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# Comparison of Rectal Suppository and Intramuscular Morphine for Management of Patients with Renal Colic Referred to the Emergency Department: A Randomized Double-blinded Controlled Trial

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**Abstract**

**Objectives:** To compare the analgesic effects of rectal suppository morphine (RSM) with intramuscular morphine (IMM) in patients suffered from renal colic referred to emergency ward (EW).

**Methods:** In a controlled, randomized, clinical trial, 74/90 patients with renal colic referred to the EW between March 2016 and March 2017 were randomly enrolled into two groups of RSM (10 mg) and IMM (10 mg/mL). Vital signs and severity of pain were recorded at admission time (0), 15, 30 and 60 min after treatment.

**Results:** The results showed that there was a significant decrease in VAS score of RSM group compared to IMM group after 30 and 60 min of administration ($P < 0.05$). Furthermore, no significant difference was recorded in vital signs, except there was a significant decrease in heart rate (15 and 60 min) and respiratory rate (60 min) of RSM group compared to IMM group ($P < 0.05$) and no side effects were recorded during the investigation.

**Conclusion:** In conclusion, the use of rectal route of morphine had higher efficiency compared to the IM route of morphine in relieving pain of patients with renal colic. Although, decreased heart and respiratory rates were recorded, the values were in normal range. As well, no major complications were recorded for each method.

**Keywords:** Renal Colic, morphine; pain management, suppositories, injections, intramuscular

## Introduction

Urolithiasis has been shown to be a common disease with incidence of 8–15% in North Americans and Europeans for centuries.[1] Approximately 2.4/1000 people in Iran suffer from renal colic, whereas it differs from 0.5 to 2 in every 1000 ones in other countries.[2] The mean cost of urolithiasis and renal colic was estimated about 2.1 billion dollars in 2000.[3] Recently, it has been reported that changes in individuals' diet and lifestyle leads to increase in incidence of renal colic worldwide.[4]

Renal colic as a frequent disorder usually presents as an acute and severe pain in the flanks due to obstruction of the urinary flow via a stone or the passage of a stone from the urinary tract, which can radiate to the abdomen and genitalia.[5,6] This type of pain is often defined as the worst pain which patient has ever experienced.[7,8] The mechanism of pain is associated with the enhanced pressure in the urinary tract along with construction of urethral smooth muscles and enhanced pressure in the regional blood flow.[9]

A wide range of analgesics are used to manage the pain. In emergency ward (EW), opioids and non-steroidal anti-inflammatory drugs (NSAIDs) are most frequent to relieve the pain.[10] According to the literature, stable doses of opioids can provide analgesic impacts for weeks or years and efficiency, low cost, and titration possibility make them popular for managing pain.[3,11] The high doses of opiates administered systemically has been shown to be related to different side effects e.g., respiratory depression, vomiting, nausea, sedation, and pruritus.[12] On the other hand, the human rectum is a body cavity in which drugs can be retained and absorbed easily and is effective rather than orally, especially in cases with nausea and vomiting.[13]

As a most common type of opioids, morphine is an analgesic with a direct impact on the central nervous system (CNS) and the most powerful analgesic drugs in managing and curing severe, acute and chronic pains.[14] Different routes of morphine have been used to control pain in patients following operation or in emergency department.[15-17] Morphine suppositories administered via rectal route are one of the newly released morphine forms. Different doses of 5, 10, 20, and 30 mg of morphine can be contained in each rectal suppository. It has been shown that about two-thirds of rectal morphine can be absorbed via the gastrointestinal tract and then, it paases through portal vein to be metabolized in the liver. The maximum effects of rectal route has been recorded 20–60 min following administration.[12]

The administration of suppository morphine is often forgotten by clinicians seeking to use the oral routs[18] and to the best of our knowledge, there was no previous study to compare the analgesic effect of rectal suppository morphine (RSM) with intramuscular morphine (IMM) to relieve pain in patients with renal colic.

## Materials and Methods

### *Study Population*

This study was a randomized, controlled, clinical trial was performed between March 2016 and March 2017. Ninety patients with renal colic (18 to 55 years) referred to EW of Kosar Hospital (Semnan University of Medical Sciences, Semnan, Iran) were randomly selected, but 74 patients were eligible to be enrolled. This trial was approved by Ethics Committee of

Semnan University of Medical Sciences (5/1/2016). Written informed consent form was signed by all subjects to accept that they had adequate information about the investigation. The study was registered at Iranian registry of clinical trial (IRCT number: IRCT2015111825098N1).

### Inclusion and Exclusion Criteria

In this study, 90 patients referred to EW with main complaint of flank pain, and the patients who clinically diagnosed for renal colic were selected. The inclusion criteria were defined as all cases with acute severe flank pain that radiated to ipsilateral groin or abdomen. Then, the urinary stone was confirmed through ultrasonography, computed tomography (CT) scan, or intravenous (IV) pyelography, or the patients with stone passage and the patients were selected for investigation.

The exclusion criteria was described as follows: patients with history of allergy to opioids, addiction, fever ≥38°C, unstable hemodynamic status, liver failure, cardiac or respiratory failure, evidence of peritoneal inflammation, renal failure or kidney transplantation, aortic aneurysm or dissection, pregnancy, receiving any analgesia within 6 h before the study and age <18 and >55 years.

An emergency medicine specialist performed all evaluations. Sixteen cases were excluded from the study due to the above exclusion criteria.

### Randomization and Intervention

In this study, a convenience sampling was used to select 90 patients (74 were eligible). Then, patients were randomly allocated into two groups (37 in each group) using permuted balanced block randomization in a completely random manner. For this purpose, six blocks of four were used in which the structure of each block was four-way, the combination of two methods of interference in a perfectly balanced way. To random assignment of blocks to each group a random digits table was carried out. Therefore, a list of eligible participants ($n$ = 74) was prepared and according to this list each case was randomly enrolled in the study group, respectively. No additional matching was performed and one of the investigators scheduled for randomization before the initiation of study. None of participants and data analysts knew about the groups. The treatment groups were defined as below:

**SS-MP group ($n$ = 37):** Patients received 10 mg morphine suppository (Opirec® 10 mg, Aburaihan pharmaceutical Co.).

**IM-MP group ($n$ = 37):** Patients received 10 mg morphine intramuscularly (IM) (Morphine Sulfate 10 mg/mL, Daou Pakhsh pharmaceutical Co.).

### Procedures and Evaluations

Data were collected using a designed checklist containing the factors as below to make the assessments:

**A:** Patient's demographic information including age, gender and weight.

**B:** History of similar pain, history of urinary stones and Main data including vital signs (blood pressure [BP], respiratory and heart rate [HR] and axillary temperature) and severity of pain using a 10-centimeter visual analogue scale (VAS).

VAS was used for evaluation of the pain severity was in several time points of admission time (0), 15, 30 and 60 min after administration of medications. VAS is a measurement instrument that tries to measure a pain severity scored 0 (no pain) -10 clinical observation.[19] Clinically, the difference of VAS score between 0 and 15 min (0–15), 0 and 30 min (0–30), 0 and 60 min (0–60) time points were calculated and compared in two groups of morphine routes. Moreover, other varibales including HR, BP (systolic and diastolic), respiratory rate, and the side effects of drugs (secondary outcomes including drowsiness, nausea & vomiting, facial flushing, and dizziness) were investigated in defined time points. After gathering the data, the VAS scores of different time points were compared. After 60 min, if the severity of pain did not relief by 50%, 5 mg/IM morphine was used to relive the pain. In this study, four patients were excluded due to missing or inconsistent data ($n$ = 3 in RSM group and $n$ = 1 in IMM group) during the study and data of 70 cases were analyzed. Due to incomplete information and data in the questionnaire, patients were excluded from the study (Figure 1).

### Sample Size Estimation and Statistical Analysis

Using the findings of the study performed by Safdar et al. (2006) reporting an average reduction of one hour of pain equal to 5.0 ± 1.6 in patients with intramuscular morphine injection compared with the average further reduction of 6.0 ± 1.6 in patients with morphine suppository in term of VAS, setting the statistical power and confidence levels to be 95%, a sample size of 136 people (68 in each group) was estimated to be enough using G*Power.3.1 software. But conservatively up to 7 people were added in each group to deal with possible data loss.[20] Data were analyzed using SPSS (ver. 22). Mean, standard deviation, frequency and percentage were used to summarize the data in tables. The analysis of variance (ANOVA) for repeated measures models applied to compare the two groups. Fisher's exact tests and Chi-square were used to determine the differences in the qualitative data. In addition, $T$- test was used for evaluation of differences in the quantitative data. Significant level was defined as $P < 0.05$.

## Results

In this study, the data of 70/74 cases ($n$ = 3 in RSM group and $n$ = 1 in IMM group were excluded) with renal colic treated

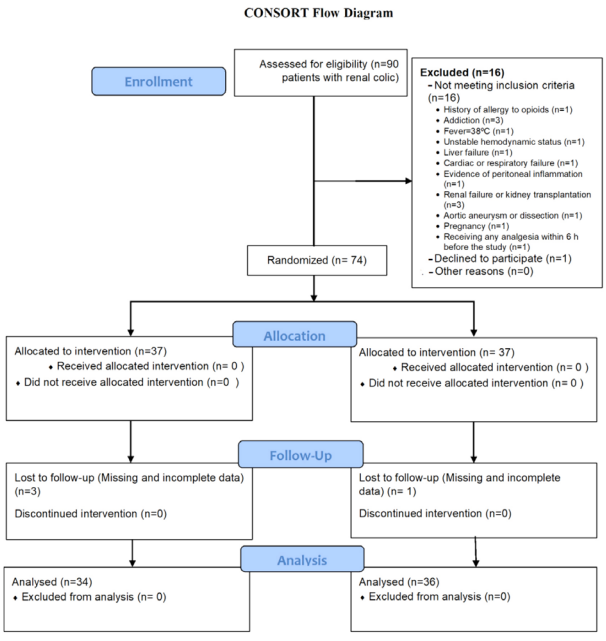


Fig. 1 **CONSORT flow diagram.**

with morphine administered via IM or rectal routes were considered. The demographic features of cases with renal colic in two groups were compared (Table 1). The mean age of patients in RSM group was 37.75 ± 10.92 year (18 to 55) and IMM group was 38.89 ± 10.46 year (18 to 55). No significant difference was reported in the mean age of two groups (Table 1, $P$ = 0.329). As well, 24 patients (70.6%) in RSM group and 29 patients (80.6%) in IMM group were male and no significant differences were seen in the distribution of sex in two groups (Table 1, $P$ = 0.331). The mean weight of patients in RSM group was 79.88 ± 14.17 Kg and in IMM group was 84.3 ± 23.41 Kg and no differences was recorded in the weight of patients in two groups (Table 1, $P$ = 0.446). The history of urinary stones and similar pains were compared between two groups as was shown in Table 1. No significant differences were reported in the distribution of history of urinary stones (Table 1, $P$ = 0.568) and similar pains (Table 1, $P$ = .756) of patients in two treatment groups. Furthermore, frequency of extra doses of opioids was not significant in two groups (Table 1, $P$ = 0.073). Using chi-square test, no significant differences were observed in the distribution of side effects in both groups (Table 1, $P$ = .599). All these results proved that two groups were similar in these characteristics before the treatment period.

The mean VAS score, systolic BP (mmHg), diastolic BP (mmHg), HR (bpm), and respiratory rate (per min) were compared in two groups (Table 2, Figure 2). A significant difference was observed in terms of pain intensity between two groups ($P$ = .017). Also, there were significant differences in VAS score of two treatment groups according to time points of 30 ($P$ = .037) and 60 ($P$ = 0.027) after treatment; but no differences were recorded in time point of 0 ($P$ = 0.58) and 15 ($P$ = 0.083). There was a significant difference in the mean VAS score difference of 0–30 ($P$ = 0.001) and 0–60 ($P$ = 0.001) time points; but no significant difference was recorded for mean VAS score difference of 0–15 min ($P$ = 0.083). Based on the results, no significant difference was also observed between groups for systolic ($P$ = 0.201) and diastolic pressure ($P$ = 0.350). As well, no significant difference was seen in the mean systolic pressure ($P$ = 0.762, $P$ = 0.068, $P$ = 0.072 and $P$ = 0.232, respectively), diastolic pressure ($P$ = 0.345, $P$ = 0.506, $P$ = 0.222, and $P$ = 0.105, respectively) on different time points of 0, 15, 30, and 60. In addition, significant difference was observed in terms of changes in the HR (per min) between the two groups ($P$ = 0.030). In addition, there were no significant differences in HR of two groups based on time points of 0 ($P$ = 0.116) and 30 ($P$ = 0.139), but significant decreases were seen in time point of 15 ($P$ = 0.04) and 60 min ($P$ = 0.014) in RSM group compared to IMM group. Comparing two groups showed that there was no significant difference in terms of changes in the respiratory rate (per min) between the two groups ($P$ = 0.622). Based on time points, respiratory rate was significantly decreased in 60 min ($P$ = 0.017) in RSM group compared to the IMM group. However, in the other time points no differences was observed (0: $P$ = 0.799, 15: $P$ = 0.291, 30: $P$ = 0.605, and 60: $P$ = 0.855, respectively) (Table 2 and Figure 1). No major complications were reported in two groups.

## Discussion

In this investigation, we aimed to compare the influence of rectal and IM morphine/pain management in patients with renal colic. In EW, management of patients with colic pain is one of the most important part of caring system.[21] NSAIDs and opioids as well as the combination of spasmolytic and anti-inflammatory drugs have been recorded to be mostly used for pain control of these patients.[10,22,23] Among these, narcotics such as morphine, tramadol, codeine and meperidine have long been used.[20,24,25] Morphine, as an opioid analgesic, has been used for pain control of patients with renal colic given by different routes.[26,27] Morphine administered with IV route is a drug of choice to manage pain in acute renal colic.[28] Nevertheless, the other routes of morphine administration, e.g., oral, IM and rectal are available to relieve pain in different conditions.[29,30]

Studies have proven that IM administration of opioids has been considered to be safer than IV.[31] Although, oral and parenteral narcotics are used usually for pain relief in EW or following surgical procedures, these routs can exacerbate the incidence of sedation, vomiting, and nausea, which ultimately delays recovery.[32-34] Thus, non-parenteral route of analgesic drugs, especially their rectal route has been suggested in different studies.[13,35,36] According to the literature, it has been proved that rectal route morphine results less analgesia and lower pain scores compared to its IV administration.[34,37]

The findings of both groups showed the similarity in the different demographic features including age, gender, weight,

Table 1. **Comparing the characteristics of patients with renal colic based on study groups**

| | Groups | | *P*-value |
|---|---|---|---|
| | SS-MP ($n$ = 34) | IM-MP ($n$ = 36) | |
| | *N* (%) or Mean ± SD* (range) | *N* (%) or Mean ± SD (range) | |
| Age (year) | 37.75 ± 10.92 (18–68) | 38.89 ± 10.46 (18–60) | 0.329 |
| Gender (male) | 24 (70.6) | 29 (80.6) | 0.331 |
| Weight (Kg) | 79.88 ± 14.17 | 84.3 ± 23.41 | 0.446 |
| History of urinary stones | 23 (67.6) | 22 (61.1) | 0.568 |
| History of simmilar pain | 22 (64.7) | 22 (61.1) | 0.756 |
| Axillary temperature (°C) | 36.76 ± 0.53 | 36.76 ± 0.32 | 0.543 |
| Opioids for pain relief | 3 (8.8%) | 9 (25) | 0.73 |

SD: Standard deviation; UPJ: Ureteropelvic junction.

Table 2. **Comparing the vital signs and pain severity (VAS) between two groups based on different time points, including admission time (0), 15, 30 and 60 min after drugs administration**

| | | Groups | | |
|---|---|---|---|---|
| | | SS-MP ($n = 34$) | IM-MP ($n = 36$) | *P*-value |
| | | Mean ± SD* | Mean ± SD | |
| VAS score | 0 | 8.26 ± 1.79 | 9 ± 1.26 | 0.116 |
| | 15 min after treatment | 5.95 ± 1.78 | 6.73 ± 1.97 | 0.139 |
| | 30 min after treatment | 4.32 ± 2.58 | 5.58 ± 2.38 | 0.018 |
| | 60 min after treatment | 2.58 ± 2.95 | 4.19 ± 3.03 | 0.081 |
| Systolic pressure (mmHg) | 0 | 124.38 ± 10.31 | 127.27 ± 16.38 | 0.762 |
| | 15 min after treatment | 116.56 ± 10.44 | 123.64 ± 14.32 | 0.068 |
| | 30 min after treatment | 113.75 ± 11.33 | 120 ± 12.82 | 0.073 |
| | 60 min after treatment | 115.31 ± 9.91 | 119.55 ± 12.14 | 0.232 |
| Diastolic pressure (mmHg) | 0 | 79.38 ± 7.0 | 79.32 ± 11.37 | 0.848 |
| | 15 min after treatment | 76.88 ± 6.02 | 77.14 ± 11.37 | 0.988 |
| | 30 min after treatment | 72.5 ± 8.37 | 77.5 ± 11.73 | 0.889 |
| | 60 min after treatment | 72.5 ± 7.53 | 77.73 ± 10.99 | 0.888 |
| Heart rate (bpm) | 0 | 78.4 ± 7.59 | 82.55 ± 8.23 | 0.115 |
| | 15 min after treatment | 76.4 ± 6.67 | 81.59 ± 7.08 | 0.04 |
| | 30 min after treatment | 76.6 ± 6.6 | 81.86 ± 7.32 | 0.073 |
| | 60 min after treatment | 75.23 ± 6.42 | 81.55 ± 8.15 | 0.017 |
| Respiratory rate (per min) | 0 | 18.21 ± 2.11 | 18.48 ± 2.6 | 0.779 |
| | 15 min after treatment | 17.14 ± 0.81 | 17.76 ± 2.23 | 0.291 |
| | 30 min after treatment | 16.79 ± 1.76 | 17.19 ± 1.91 | 0.073 |
| | 60 min after treatment | 16.93 ± 1.77 | 17.05 ± 2.01 | 0.017 |

*SD: Standard deviation.

and also history of urinary stones and similar pain. Based on the findings of present study, rectal route of morphine could decrease the VAS score significantly compared to the IMM group. Additionally, the score differences of 0–30 and 0–60 showed significant improvement in RVS group. Taken together, administration of rectal route of morphine could be successful in the management of pain in patients with renal colic. Although the mean heart and respiratory rate decreased in rectal route group compared to IM group, these criteria were within normal range in this group, which were not a cause for concern. As well, no serious complications have been reported in these two groups.

Based on the literature, efficiency of different routes of morphine have been compared in a wide range of painful conditions. To show the efficiency and safety of morphine administered via rectal route in relieving pain, Rahimi et al. (2016) used preemptive suppository morphine after laparoscopic cholecystectomy in a placebo-controlled study. The results from VAS score proved that administration of morphine suppository was effective in analgesic requirements following laparoscopic cholecystectomy.[12] In a randomized controlled trial, Butler et al. (2017) evaluated the effects of belladonna and opium suppositories for reduction of pain in vaginal surgery and showed that these drugs are safe to use following this surgery.[37] As well, Cole et al. (1990) demonstrated that morphine hydrogel suppository appears to be effective in management of postoperative pain.[38]

Studies to compare the different routes of morphine especially the rectal and intramuscular routes of morphine are so limited. Guldbrand and Mellstrom (1995) compared the rectal rout of morphine-scopolamine with IM route as a premedication in healthy children scheduled for minor ENT surgery. Their findings indicated that administration of rectal route of drug worked better and resulted in slightly less post-operative pain and nausea. They suggested to use rectal route of morphine-scopolamine as a premedication for minor ENT surgery on children as a good alternative compared to the IM route.[39] Additionally, in a study by Wilkinson et al. (1992), the effectiveness of rectal vs. oral sustained-release morphine were compared in the patients with cancer. They found no significant difference between the oral and the rectal route in measurements based on VAS score or side effects. As well, they recommended to use the rectal route of morphine, when the oral route is not accessible for long time.[40] The bioavailability of IM morphine is roughly complete (100%), whereas the bioavailability of rectal morphine is only 50–60%.[41,42] Therefore, the poorer rectal bioavailability leads to lower plasma concentrations of morphine compared with the IM application. However, the evidence showed that the rectal and IM morphine reached the peak plasma concentration after 30 min and 1 hour, respectively, indicating that the absorption was rapid in the rectal route.[43]

According to the results, no major complications were recorded for two forms of administrations. The safety and

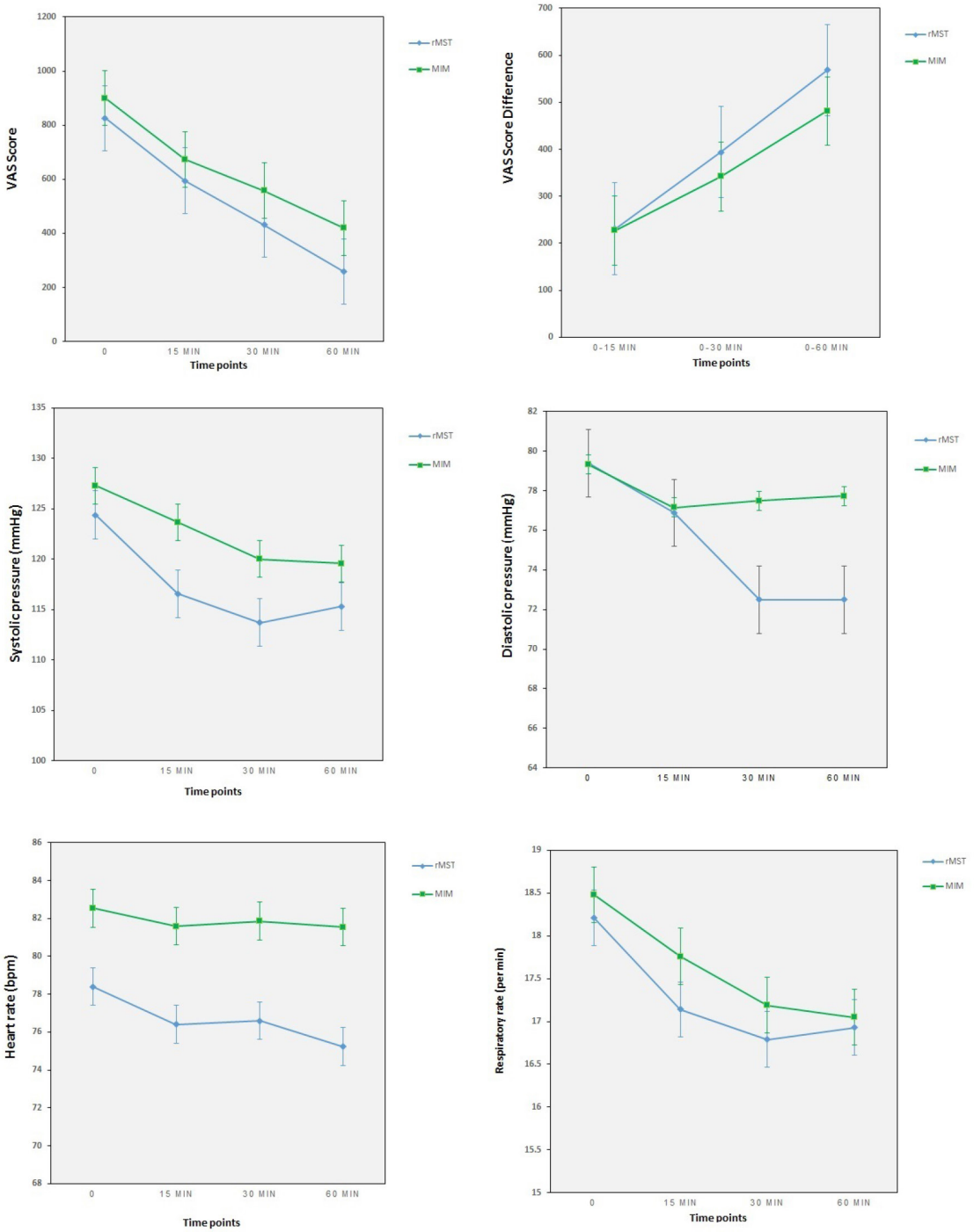


Fig. 2 **Comparing the vital signs and pain severity between two groups based on different time points including admission time (0), 15 min, 30 min, and 60 min after drug administration.**

effectiveness of morphine suppository in relieving pain have been proven in different studies. Westerling et al. evaluated the bioavailability and absorption of rectally administered morphine in 21 healthy women undergoing gynaecological operations and demonstrated that the mean bioavailability was 31% (range 12%–61%) and none of the cases showed any clinical sign of respiratory depression.[43] Furthermore, Babul et al. (2013) compared the safety and effectiveness of controlled-release morphine tablets and suppositories in pain management of patients with cancer and reported that controlled-release morphine suppositories provides pain control comparable to that provided by tablets when received every 12 h at a 1/1 dose ratio, and suggested a reliable alternative approach of pain management for patients unable to take oral opioid medications.[44] In an experimental study by Barnhart et al. (2000), the systemic bioavailability and therapeutic plasma levels of morphine following IV and IM administration as well as respiratory, cardiovascular, and analgesic values were compared in dogs. No differences were recorded in analgesia values and vital organs e.g., respiratory and cardiovascular between control and morphine groups.[45]


Fig. 3 **The schematic summary of the study.**

## Conclusion

Our findings indicated that the use of rectal morphine suppositories may be more effective in diminishing pain in cases referred to EW with renal colic compared with IM route in EW. Since the morphine suppositories are due to no adverse impact on the vital signs of patients and also have no other major complication, we recommend to use rectal route of morphine as a safe and more effective method in relieving pain of renal colic patients in EW (Figure 3).

## Limitation

One of our study limitations was that the possibility of evaluating other variables attributed to alterations of pain severity. One of these limitations is the differences in the level of education and awareness of the patients under study that may have been effective in expressing the severity of pain based on VAS. On the other hand, there are several variables that affect the pain severity, which of course has not been possible to consider all of them in one study.

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## Competing Interest

Author declares no conflict of interest.

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