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

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Abstract: Introduction: The main purpose of emergency department (ED) management for renal colic is prompt pain relief. The present study aimed to compare the analgesic effects of intravenous (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 minutes 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

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 management 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 have the risk of dependency and respiratory depression and cause more adverse side effects compared to NSAIDs (7). In addition, the pain won't be relieved in up to 42% of renal colic patients treated with morphine and 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...
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 with sedative 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 with morphine 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 who were presented to ED with chief complaint of flank pain and highly suspect renal colic. All patients, whose pain severity was greater than 7 and did not respond to 30 mg intravenous (IV) ketorolac, were included using 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 permuted 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 10 minutes, 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 continuous monitoring 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 analysis

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 absolute risk reduction (ARR), as well as number needed to harm (NNH) and absolute 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 between the 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 minutes 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: Demographic 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: Comparison of treatment effects and complications 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 patients treated with ketofol will be affected with hallucination and agitation. This relatively high NNH could limit routine application of ketofol in this regard. We didn’t find any study that verified using ketofol for treating acute pain of urolithiasis 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, needed a rescue dose of analgesics more frequently (1). Safdar et al. investigated the effect of ketorolac and morphine for treating renal colic. They reported that 30% of the patients who received a combination of ketorolac and morphine needed a rescue dose (8). Massoumi 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 morphine, and showed that lidocaine is significantly 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 anesthesia 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 suggest routine 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 is single blind.
Conveniences ampling and 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. Acknowledgment

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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

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