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Intravenous Acetaminophen Versus Intravenous Morphine Sulfate for Isolated Diaphyseal Long Bone Fractures: A Randomized Clinical Trial

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Abstract

Objectives: Pain management is an important issue in traumatic patients. The aim of this randomized clinical trial was to compare the analgesic effect of intravenous acetaminophen with intravenous morphine sulfate in patients with traumatic diaphyseal long bone fracture.

Methods: This double-blind randomized clinical trial was carried out in an academic trauma center in Mashhad, Iran, from February to October 2013. After primary modalities like limb elevation, ice and limb splinting, patients were allocated to receive either acetaminophen 15 mg/kg or morphine sulfate 0.1 mg/kg randomly. The pain severity was measured using a visual analogue scale before drug administration and 5 and 30 minutes after drug administration. Then, the results were compared.

Results: Of the 50 patients recruited over 9 months 26 patients received intravenous morphine sulfate and 24 patients received intravenous acetaminophen. A significant difference was observed between the two groups at 5 minutes after drug administration; the morphine sulfate group showed more reduction in pain severity after 5 minutes ($P < 0.0001$). However, there was no significant difference in pain severity at 30 minutes after drug administration between the two groups ($P = 0.85$).

Conclusions: It seems that after 30 minutes, intravenous acetaminophen is as effective as intravenous morphine sulfate in pain management of isolated diaphyseal long bone fracture. However, it should be noted that the analgesic effect of acetaminophen begins with a delay. Thus, we suggest using intravenous acetaminophen when morphine administration is contraindicated.

Keywords: Intravenous Acetaminophen, Intravenous Morphine Sulfate, Visual Analogue Scale, Long Bone Fracture

1. Background

Pain management is one of the most important concepts in emergency settings. There are different methods to reduce pain including splinting, elevation of injured limb, and administration of analgesics (1). Traditionally, morphine has been the most important analgesic agent for moderate to severe pain management in patients with isolated limb trauma. However, morphine has some side effects including respiratory depression, nausea, sedation, histamine release, and addiction (1). Additionally, some patients who are under addiction recovery are reluctant to use morphine for pain management (2).

Acetaminophen is an analgesic agent that can be used in renal failure and mild hepatic failure (1). A single-blind emergency department study over patients presenting with renal colic found that intravenous acetaminophen was equally effective as intravenous morphine (3). There are also some other studies showing that intravenous acetaminophen is as effective as intravenous morphine in pain management (4-9).

Since there was no study to compare these two analgesic agents on Asian population. The goal of our study was to compare the analgesic effect of intravenous acetaminophen versus intravenous morphine in patients with traumatic isolated diaphyseal long bone fractures.

2. Methods

After obtaining ethics committee approval, we completed a randomized, double-blind study on 50 trauma patients who had isolated diaphyseal long bone fracture in the emergency department of Shahid Hasheminejad hospital.

The inclusion criteria were age between 18 and 60 years, weight > 50 kg, and isolated diaphyseal long bone fracture. Patients with decreased level of consciousness (Glasgow Coma scale < 15), liver disease or clinical jaundice, renal disease, known pregnancy and breast feeding, allergy to morphine or acetaminophen, opium addiction, and existence of any other painful lesion.

The study was approved by the ethics committee of Mashhad University of Medical Sciences. The registration code of this study is IRCT2012123111956N1 in Iranian registry of clinical trials (IRCT).

Participants were offered verbal information about the study as well as a written informed consent.

The baseline data collected were name, sex, age, body weight, and the type of the fracture. Any adverse reaction including nausea, vomiting, hypotension, respiratory depression, and allergic reaction was also recorded. Convenience sampling was used for sample collection. Patients were divided into two treatment groups by using randomized allocation to receive intravenous morphine or intravenous acetaminophen. The randomization scheme was generated by using the Web site: Randomization.com. After primary modalities like limb elevation, ice and limb splinting and before administration of analgesic agent, our colleague (who was not aware of the type of the analgesic agent) asked the patient to quantify his/her pain severity on a 100 mm visual analogue scale. Then, patients in the morphine sulfate group received 0.1 mg/kg of intravenous morphine sulfate and patients in the acetaminophen group received 15 mg/kg of intravenous acetaminophen.

2.1. Sample Size

The sample size was calculated as 24 patients for each group.

2.2. Statistical Analysis

Analyses were performed using SPSS (statistical package for social sciences) version 11.5. Absolute number and percentages were computed to describe data. Data were expressed as mean $\pm$ SD (standard deviation) for continuous variables. Categorical variables were compared between the two groups using chi square test or Fisher exact test as appropriate. Regarding the normal distribution of data, the mean of the two independent groups was compared using Independent t test. To assess the trend over time in each group, repeated measurement test was used. For all of the tests, P value equal to or lower than 0.05 was considered as significant.

3. Results

Finally, 50 patients were divided into two treatment groups by using randomized allocation. The patients consisted of 39 men (78%) and 11 women (22%). The mean age of the patients was 39 $\pm$ 14.6.

Two analgesic agents were randomized among our 50 patients. The intravenous morphine group comprised 26 patients including 21 men (80.8%) and 5 women (19.2%) while the intravenous acetaminophen group was composed of 24 patients including 18 men (75%) and 6 women (25%). There was no significant difference in sex between the two groups (P = 0.62).

In the morphine group, 13 patients (50%) had upper extremity fracture and 13 patients (50%) had lower extremity fracture. Similarly in the acetaminophen group, 9 patients (37.5%) suffered upper extremity fracture and 15 patients (62.5%) suffered lower extremity fracture. There was no significant difference in fracture type between the two groups (P = 0.37).

The baseline characteristics of the two groups did not show significant statistical differences (Table 1).

There was a statistically significant difference in pain severity between the two groups at 5 minutes after injection; pain severity was lower in the morphine group (P value $<$ 0.0001). However, according to independent t test, there was no significant difference in pain severity between the two groups at 30 minutes (P value = 0.85) (Tables 2 - 4).

4. Discussion

In general, intravenous acetaminophen and intravenous morphine are used to control pain in emergency departments and their effectiveness have been proven (10). The aim of this study was to compare the analgesic effectiveness of these two drugs in long bone fracture.

In this randomized clinical trial, there was no significant difference in pain reduction with administration of intravenous acetaminophen and intravenous morphine after 30 minutes. Additionally, a significant pain reduction was observed in both groups over the time. On the other hand, pain reduction 5 minutes after analgesic administration in the morphine group was more significant than the acetaminophen group. Since rapid pain control in traumatic patients is an important issue, this is an unfavorable effect of intravenous acetaminophen in our study.

Results of the similar studies did not show any significant difference in the analgesic effect of intravenous acetaminophen and morphine (3-9).

Generally, acetaminophen side effects are less common than those of morphine (11). Opioid side effects are nausea, vomiting, histamine release, urinary retention, confusion, and respiratory depression. Hypotension may also occur due to histamine release that may be problematic in multiple trauma patients with hemorrhage (11).

Acetaminophen does not have the aforementioned side effects (10); so, it seems more favorable in patient with trauma and long bone fractures.

Onset of action of morphine is shorter than that of acetaminophen. This can explain the significant difference of pain severity at 5 minutes after injection between the two groups.

Table 1. The Baseline Characteristics of the Patients[a]

Variables	Group		P Value	Difference	95% Confidence Interval
	Morphine	Acetaminophen			
Age, y	39.04 ± 15.23	39.63 ± 14.39	0.89	-0.59	-9.03 to 7.85
Weight, kg	68.27 ± 10.08	71.42 ± 8.93	0.25	-3.15	-8.58 to 2.28
Pain severity before injection, mm	89.69 ± 7.71	91.04 ± 4.26	0.45	-1.35	-4.93 to 2.23

[a]Values are expressed as mean ± SD.

Table 2. Pain Severity After Injection of Analgesic Agent[a]

Pain Severity After Injection	Group		P Value	Mean Difference	95% Confidence Interval
	Morphine	Acetaminophen			
5 minutes	67.62 ± 16.30	83.54 ± 7.07	< 0.0001	-15.93	-23.18 to -8.67
30 minutes	56.65 ± 17.56	55.75 ± 16.09	0.85	0.90	-8.70 to 10.50

[a]Values are expressed as mean ± SD.

Table 3. Pain reduction After Injection of Analgesic Agents[a]

Pain Reduction After Injection	Morphine Group	Acetaminophen Group	P Value	Mean Difference	95% Confidence Interval
5 minutes	22.08 ± 12.52	7.5 ± 5.83	< 0.0001	14.57	8.9 to 20.2
30 minutes	33.03 ± 14.04	35.29 ± 15.77	0.59	-2.25	-10.7 to 6.2

[a]Values are expressed as mean ± SD.

Table 4. The Trend of Pain Reduction in the Two Groups[a]

Varibales	Pain severity, mm			P Value
	Before injection	5 minutes	30 minutes	
Morphine group	89.69 ± 7.71	67.62 ± 16.30	56.65 ± 17.56	< 0.0001
Acetaminophen group	91.04 ± 4.26	83.54 ± 7.07	55.75 ± 16.09	< 0.0001

[a]Values are expressed as mean ± SD.

On the other hand, elimination half-life of acetaminophen is longer than that of morphine (3 hours versus 2 hours); so, the duration of action of acetaminophen may be longer than that of the morphine (11).

In a previous study, patients who received both oxycodone and acetaminophen had more nausea than those who received only morphine (10).

4.1. Conclusion

Intravenous acetaminophen can be used as an alternative for intravenous morphine. However, it should be noted that the analgesic effect of acetaminophen begins with delay. Thus, we suggest using intravenous acetaminophen when morphine administration is contraindicated.

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Footnotes

Conflict of Interests: The authors have no conflicts of interest.

Trial Registration Number: IRCT2012123111956N1.

References

1. Tintinalli JE, Stapczynski JS, Cline DM, Ma OJ, Cydulka RK, Meckler GD. Emergency Medicine. 7th ed. New York: Mc Graw Hill; 2011.
2. Bell J, Reed K, Gross S, Witton J. The management of pain in people with a past or current history of addiction 2013 Available from: http://www.actiononaddiction.org.uk/Documents/The-Management-of-Pain-in-People-with-a-Past-or-Cu.aspx.
3. 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].
4. Serinken M, Eken C, Turkcuer 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/emermed-2011-200165. [PubMed: 22186009].
5. Alhashemi JA, Alotaibi QA, Mashaat MS, Kaid TM, Mujallid RH, Kaki AM. Intravenous acetaminophen vs oral ibuprofen in combination with morphine PCIA after Cesarean delivery. *Can J Anaesth.* 2006;**53**(12):1200–6. doi: 10.1007/BF03021581. [PubMed: 17142654].
6. Alhashemi JA, Daghistani 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. doi: 10.1093/bja/ael084. [PubMed: 16613928].
7. Arici S, Gurbet A, Turker G, Yavascaoglu B, Sahin S. Preemptive analgesic effects of intravenous paracetamol in total abdominal hysterectomy. *Agri.* 2009;**21**(2):54–61. [PubMed: 19562533].
8. Hoogewijs J, Diltoer MW, Hubloue I, Spapen HD, Camu F, Corne L, et al. A prospective, open, single blind, randomized study comparing four analgesics in the treatment of peripheral injury in the emergency department. *Eur J Emerg Med.* 2000;**7**(2):119–23. doi: 10.1097/00063110-200006000-00006. [PubMed: 11132072].
9. Craig M, Jeavons R, Probert J, Benger 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].
10. Dijkstra BM, Berben SA, van Dongen RT, Schoonhoven L. Review on pharmacological pain management in trauma patients in (pre-hospital) emergency medicine in the Netherlands. *Eur J Pain.* 2014;**18**(1):3–19. doi: 10.1002/j.1532-2149.2013.00337.x. [PubMed: 23737462].
11. Sweetman SC, Blake PS, Mc-Glashan JM, Neathercoat GC, Parsons AV. Martindale: The Complete Drug Reference. 34th ed. Chicago: Pharmaceutical Press; 2005.