Emergency. 2016; 4 (4): 202-206

OPEN ACCESS

ORIGINAL RESEARCH

Intravenous Morphine vs Intravenous Ketofol for Treating Renal Colic; a Randomized Controlled Trial

Gholamreza Faridaalaee[1], Neda Mohammadi[2*], Seyedeh Zahra Merghati[3], Fatemeh Keyghobadi Khajeh[4], Bahman Naghipour[5], Mahboob Pouraghaei[6], Sajjad Ahmadi[1]

1. Emergency MedicineDepartment, Maragheh University of Medical Sciences, Maragheh, Iran.
2. Emergency MedicineDepartment, Urmia University of Medical Sciences, Urmia, Iran.
3. International branch of Urmia University of Medical Sciences, Urmia, Iran.
4. Department of Community Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
5. AnesthesiologyDepartment, Tabriz University of Medical Sciences, Tabriz, Iran.
6. Department of Emergency Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.

Received: 2 December 2015; Accepted: 1 January 2016

Abstract: **Introduction:** The main purpose of emergency department (ED) managementfor renal colic is prompt pain relief. The present study aimed to compare the analgesic effects of intravenus (IV) ketofol with morphine in management of ketorolac persistent renal colic. **Methods:** This study is a single blind randomized, clinical trial, on patients who were presented to ED with renal colic, whose pain was resistant to 30 mg IV ketorolac. The patients were randomly assigned to either IV morphine (0.1 mg/kg) or IV ketofol (0.75 mg/kg propofol and 0.75 mg/kg) and the measures of treatment efficacy were compared between the groups after 5 and 10 minutes. **Results:** 90 patients with mean age of 38.01 ± 9.78 years were randomly divided into 2 groups of 45 (66.7% male). Treatment failure rate was significantly lower in ketofol group after 5 (20% vs 62.2%, $p < 0.001$) and 10 minutes (11.1% vs 44.4%, $p < 0.001$). ARR and NNT for ketofol after 5 miutes were 42.22% (95% CI: 23.86 - 60.59) and 3 (95% CI: 1.7 - 4.2), respectively. After 10 minutes, these measures reached 33.33 (95% CI:16.16 - 50.51) and 4 (95% CI: 2.0 - 6.2), respectively. NNH and ARI for hallucination or agitation were 12 (95% CI: 5.8 - 174.2) and 8.89% (0.57 - 17.20), respectively. **Conclusion:** The results of the present study, showed the significant superiority of ketofol (NNT at 5 minute = 3 and NNT at 10 minute = 4) in ketorolac resistant renal colic pain management. However, its NNH of 12, could limit its routine application in ED for this purpose.

Keywords: Renal colic; pain; morphine; propofol; ketamine

Cite this article as: Faridaalaee Gh, Mohammadi N, Merghati SZ, Keyghobadi Khajeh F, Naghipour B, Pouraghaei M, Ahmadi S. Intravenous Morphine vs Intravenous Ketofol for Treating Renal Colic; a Randomized Controlled Trial. Emergency. 2016; 4 (4): 202-206.

1. Introduction

Renal colic usually presents as a severe and intermittent flank pain that can radiate to the genitalia, abdomen and groin (1, 2). It is a common cause for emergency department (ED) visits and affects 3-5% of the general population (3). Its incidence is higher in men and increases with age (4). The main purpose of ED managament is prompt pain relief. Both non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are usually used in this regard (1). In a meta-analysis, NSAIDs were found to be as effective as analgesic agents in treatment of acute renal colic (5). NSAIDs are cheap and easily available but may cause complications such as renal failure and gastrointestinal bleeding (6). Opioids are highly potent drugs as well, but havethe risk of dependency and respiratory depression and cause more adverse side effects compared to NSAIDs (7). In addition, the painwon't be relieved inup to 42% of renal colic patients treated with morphineand 33% of those treated with ketorolac (8). Alternative choices such as ketofol (a combination of ketamine and propofol) are available for this population (9). Ketamine

*Corresponding Author: Neda Mohammadi; Department of Emergency Medicine, Imam Khomeini Hospital, Ershad Avenue, Urmia, Iran; Tel: +989122347140, fax: +984433457286; Email: neda.mohammadi@gmail.com.

is a phencyclidine derivative drug with analgesic, amnestic and sedative effects without respiratory side effects (10, 11). In addition, ketamine has antidepressive and smooth muscle relaxant effects that can facilitate stone passage (12). Propofol is an alkylphenol derivative drug withsedative effect (13). In ketofol, ketamine and propofol have a synergistic effect with fewer side effects compared to both ketamine and propofol alone (9). Based on the above-mentioned points, the present study was aimed to compare the analgesic effects of ketofol withmorphine sulphate in management of ketorolac resistant renal colics.

2. Methods

2.1. Study setting and design

This study is a randomized, controlled, single blind, parallel, clinical trial, which was performed in the ED of Imam Khomeini Hospital, Urmia, Iran between 23 July 2014 and 18 March 2015. The Ethics Committee of Urmia University Of Medical Sciences approved the study on 20 May 2014 (approval number is umsu. rec. 1393.66). Written informed consent was obtained from all participants. The study was registered at Iranian registry of clinical trial (IRCT number: IRCT2014052417812N1).

2.2. Participants

This study was conducted on patients whowere presented to ED with chief complaint of flank pain and highly suspectedrenal colic. All patients, whose pain severity was greater than 7 and did not respond to 30 mg intravenous (IV) ketorolac, were includedusing convenience sampling. The exclusion criteria were possible allergy to NSAIDs, opioids, propofol, egg, and ketamine; addiction to opioid; renal failure; gastrointestinal bleeding and recent use of analgesics. Renal colic was defined as acute severe flank pain that radiated to ipsilateral groin. The intensity of pain was measured on a 100 millimeter (10 numerical) visual analogue scale (VAS). 10 was considered the worst possible pain and 0 was considered painless.

2.3. Intervention

Patients were randomly divided into two groups using permutated blocks of 4. Each block contained a pre-specified number of treatment assignments in a random order. Allocation was planned before starting the study by one of the authors. Participants and data analysts were blinded to treatment allocation. We could not blind the researcher as a result of rapid sedative effects of ketofol. All renal colic patients received 30 mg IV ketorolac, and pain intensity was measured before and 10 minutes after injection. If patients pain score had not decreased by at least 3 scores after 10minutes, the second step was begun and the patient was enrolled in the study. In group 1, (control group) patients were given 0.1 mg/kg IV morphine sulfate and in group 2 (intervention group) patients were given IV ketofol (combination of 0.75 mg/kg propofol and 0.75 mg/kg ketamine) (14). The ketorolac, morphine, ketamine, and propofol (PROVIVE) used, were made by Alborz darou company of Iran, Darou pakhsh company of Iran, Hameln company of Germany and Claris company of India, respectively.

2.4. Outcome

Based on previous studies, 13mm reduction on VAS is clinically significant; but in patients with severe pain, a greater change on VAS is considered pain reduction (15-17). Thus,a treatment leading to at least 3 scores reduction in pain intensity was considered effective. If pain score had not dropped by at least 30 mm after 10 minutes, pain management was considered unsuccessful. The patients were under continuousmonitoring of blood pressure, O2 saturation, and respiratory and heart rates. Respiratory depression, hallucination, agitation, nausea, vomiting, and emergence phenomenon were considered as secondary outcomes (complication).

2.5. Statistical analaysis

Considering 80% power, 95% confidence interval (CI), 1.7 variance of pain severity, and 0.8 minimum significant difference, sample size of 45 patients in each group was calculated to be enough. Data were analyzed using SPSS 19. Quantitative variables difference were assessed by Mann Whitney U test, and qualitative and numerical variables difference were assessed by Chi-square and Fishers exact tests. Number needed to treat (NNT), relative risk reduction (RRR), and absulute risk reduction (ARR), as well asnumber needed to harm (NNH) and absulute risk increase (ARI)were used as measures of treatment efficacy. $P< 0.05$ was considered statistically significant.

3. Results

90 patients with mean age of 38.01 ± 9.78 years (22-78) were randomly divided into 2 groups of 45(66.7% male). Table 1 summarizes demographic data of the participants. Initial pain score was 9.0 ± 1.2 in morphine and 9.2 ± 1.1 in ketofol groups ($P = 0.469$). Table 2 compares the characteristics of pain management and complications betweenthe 2 groups.Treatment failure rate was significantly lower in ketofol group after 5 (20% vs 62.2%, $p <0.001$) and 10 minutes (11.1% vs 44.4%, $p < 0.001$). ARR and NNT for ketofol after 5 miutes were 42.22% (95% CI: 23.86 - 60.59) and 3 (95% CI: 1.7 - 4.2), respectively. After 10 minutes, these measures reached 33.33 (95% CI:16.16 - 50.51) and 4 (95% CI: 2.0 - 6.2), respectively. NNH and ARI for hallucination or agitation were 12 (95% CI: 5.8 - 174.2) and 8.89% (0.57 - 17.20), respectively.

Table 1: Demoghraphic characteristics of the studied patients

Variables	Morphine sulfate	Ketofol	P-Value
Sex; n (%)			
Male	31 (68.9)	29 (64.4)	0.823
Female	14 (31.1)	16 (35.6)	
Age mean ± SD (year)	39.29 ± 12.40	36.73 ± 6.05	0.217
Weight mean ± SD (Kg)	70.73 ± 13.28	75.82 ± 10.83	0.049
Stone size mean ± SD (mm)	6.38 ± 1.85	6.04 ± 1.76	0.383

SD: standard deviation.

Table 2: Comparision of treatment effects and cmplications between morphine and ketofol groups

Variables	Morphine sulfate	Ketofol	P-Value
Pain Intensity mean± SD			
On admission	9.00 ± 1.22	9.18 ± 1.09	0.469
5 minutes after administration	6.76 ± 3.13	3.24 ± 2.83	< 0.001
10 minutes after administration	4.96 ± 3.83	2.40 ± 2.77	<0.001
Failure rate; n (%)			
5 minutes after administration	28 (62.2)	9 (20)	< 0.001
10 minutes after administration	20 (44.4)	5 (11.1)	< 0.001
Complication; n (%)			
Hallucination, agitation	0 (0)	4 (8.9)	< 0.058
Nausea, vomiting	2 (4.4)	0 (0)	< 0.041
Stone size mean ± SD (mm)	6.38 ± 1.85	6.04 ± 1.76	0.383

SD: standard deviation.

4. Discussion

The results of the present study, showed the significant superiority of ketofol (NNT at 5 minute = 3 and NNT at 10 minute = 4) in rapid pain management of patients presented to ED complaining from renal colic and resistant to ketorolac. NNT of 3 means that about one in every 3 patients treated with ketofol will benefit from the treatment after 5 minutes. However, its NNH was 12, which means that about one in every 12 patientstreated with ketofol will be affected with hallucination andagitation. This relatively high NNH could limit routine application of ketofol in this regard. We didn't find any studiesthatverified using ketofol for treating acute pain of urolithiasisup to the time of writing this article. Thus, this study is the first to verify the effect of ketofol, and compare IV ketofol with IV morphine for treating acute renal colic. Regarding the opioid agents for treating acute renal colic, the result of our study is similar to those previously published (1, 18-23). Holdgate and Pollock, performed a systematic review on efficacy of NSAIDs and opioids. They reported that patients who received opioids, neededa rescue dose of analgesicsmore frequently (1). Safdar et al. investigated the effect of ketorolac and morphine for treating renal colic. They reportedthat 30% of the patients who received a combination of ketorolac and morphine needed a rescue dose (8). Masoumi et al. compared IV acetaminophen with morphine for treating renal colic and concluded that acetaminophen is more effective than morphine (24). In contrast, azizkhani et al. reported that morphine is more effective than acetaminophen for this purpose (25). However, both groups reported that morphine had more side effects (24, 25). In addition, Soleimanpour et al. compared IV lidocaine and morphie, and showed that lidocaine is siginificantly more effective in relieving pain in renal colic patients (26). Yet, Bektas et al. revealed that paracetamol and morphine are equally effective for this purpose (27). Researchers have been trying to verify an alternative drug for treating acute renal colic in emergency settings (28). Ketofol has been used in anesthesiology and has recently begun to spread into ED (29). Nejati et al. compared ketamine/propofol and midazolam/fentanyl in the ED and found that ketamine/propofol is safe and effective for sedation and analgesia (14). Willman et al. evaluated the effectiveness of ketofol for orthopedic procedural sedation in ED. They concluded that ketofol is an effective drug with minimal and transient side effects (9). The present study illustrated that efficacy of ketofol in renal colic pain relief is more than morphine. However, further study is needed before we suggestroutine use of ketofol, in this regard.

4.1. Limitations

Due to sedative effect of ketofol, we could only blind the patients and not the researchers, thus this study issingle blind.

Conveniences amplingand short duration of follow-up are also among the most important limitations of the present trial.

5. Conclusion

The results of the present study, showed the significant superiority of ketofol (NNT at 5 minute = 3 and NNT at 10 minute = 4) in ketorolac resistant renal colic pain management. However, it's NNH of 12, could limit its routine application in ED for this purpose.

6. Appendix

6.1. Acknowlegdment

All authors would like to thank all the staff of Imam Khomeini Hospital of Urmia and the research center of Urmia University of Medical Sciences.

6.2. Author contribution

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors.

6.3. Conflict of interests

None

6.4. Funding

None

References

1. Holdgate A, Pollock T. Systematic review of the relative efficacy of non-steroidal anti-inflammatory drugs and opioids in the treatment of acute renal colic. BMJ. 2004; 328 (7453): 1401.
2. Green BR. Renal Calculi: Emergency Department Diagnosis And Treatment. Emerg Med Pract. 2011; 13 (7):1-17.
3. Hiatt RA, Dales LG, Friedman GD, Hunkeler EM. Frequency of urolithiasis in a prepaid medical care program. Am J Epidemiol. 1982; 115 (2): 255-65.
4. Soucie JM, Thun MJ, Coates RJ, McClellan W, Austin H. Demographic and geographic variability of kidney stones in the United States. Kidney Int. 1994; 46 (3):893-9.
5. Labrecque M, Dostaler L, Rousselle R, Nguyen T, Poirier S. Efficacy of nonsteroidal anti-inflammatory drugs in the treatment of acute renal colic: A meta-analysis. Arch Intern Med. 1994; 154 (12): 1381-7.
6. Tramr'r DM, Williams J, Carroll D, Wiffen P, Moore R, McQuay H. Comparing analgesic efficacy of non- steroidal anti- inflammatory drugs given by different routes in acute and chronic pain: a qualitative systematic review. Acta Anaesthesiol Scand. 1998; 42 (1): 71-9.
7. Ricardo Buenaventura M, Rajive Adlaka M, Nalini Sehgal M. Opioid complications and side effects. Pain physician. 2008; 11: S105- S20.
8. Safdar B, Degutis LC, Landry K, Vedere SR, Moscovitz HC, D'onofrio G. Intravenous morphine plus ketorolac is superior to either drug alone for treatment of acute renal colic. Ann Emerg Med. 2006; 48 (2): 173-81.
9. Willman EV, Andolfatto G. A prospective evaluation of "ketofol" (ketamine/ propofol combination) for procedural sedation and analgesia in the emergency department. Ann Emerg Med. 2007; 49 (1): 23-30.
10. White PF, Way WL, Trevor AJ. Ketamine- its pharmacology and therapeutic uses. Anesthesiology. 1982 (56): 119-36.
11. Green SM, Rothrock SG, Lynch EL, et al. Intramuscular ketamine for pediatric sedation in the emergency department: safety profile in 1,022 cases. Ann Emerg Med. 1998;31 (6): 688-97.
12. Katalinic N, Lai R, Somogyi A, Mitchell PB, Glue P, Loo CK. Ketamine as a new treatment for depression: A review of its efficacy and adverse effects. Aust N Z J Psychiatry. 2013; 47 (8): 710-27.
13. Shafer A, Doze V, Shafer S, White P. Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. Anesthesiology. 1988; 69 (3): 348-56.
14. Nejati A, Moharari RS, Ashraf H, Labaf A, Golshani K. Ketamine/Propofol Versus Midazolam/ Fentanyl for Procedural Sedation and Analgesia in the Emergency Department: A Randomized, Prospective, Double-Blind Trial. Acad Emerg Med. 2011; 18 (8): 800-6.
15. Bird SB, Dickson EW. Clinically significant changes in pain along the visual analog scale. Ann Emerg Med. 2001; 38 (6): 639-43.
16. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med. 2001; 38 (6): 633-8.
17. Todd KH. Clinical versus statistical significance in the assessment of pain relief. Ann Emerg Med. 1996; 27 (4): 439-41.
18. Cordell WH, Wright SW, Wolfson AB, et al. Comparison of intravenous ketorolac, meperidine, and both (balanced analgesia) for renal colic. Ann Emerg Med. 1996; 28 (2): 151-8.
19. Larkin GL, Peacock WF, Pearl SM, Blair GA, D'Amico F. Efficacy of ketorolac tromethamine versus meperidine in the ED treatment of acute renal colic. Am J Emerg Med. 1999; 17 (1): 6-10.
20. Oosterlinck W, Philp N, Charig C, Gillies G, Hetherington J, Lloyd J. A Double-Blind Single Dose Comparison of

Intramuscular Ketorolac Tromethamine and Pethidine in the Treatment of Renal Colic. J Clin Pharmacol. 1990; 30 (4): 336-41.
21. Persson NH, Bergqvist D, Melander A, Zederfelt B. Comparison of a narcotic (oxicone) and a non-narcotic anti-inflammatory analgesic (indoprofen) in the treatment of renal colic. Acta Chir Scand. 1985; 151 (2): 105-8.
22. Sandhu D, Iacovou J, Fletcher M, Kaisary A, Philip N, Arkell D. A comparison of intramuscular ketorolac and pethidine in the alleviation of renal colic. Br J Urol. 1994; 74 (6): 690-3.
23. Smith LA, Carroll D, Edwards JE, Moore RA, McQuay HJ. Single-dose ketorolac and pethidine in acute postoperative pain: systematic review with meta-analysis. Br J Anaesth. 2000; 84 (1): 48-58.
24. Masoumi K, Forouzan A, Asgari Darian A, Feli M, Barzegari H, Khavanin A. Comparison of clinical efficacy of intravenous acetaminophen with intravenous morphine in acute renal colic: a randomized, double-blind, controlled trial. Emerg Med Int. 2014; 2014: 571326.
25. Azizkhani R, Pourafzali SM, Baloochestani E, Masoumi B. Comparing the analgesic effect of intravenous acetaminophen and morphine on patients with renal colic pain referring to the emergency department: A randomized controlled trial. J Res Med Sci. 2013; 18 (9): 772-6.
26. Soleimanpour H, Hassanzadeh K, Vaezi H, EJ Golzari S, Esfanjani RM, Soleimanpour M. Effectiveness of intravenous lidocaine versus intravenous morphine for patients with renal colic in the emergency department. BMC Urol. 2012; 12(1): 1-5.
27. 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.
28. Esmailian M, Keshavarz M. Synergistic Effects of Citalopram and Morphine in the Renal Colic Pain Relief; a Randomized Clinical Trial. Emergency. 2014; 2 (1): 26-9.
29. Arora S. Combining ketamine and propofol (ketofol) for emergency department procedural sedation and analgesia: a review. West J Emerg Med. 2008; 9 (1): 20-3.