (5-10). Paracetamol also lacks significant drug interactions (5). Therefore, it may be a suitable drug in the treatment of mild and moderate pain including headache, minor musculoskeletal pain, and the common cold. The oral and rectal forms of paracetamol have been available for years and an intravenous (IV) form of the drug has recently become available in our country. The efficacy, safety, and narcotic sparing effect of IV paracetamol, either alone or as an adjunctive treatment, have been established in different settings including postoperative pain, cancer pain and intravenous regional anesthesia (11-16). In acute pain management, however, it

has been studied only in a few studies (6-10). Considering the limitations of the previous studies, it has been recommended that further studies need to be undertaken.

## 2. Objectives

The aim of this study was to compare the efficacy and safety of IV single-dose paracetamol with IV morphine sulfate in patients with moderate to severe pain after acute limb trauma in the ED. We hypothesized that paracetamol reduces acute traumatic limb pain; we also investigated the need for rescue analgesia and the incidence of side effects.

## 3. Patients and Methods

### 3.1. Study Design

We conducted a randomized, double-blind, controlled clinical trial in the emergency department of two tertiary healthcare centers with a census of approximately 65,000 adult visits per year, for the treatment of pain associated with acute limb trauma; 2 treatment groups were assessed namely IV paracetamol and IV morphine sulfate. All participants signed informed consent and the ethics committee approved the study protocol. The trial was registered with clinical trials with the gov identifier (NCT01465984). Participation was voluntary and those who refused to participate in our study received IV morphine according to the emergency department's usual practice.

### 3.2. Population

All adult patients (aged 18 or more) with acute limb trauma and a pain score of greater than 3/10 were eligible for inclusion in the study. Exclusion criteria included known allergy or contraindication to morphine or paracetamol, hemodynamic instability (systolic blood pressure less than 90 mmHg), documented or suspected pregnancy, any analgesic drug use within 6 hours before ED presentation, previous study involvement and patients with known pulmonary, cardiac, renal, or hepatic failure. Patients were also excluded if they declined to take part. Randomization and allocation concealment was performed using a sealed envelope that provided a computer-generated random allocation.

### 3.3. Intervention

After agreement of the patient to enter the study, the investigator opened a sealed envelope and assigned the patient to the designated group. In group 1 (treatment group) a single dose of IV paracetamol (1 g in 100 mL normal saline solution) and in group 2 (control group) morphine sulfate (0.1 mg/kg in 100 mL normal saline solution) was infused. Both paracetamol and morphine sulfate were infused within 15 minutes. Data were documented at baseline and at 15- and 30-minute intervals after drug

administration. Documented data included a pain score according to numeric rating scale (NRS), systolic and diastolic blood pressure (mmHg), heart rate (beats per minute), respiratory rate (per minute), oxygen saturation (%). Reports of adverse reactions were documented and categorized as nausea/vomiting, headache, dizziness, allergy, dry mouth or altered mental status. Other data including demographic characteristics of patients, time (duration), mechanism of trauma (direct, motor vehicle accident, falling), type of trauma (dislocation, fracture, soft tissue injury, mixed) and location of trauma (upper extremity, lower extremity) were registered in data collection sheets at the beginning of the study. At 30 minutes if NRS was greater than 4, intravenous morphine sulfate titrated to effect was used as 'rescue analgesia'. After 30 minutes of observation, patients' treatment continued as indicated. If admitted, they received additional analgesia as needed but not more than 3 g of paracetamol in the next 24 hours. If they were discharged, they were advised not to take more than 3 g paracetamol in the next 24 hours. Data were collected by an emergency medicine resident who was blinded to the drug administered.

### 3.4. Measurement

Our primary outcome measure was the change in pain score, measured using 10-point NRS at 15 and 30 minutes. Secondary outcome measures included the requirement for rescue analgesia at 30 minutes, and any adverse events.

### 3.5. Sample Size

To detect a statistically significant difference in NRS score with two sided type 1 error of 5% and power of 80% sample size of 8 per group were calculated; to increase the power of the study at least 30 patients per group were considered.

### 3.6. Statistical Analysis

All statistical analyses were performed using SPSS for Windows version 16.0 (SPSS, Inc. Chicago, Illinois, USA). We compared the primary outcome measure of pain relief at 15 and 30 minutes between patients who received paracetamol and those who received morphine using Mann-Whitney test. The Mann-Whitney test was also used for comparison of NRS at each time point. We also used multivariate analysis of variance (MANOVA) for demographic characteristics of patients, time, mechanism, type and location of trauma, and the Kruskal-Wallis test for evaluating the changes of vital signs. Results appear as mean, SD and number (percentage), as required. A p value of < 0.05 was accepted as indicating statistical significance.

## 4. Results

Sixty subjects were enrolled in the study and randomly assigned to receive either paracetamol (n = 30) or morphine (n = 30).

There was no statistically significant difference between the baseline characteristics of groups. Mean baseline pain intensity scores on the NRS were 7.87 (SD = 0.9) and 7.37 (SD = 1.62) in the paracetamol and morphine groups ( $P = 0.1$ ), respectively. The numeric rating scale decreased in a time-dependent manner in both groups. The amount of decrease of NRS at 30 minutes was significantly lower in the paracetamol group ( $P < 0.001$ ).

Fifteen patients (15%) in the morphine group and 4 patients (13.3%) in the paracetamol group required rescue analgesia ( $P < 0.002$ ).

There was no significant difference between the two groups regarding the number of patients experiencing adverse effects. Two patients in the morphine group had dizziness and 3 patients in the paracetamol group had dry mouth (although all of them had it before administration of the drug).

## 5. Discussion

The results of our study suggest that acetaminophen is an efficacious and safe nonopioid analgesic for ED patients with acute traumatic limb pain. We have shown that although IV morphine sulfate is effective for pain management in patients with acute limb trauma, a single 1-gram dose of IV paracetamol provided a higher level of analgesia than morphine and this effect became more pronounced. In our study morphine consumption was significantly lower in the paracetamol group. Our sample size was not sufficient to definitively show the difference of adverse reactions between the groups. While there were no serious adverse events in either group.

Our findings on potential effectiveness of intravenous paracetamol in acute pain management are compatible with previous studies. However, most of them showed the analgesic effect of IV paracetamol was similar to those of IV morphine sulfate. A study by Craig et al. for comparison of IV paracetamol and IV morphine sulfate for pain management of acute limb trauma in the ED found no significant difference in analgesic effect between the paracetamol and morphine groups at any time point (7). They used 10 mg of intravenous morphine sulfate that was greater than the morphine dose we used (0.1 mg/kg) and this may account for the difference observed between our results and those of Craig's. In their study there were significantly more adverse events in the morphine group (7).

A randomized, placebo-controlled trial study by Bektas et al. compared the analgesic efficacy of IV paracetamol and IV morphine for the treatment of renal colic, although statistically significant reductions in pain intensity compared with those with placebo were observed for paracetamol and morphine, no differences were observed between paracetamol and morphine (8). In this study, no serious adverse reactions were documented. Grissa et al. designed a randomized controlled trial to compare the analgesic efficacy of 1 g of IV paracetamol to 20 mg of intramuscular piroxicam to relieve pain in

renal colic and they showed that analgesia was obtained earlier with paracetamol, and VAS at 90 minutes was significantly lower in the paracetamol group (9). They recorded a case of rash related to NSAID and an episode of vomiting with paracetamol (9). Sinatra et al. evaluated the efficacy and safety of single and repeated administration of 1 g paracetamol for pain management after major orthopedic surgery (10). In this study, the mean VAS pain intensity scores and morphine use were significantly decreased whereas no side effects were developed throughout the 24 postoperative hours compared to the placebo (10).

In conclusion, our data suggest that IV paracetamol administered as a single 1-gram dose is an efficacious and safe treatment for ED patients with acute limb trauma, and appears to provide a better analgesia than IV morphine sulfate. On the basis of our observation, we suggest that IV paracetamol may be an alternative analgesic to currently available parenteral agents especially after acute limb trauma. We believe that it would be useful to repeat this study with a much larger number of subjects.

## Footnotes

**Authors' Contribution:** Mohammad Jalili: study concept and design, critical revision of the manuscript for important intellectual content, administrative, technical, and material support and study supervision; Ali Mozaffarpour Noori: acquisition of data and drafting of the manuscript; Mojtaba Sedaghat: analysis and interpretation of data and statistical analysis; Arash Safaie: drafting of the manuscript and critical revision of the manuscript for important intellectual content.

**Funding/Support:** This study was funded by Tehran University of Medical Sciences.

## References

1. Gueant S, Taleb A, Borel-Kuhner J, Cauterman M, Raphael M, Nathan G, et al. Quality of pain management in the emergency department: results of a multicentre prospective study. *Eur J Anaesthesiol.* 2011;**28**(2):97-105. doi: 10.1097/EJA.0b013e3283418fb0. [PubMed: 21119516]
2. Rupp T, Delaney KA. Inadequate analgesia in emergency medicine. *Ann Emerg Med.* 2004;**43**(4):494-503. doi: 10.1016/S0196064403012265. [PubMed: 15039693]
3. Ware LJ, Epps CD, Clark J, Chatterjee A. Do ethnic differences still exist in pain assessment and treatment in the emergency department? *Pain Manag Nurs.* 2012;**13**(4):194-201. doi: 10.1016/j.pmn.2010.06.001. [PubMed: 23158701]
4. Bounes V, Barniol C, Minville V, Houze-Cerfon CH, Ducasse JL. Predictors of pain relief and adverse events in patients receiving opioids in a prehospital setting. *Am J Emerg Med.* 2011;**29**(5):512-7. doi: 10.1016/j.ajem.2009.12.005. [PubMed: 20825821]
5. Babl FE, Theophilos T, Palmer GM. Is there a role for intravenous acetaminophen in pediatric emergency departments? *Pediatr Emerg Care.* 2011;**27**(6):496-9. doi: 10.1097/PEC.0b013e31821d8629. [PubMed: 21629146]
6. Serinken M, Eken C, Turkcuier I, Elicabuk H, Uyanik E, Schultz CH. Intravenous paracetamol versus morphine for renal colic in the emergency department: a randomised double-blind controlled trial. *Emerg Med J.* 2012;**29**(11):902-5. doi: 10.1136/emered-2011-200165. [PubMed: 22186009]

7. Craig M, Jeavons R, Probert J, Bengler J. Randomised comparison of intravenous paracetamol and intravenous morphine for acute traumatic limb pain in the emergency department. *Emerg Med J*. 2012;**29**(1):37-9. doi: 10.1136/emj.2010.104687. [PubMed: 21362724]
8. Bektas F, Eken C, Karadeniz O, Goksu E, Cubuk M, Cete Y. Intravenous paracetamol or morphine for the treatment of renal colic: a randomized, placebo-controlled trial. *Ann Emerg Med*. 2009;**54**(4):568-74. doi: 10.1016/j.annemergmed.2009.06.501. [PubMed: 19647342]
9. Grissa MH, Claessens YE, Bouida W, Boubaker H, Boudhib L, Kerkeni W, et al. Paracetamol vs piroxicam to relieve pain in renal colic. Results of a randomized controlled trial. *Am J Emerg Med*. 2011;**29**(2):203-6. doi: 10.1016/j.ajem.2009.09.019. [PubMed: 20934829]
10. Sinatra RS, Jahr JS, Reynolds LW, Viscusi ER, Groudine SB, Payen-Champenois C. Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. *Anesthesiology*. 2005;**102**(4):822-31. [PubMed: 15791113]
11. Olonisakin RP, Amanor-Boadu SD, Akinyemi AO. Morphine-sparing effect of intravenous paracetamol for post operative pain management following gynaecological surgery. *Afr J Med Med Sci*. 2012;**41**(4):429-36. [PubMed: 23672109]
12. 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. *J Clin Anesth*. 2013;**25**(3):188-92. doi: 10.1016/j.jclinane.2012.09.004. [PubMed: 23567482]
13. He X, Li S, Huang H, Li Z, Chen L, Ye S, et al. A pharmacokinetic and safety study of single dose intravenous combretastatin A4 phosphate in Chinese patients with refractory solid tumours. *Br J Clin Pharmacol*. 2011;**71**(6):860-70. doi: 10.1111/j.1365-2125.2011.03928.x. [PubMed: 21276042]
14. Tasmacioglu B, Aydinli I, Keskinbora K, Pekel AF, Salihoglu T, Sonsuz A. Effect of intravenous administration of paracetamol on morphine consumption in cancer pain control. *Support Care Cancer*. 2009;**17**(12):1475-81. doi: 10.1007/s00520-009-0612-8. [PubMed: 19343373]
15. Mirkheshti A, Aryani MR, Shojaei P, Dabbagh A. The Effect of Adding Magnesium Sulfate to Lidocaine Compared with Paracetamol in Prevention of Acute Pain in Hand Surgery Patients Under Intravenous Regional Anesthesia (IVRA). *Int J Prev Med*. 2012;**3**(9):616-21. [PubMed: 23024850]
16. Ko MJ, Lee JH, Cheong SH, Shin CM, Kim YJ, Choe YK, et al. Comparison of the effects of acetaminophen to ketorolac when added to lidocaine for intravenous regional anesthesia. *Korean J Anesthesiol*. 2010;**58**(4):357-61. doi: 10.4097/kjae.2010.58.4.357. [PubMed: 20508792]