ORIGINAL ARTICLE

Comparison of morphine–midazolam versus morphine injection for pain relief in patients with limb fractures - a clinical trial

Alireza Majidi, M.D.,[1] Hossein Dinpanah, M.D.,[1] Sahar Ashoori, M.D.,[1] Hassan Motamed, M.D.,[2#] Ali Tabatabaey, M.D.[1*]

[1]Department of Emergency Medicine, Shahid Beheshti Medical University, Tehran, Iran;
[2]Department of Emergency Medicine, Jundishapoor University of Medical Sciences, Ahvaz, Iran

ABSTRACT

BACKGROUND: Pain relief, using opiates as a primary choice, is an important part of treating limb fractures. Yet, in order to reduce opiate consumption, other combinations have been introduced. This study aimed to compare pain reduction by a combination of morphine–midazolam with morphine injection in patients with limb fractures.

METHODS: A randomized double-blind study of patients with upper or lower extremity fractures was conducted. Patients' response to treatment with either morphine-midazolam solution or morphine at 15, 30, 45, 60, 120, and 180 minutes were assessed. The Kaplan-Meier curves and generalized estimating equations were examined to evaluate the success of treatment.

RESULTS: A total of seventy-two patients aged 18-60 (80.6% male; mean age: 35±17.9 years) were included. At 15, 30, 45, and 60 minutes, successful pain control was seen in 8.83 22.2%, 33.3% and 63.9% of the patients in the morphine group, and 11.1%, 27.7%, 44.4% and 63.8% in the midazolam-morphine group. By the third hour, pain-control was achieved in all patients receiving morphine while pain persisted in one patient receiving morphine-midazolam. Log-rank test showed no significant difference between the two groups (p=0.55).

CONCLUSION: Our findings revealed that adding midazolam to morphine did not improve its pain-relief profile.

Key words: Bone fracture; midazolam; morphine; pain.

INTRODUCTION

Pain reduction of limb fracture patients in the emergency department (ED) is a treatment priority for the emergency physician.[1-3] Pain control is closely related to patient satisfaction.[2,4] For years, opiates, namely Morphine sulfate (MS), have been the primary pain relief medication. Many current guidelines support intravenous administration of MS for acute and severe pain.[5,6] Such guidelines recommend the use of MS for patients with a pain score of 6 or higher on the visual analogue scale (VAS) until the pain is controlled (severity of pain reduced to 3 or lower).

Yet, using MS is limited by a variety of factors including fear of side effects, impairment of physical examination, and fear of addiction.[7] Furthermore, dose adjustment is required on a personal bases to achieve balance between pain control and these concerns. Recent evidence has pointed to the fact that MS is not as effective as once thought in ED patients. It has been suggested that within 15 minutes of administration, only 50% of the patients experience pain control.[4,8,9] Therefore, despite noticeable strides, pain control in the ED is still an unresolved issue.[3,1-12] Consequently, researchers have proposed other drug regimens to reduce MS consumption in the ED. Combination drug therapy is one such regimen aiming to improve pain control whilst reducing MS use.[13-15]

Midazolam is an imidazobenzodiazepine with unique characteristics. It acts faster than other drugs in this category and is a stronger sedative, hypnotic, and anxiolytic. These proper-

*Current affiliation: #Department of Emergency Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; *Department of Emergency Medicine, Qom University of Medical Sciences, Qom, Iran*

Address for correspondence: Ali Tabatabaey, M.D.
Department of Emergency Medicine, Qom University of Medical Sciences, Qom, Iran
Tel: +98 2536122000 E-mail: alitabtab@gmail.com

Qucik Response Code

Ulus Travma Acil Cerrahi Derg
2015;21(1):22-26
doi: 10.5505/tjtes.2015.64494

ties have led to its increased use in the ED, either as a sole drug or in combination with Fentanyl or Ketamine. The use of morphine-midazolam (M/M) combination in painful conditions is based on the well-known relationship between anxiety and pain.[16,17] Despite animal studies suggesting the possibility of increased nociception with the use of midazolam,[18] the bulk of clinical studies have either reported better pain control,[16,19,20] or no significant effect.[21-23] This study aimed to compare M/M combination with MS in pain control of patients suffering from isolated traumatic fracture of extremities.

MATERIALS AND METHODS

This was a double-blind randomized clinical trial on patients aged 18 to 60 brought to the ED of our teaching hospital with isolated upper or lower extremity fractures. The study protocol was approved by the hospital ethical committee. The patients were randomly attributed to one of the two groups receiving either MS or M/M. With a confidence interval of 95% and a power of 90%, the required sample size was estimated to be 20 patients. Patients were included based on the following criteria: 18-60 years of age, isolated extremity fracture, and an initial pain score greater than 7 on verbal numerical rating scale (VNRS). Patients were excluded if they refused to participate, had history of allergies to opiates or benzodiazepines, if opiates had been used in pre-hospital setting, if there were any contraindications to opiate use (i.e. chronic respiratory failure, under treatment for opiate addiction), pregnancy or lactation, history of chronic pain, and if they were unable to determine the severity of pain (i.e. intoxication, dementia).

On arrival, the patient's pain level was determined by asking them to rate their pain on an 11-point (0-10) numerical rating scale.[24] Based on the randomization sheet, each patient was administered a prepared solution of either M/M (0.05 mg/kg Morphine and 0.02 mg/kg Midazolam) or MS (0.05 mg/kg Morphine sulfate) intravenously. Patient pain scores and side effects were then re-measured at 15, 30, 45, 60, 120, and 180 minutes after drug administration. In order to reassure the study's double blind design, the preparation, administration, and recording of pain scores were performed by three different clinicians. If any adverse side-effects were recorded, the content of the injected solution was made available to the clinician and the patient was removed from the study. At 15 minutes, if the patient required further pain control, a rescue dose of the original combination with the same dosing was injected.

The data were analyzed using SPSS 11.5 and STATA 11.0 software. Pain scores on determined intervals were described using means and standard deviations and the difference between the two groups was tested using T-test. The effect of gender and site of injury on pain relief was tested using the Chi-Square test. Generalized Estimating Equations (GEE) were used to analyze the effects of difference in pain severity in both groups. Finally, the Kaplan-Meier plot was drawn to describe and compare success between the two groups within the first 3 hours. A 50% or more reduction in pain severity was considered successful pain control and a p-value of less than 0.05 was considered significant.

RESULTS

A total of seventy-two patients were included into the study, 36 being in each group. The demographics and initial pain scores are summarized in Table 1. T-test and chi-square test were used to determine any significant differences between the two groups.

Administration of both MS and M/M significantly reduced pain in all time intervals ($p<0.0001$, $df=13.2$, $F=109.7$). There was also a significant trend towards pain reduction in both groups as time passed ($p_{trend}<0.0001$). Table 2 summarizes mean and

Table 1. Pre-intervention demographics

Variable	Morphine			Morphine-Midazolam			p
	n	%	Mean±SD	n	%	Mean±SD	
Age			30.3±15.3			39.7±19.3	0.03
Gender							
Male	31	86.1		27	75.0		0.2
Female	5	13.9		9	25.0		
Site of injury							
Upper ext.	5	13.9		5	13.9		0.58
Lower ext.	19	52.8		22	61.1		
Other†	12	33.3		9	25		
Baseline pain score			9.1±0.9			8.9±0.8	0.42

†Factures in multiple limbs or associated with significant soft tissue injury.

Table 2. Mean pain scores at determined intervals in both groups

Time	Morphine	Morphine-Midazolam	p
	Mean±SD	Mean±SD	
Baseline (min)	9.1±0.9	8.9±0.8	
15	7.3±1.5	7.4±1.4	
30	6.1±1.8	6.0±1.6	
45	5.2±1.5	4.7±1.6	0.55
60	4.4±1.4	3.7±1.6	
120	3.0±1.2	2.7±1.0	
180	2.0±1.1	1.9±0.8	

standard deviation of pain scores in each interval. GEE test failed to discover any significant difference in pain reduction between the two groups.

The Kaplan-Meier plot was drawn to demonstrate success rates in both groups. Any patient experiencing over 50% reduction in pain as compared to the initial score was calculated as a success. As demonstrated in Figure 1, in the first 15 minutes after injection, MS and M/M achieved success in 8.3 and 11.1% of the cases, respectively. This number increased to 22.2 and 27.7% in the 30th minute, and then to 33.3 and 44.4% at the 45th minute. MS achieved success in 63.9, 88.9, and 100% of the group by the first, second, and third hour, respectively. On the other hand, M/M achieve 63.8 and 91.7% in the first and second hours while by the third hour it failed to control pain in only one patient. A rescue dose also failed to achieve success in this patient. The Log-rand test failed to recognize any significant difference in success rate or trend within the two groups (p=0.55).

DISCUSSION

This clinical trial showed that M/M combination was not superior to MS for relieving the pain of isolated limb fractures.

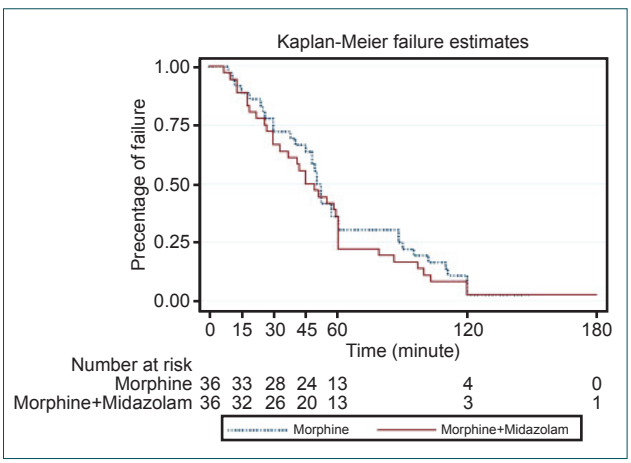

Figure 1. Trend in treatment success during the experiment period.

MS has a proven role in pain control established in different settings.[4,7,10,21] Yet, due to its adverse effects and problems in determining the effective dose, researchers have turned to drug combinations. Galinski and colleagues have combined low-dose ketamine with morphine and have been able to reduce morphine requirements by 26%.[25]

A possible role for targeting gamma-amino-butyric acid (GABA) receptors for pain control has been suggested.[26] Like other benzodiazepines, Midazolam is an agonist of benzodiazepine receptors acting on GABA receptors and facilitate the influx of chloride ions into neurons. The affinity of midazolam to these receptors is twice that of diazepam reflecting its increased potency. Midazolam is different from other benzodiazepines in its short half-life, multiple routes of administration, and better safety profile.[27] As a result, midazolam was our choice as a possible combination to morphine sulfate. Morphine works essentially in the medulla and reduces the conduction of signals within the pain pathway.[28] On the other hand, midazolam works in the cortex and increases the sensitivity of GABA receptors.[29] We hypothesized that combining these two drugs utilizing different mechanisms of action could be a more efficient approach to pain control as opposed to morphine alone.

This hypothesis has previously been reinforced by several studies. In 1996, Gilliland and colleagues studied the effects of bolus and continuous midazolam infusion on fifty patients undergoing elective hysterectomy. This placebo-controlled double-blind randomized controlled trial showed that during the first 12 hours after surgery, MS consumption was significantly lower in the midazolam group.[30] In 2000, while assessing postoperative anxiety, Kain et al. found that patients treated with midazolam 30 min before surgery reported a greater reduction in postoperative pain throughout the first postoperative week and patients reported less ibuprofen use.[16] In a recent study, Day and colleagues examined archival data from a parallel-group, double-blinded, placebo-controlled randomized controlled trial in which patients self-administered pain or anxiety medication. The researchers found that although

there was no significant difference in pain scores, the treatment group used significantly less morphine than the control group and felt better.[19]

On the other hand, several studies have questioned analgesic enhancement by midazolam. Wille-Ledon and colleagues have demonstrated a similar pain relief profile for Morphine and Morphine-Midazolam combination in the pediatric population with limb fractures.[21] More recently, Auffret et al. have studied the role of adding midazolam to MS in pre-hospital trauma patients. The study was a prospective randomized double-blind placebo-controlled trial. Pain was assessed using a NRS and a difference of 3 points between the groups was considered significant effect. The study failed to find any benefit of midazolam adjunctive therapy to morphine in pain control.[23]

To our knowledge, ours is the first study comparing M/M and MS in the setting of adult trauma patients in the emergency department. Like that of Wille-Ledon and Auffret, our results failed to prove an added analgesic effect when midazolam was added to morphine. In our study, patients in both groups showed a similar amount and trend in pain reduction and the success rate in both groups was comparable. Furthermore, our results showed that despite even using a rescue dose, more than half of the patients still suffered from significant pain 30 minutes after either MS or M/M injection, reflecting, to some extent, the unreliability of morphine in its initial dose and justifying the search for a more effective and reliable analgesic in limb fractures.

Limitations and Conclusion

This study was the first double-blind randomized control trial to compare the effects of M/M to MS for pain reduction in acute isolated limb fractures. Since the study was set in the emergency department, only short term results were sought and possible long-term outcomes derived from the combination therapy were not evaluated. A placebo group was not used for ethical concerns. Another limitation was homogeneity of the two groups. As seen in Table 1, both groups were found to be significantly different regarding age (p=0.03). Taking into account the mean age of both groups, it is to our belief that this should not affect the interpretation of our findings. Results of the current study showed that adding midazolam to morphine did not improve its pain relieving characteristics in limb fractures.

Acknowledgement and Conflict of Interest

The study was funded by the authors' academic grants and the authors have no conflict of interest to report.

REFERENCES

1. Jennings PA, Cameron P, Bernard S. Epidemiology of prehospital pain: an opportunity for improvement. Emerg Med J 2011;28:530-1. CrossRef
2. Le May S, Gouin S, Fortin C, Messier A, Robert MA, Julien M. Efficacy of an ibuprofen/codeine combination for pain management in children presenting to the emergency department with a limb injury: a pilot study. J Emerg Med 2013;44:536-42. CrossRef
3. Brown JC, Klein EJ, Lewis CW, Johnston BD, Cummings P. Emergency department analgesia for fracture pain. Ann Emerg Med 2003;42:197-205.
4. Bounes V, Charpentier S, Houze-Cerfon CH, Bellard C, Ducassé JL. Is there an ideal morphine dose for prehospital treatment of severe acute pain? A randomized, double-blind comparison of 2 doses. Am J Emerg Med 2008;26:148-54. CrossRef
5. Ward KR, Yealy DM. Systemic analgesia and sedation in managing orthopedic emergencies. Emerg Med Clin North Am 2000;18:141-66.
6. Smally AJ, Nowicki TA, Simelton BH. Procedural sedation and analgesia in the emergency department. Curr Opin Crit Care 2011;17:317-22.
7. Gallagher EJ, Esses D, Lee C, Lahn M, Bijur PE. Randomized clinical trial of morphine in acute abdominal pain. Ann Emerg Med 2006;48:150-60 .e1-4.
8. Galinski M, Dolveck F, Borron SW, Tual L, Van Laer V, Lardeur JY, et al. A randomized, double-blind study comparing morphine with fentanyl in prehospital analgesia. Am J Emerg Med 2005;23:114-9. CrossRef
9. Rickard C, O'Meara P, McGrail M, Garner D, McLean A, Le Lievre P. A randomized controlled trial of intranasal fentanyl vs intravenous morphine for analgesia in the prehospital setting. Am J Emerg Med 2007;25:911-7. CrossRef
10. Bijur PE, Kenny MK, Gallagher EJ. Intravenous morphine at 0.1 mg/kg is not effective for controlling severe acute pain in the majority of patients. Ann Emerg Med 2005;46:362-7. CrossRef
11. Todd KH. Emergency medicine and pain: a topography of influence. Ann Emerg Med 2004;43:504-6. CrossRef
12. Rupp T, Delaney KA. Inadequate analgesia in emergency medicine. Ann Emerg Med 2004;43:494-503. CrossRef
13. Chang AK, Bijur PE, Lupow JB, John Gallagher E. Randomized clinical trial of efficacy and safety of a single 2-mg intravenous dose of hydromorphone versus usual care in the management of acute pain. Acad Emerg Med 2013;20:185-92. CrossRef
14. Chaplin S, Campbell W. Properties and use of compound analgesics in pain management. Prescriber 2013;24:38-40. CrossRef
15. Leung S, Bulloch B, Young C, Yonker M, Hostetler M. Effectiveness of standardized combination therapy for migraine treatment in the pediatric emergency department. Headache 2013;53:491-197. CrossRef
16. Kain ZN, Sevarino F, Pincus S, Alexander GM, Wang SM, Ayoub C, et al. Attenuation of the preoperative stress response with midazolam: effects on postoperative outcomes. Anesthesiology 2000;93:141-7. CrossRef
17. Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R, et al. Exacerbation of pain by anxiety is associated with activity in a hippocampal network. J Neurosci 2001;21:9896-903.
18. Ito K, Yoshikawa M, Maeda M, Jin XL, Takahashi S, Matsuda M, et al. Midazolam attenuates the antinociception induced by d-serine or morphine at the supraspinal level in rats. Eur J Pharmacol 2008;586:139-44. CrossRef
19. Day MA, Rich MA, Thorn BE, Berbaum ML, Mangieri EA. A placebo-controlled trial of midazolam as an adjunct to morphine patient-controlled analgesia after spinal surgery. J Clin Anesth 2014;26:300-8. CrossRef
20. Aydogan MS, Parlakpinar H, Ali Erdogan M, Yucel A, Ucar M, Sağır M, et al. Effects of dexmedetomidine and midazolam on motor coordination and analgesia: a comparative analysis. Curr Ther Res Clin Exp 2013;75:22-6. CrossRef
21. Wille-Ledon C, Chappuy H, Giraud C, Tréluyer JM, Chéron G. Comparison of a morphine and midazolam combination with morphine alone for paediatric displaced fractures: a randomized study. Acta Paediatr

2011;100:e203-7. CrossRef

22. Bauer KP, Dom PM, Ramirez AM, O'Flaherty JE. Preoperative intravenous midazolam: benefits beyond anxiolysis. J Clin Anesth 2004;16:177-83. CrossRef
23. Auffret Y, Gouillou M, Jacob GR, Robin M, Jenvrin J, Soufflet F, et al. Does midazolam enhance pain control in prehospital management of traumatic severe pain? Am J Emerg Med 2014;32:655-9. CrossRef
24. Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. Ann Emerg Med. 1996;27:485-9. CrossRef
25. Galinski M, Dolveck F, Combes X, Limoges V, Smaïl N, Pommier V, et al. Management of severe acute pain in emergency settings: ketamine reduces morphine consumption. Am J Emerg Med 2007;25:385-90. CrossRef
26. Jasmin L, Wu MV, Ohara PT. GABA puts a stop to pain. Curr Drug Targets CNS Neurol Disord 2004;3:487-505. CrossRef
27. Hardmeier M, Zimmermann R, Rüegg S, Pflüger M, Deuster S, Suter K, et al. Intranasal midazolam: pharmacokinetics and pharmacodynamics assessed by quantitative EEG in healthy volunteers. Clin Pharmacol Ther 2012;91:856-62. CrossRef
28. Yaksh TL. Pharmacology and mechanisms of opioid analgesic activity. Acta Anaesthesiol Scand 1997;41(1 Pt 2):94-111. CrossRef
29. Rogers WK, McDowell TS. Remimazolam, a short-acting GABA(A) receptor agonist for intravenous sedation and/or anesthesia in day-case surgical and non-surgical procedures. IDrugs 2010;13:929-37.
30. Gilliland HE, Prasad BK, Mirakhur RK, Fee JP. An investigation of the potential morphine sparing effect of midazolam. Anaesthesia 1996;51:808-11. CrossRef

KLİNİK ÇALIŞMA - *ÖZET*

Ekstremite kırıkları olan hastalarda ağrı giderimi için morfin-midazolama karşın morfin enjeksiyonunun karşılaştırılması - klinik çalışma

Dr. Alireza Majidi,[1] Dr. Hossein Dinpanah,[1] Dr. Sahar Ashoori,[1] Dr. Hassan Motamed,[2] Dr. Ali Tabatabaey[1]

[1]Shahid Beheshti Tıp Üniversitesi, Acil Tıp Anabilim Dalı, Tehran, Iran;
[2]Jundishapoor Tıp Bilimleri Üniversitesi, Acil Tıp Anabilim Dalı, Ahvaz, Iran

AMAÇ: Ağrı giderimi için ilk olarak opiyatların kullanılması ekstremite kırıkları tedavisinin önemli bir bölümünü oluşturur. Ancak opiyat tüketiminin azaltılması için başka kombinasyonlar da ortaya atılmıştır. Bu çalışma, bu hastalarda ağrıyı hafifletmede morfin-midazolam kombinasyonuyla morfin enjeksiyonunu karşılaştırmayı amaçlamaktadır.

GEREÇ VE YÖNTEM: Alt ve üst ekstremite kırıkları olan hastalarda bir randomize çift-kör çalışma yürütüldü. Hastaların morfin-midazolam çözeltisi veya morfin tedavisine yanıtları 15., 30., 45., 60., 120. ve 180. dakikalarda değerlendirildi. Tedavinin başarısını değerlendirmek için Kaplan-Meier eğrileri ve genelleştirilmiş tahmin denklemleri incelendi. Anlamlılık düzeyi olarak $p<0.05$ kabul edildi.

BULGULAR: Çalışmaya 18-60 yaş arası toplam 72 hasta (%80.6 erkek; yaş ortalaması: 35±17.9 yıl) alındı. On beşinci, 30., 45. ve 60. dakikalarda morfin grubunda hastaların sırasıyla %8.83; %22.2; %33.3 ve %63.9'unda, midazolam-morfin grunda ise %11.1; %27.7; %44.4 ve %63.8'inde ağrının kontrolü başarıldı. Üçüncü saate gelindiğinde morfin alanların hepsinde ağrı kontrolü gerçekleşmişken morfin-midazolam grubunda yalnızca bir hastada ağrı sebat etmiştir. Log-sıra testi iki gruplar arasında herhangi bir anlamlı farklılık göstermedi ($p=0.55$).

TARTIŞMA: Bulgularımız midazolamın morfine ilavesinin ağrı giderimi profilini iyileştirmediğini göstermektedir.

Anahtar sözcükler: Ağrı; kemik kırığı, midazolam; morfin.

Ulus Travma Acil Cerrahi Derg 2015;21(1):22-26 doi: 10.5505/tjtes.2015.64494