Original Contribution

Does co-treatment with ultra-low-dose naloxone and morphine provide better analgesia in renal colic patients?

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A R T I C L E I N F O

A B S T R A C T

Objective: This study attempted to evaluate the efficacy of ultra-low-dose intravenous (IV) naloxone combined with IV morphine, as compared to IV morphine alone, in terms of reducing pain and morphine-induced side effects in patients with renal colic.

Methods: In this double-blind clinical trial, 150 patients aged 34 to 60 years old who presented to the emergency department (ED) with renal colic were randomly allocated to either an intervention group that received ultra-low-dose IV naloxone combined with IV morphine or to a control group that received morphine plus a placebo. The severity of pain, sedation, and nausea were assessed and recorded for all patients at entrance to the ED (T1), then at 20 (T2), 40 (T3), 60 (T4), 120 (T5), and 180 (T6) minutes after starting treatment. The Numeric Rating Scale (NRS) was used for the assessment of pain and nausea intensities, and the Ramsay Sedation Scale (RSS) was used to assess sedation.

Results: A GEE model revealed that patients in the naloxone group had non-significantly reduced pain scores compared to those in the morphine group (coefficient = −0.68; 95% CI: −1.24 to −0.11, Wald $X2$ (1) = 5.41, $p = 0.02$). The sedation outcome demonstrated no statistically significant differences at T1 to T4 among patients with renal colic compared to the ones who only received morphine. At T5 and T6, 1.5% vs. 20% and 1.5% vs. 16.9% of subjects from the naloxone group versus the morphine group obtained RSS scores equal to 3, respectively ($p = 0.001$ and $p = 0.004$, respectively).

Conclusions: Compared to patients who only received IV morphine, co-treatment of ultra-low-dose naloxone with morphine could not provide better analgesia and sedation/agitation states in renal colic patients.

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1. Introduction

Renal colic as a painful medical emergency is a common, acute presentation of stones in the kidney and ureter (nephrolithiasis and urolithiasis) that needs immediate intervention to reduce pain [1]. The lifetime prevalence of *nephrolithiasis* is reported to be approximately 8.8% [2] with recurrence rates near 50% [3], while overall incidence of urolithiasis is estimated to be 4% to 20% [4]. Numerous factors have roles in the development of renal colic pain, including urinary obstruction with stone, ureter smooth muscle spasms, stone area tissue edema, peristalsis aggravation, and inflammation [5].

Several analgesic agents are recommended as standard care for pain control in renal colic patients, including intravenous (IV) opioids (e.g. morphine) and non-steroidal anti-inflammatory drugs (NSAIDs, e.g. diclofenac) [6-8]. Opioid medications are the first-line agents for pain relief and are effective in relieving acute pain following renal colic [8]. However, the high incidence of undesirable side effects of opioids

have resulted in their decreased use as analgesic agents [8]. The use of opioids is associated with dose-dependent complications, such as respiratory depression, nausea, vomiting, urinary retention, pruritus, drowsiness, and the possibility of drug dependency [9,10]. Moreover, reducing the use of IV opioids is associated with decreased length of hospital stays and lower hospital costs [11]. Additionally, routine use of NSAIDs has been discouraged due to their negative effects on the gastrointestinal and renal systems [8]. Studies are ongoing to determine an effective and safe strategy and to develop best practices and protocols for excellent pain management in renal colic patients. Pain management in hospitals has become an important issue, especially in emergency services and in patients experiencing severe pain from renal colic [12].

Naloxone is an opioid antagonist at doses of 0.01 to 0.04 mg kg^{-1} [13]. Several non-clinical studies have indicated the analgesic enhancer effect of naloxone at an ultra-low-dose in combination with opioids [11,13-17]. In addition to the effectiveness of ultra-low-dose naloxone as an adjunct medication along with opioids in pain relief, some investigations have found that the combination reduces the adverse effects of opioids [11,15-18]. However, other studies have found no positive effects on pain reduction following the addition of naloxone to opioids [14,19-22]. Almost all clinical trials regarding naloxone as a supplementary agent added to morphine were carried out on patients undergoing surgery [14,17,23-25].

We hypothesized that the combination of naloxone with morphine can be advantageous in patients with renal colic who suffer from the worst possible pain, and who usually receive a relatively high dose of opioids [26,27]. Moreover, this combination therapy could be an appropriate choice for reducing pain intensity and decreasing morphine-induced sedation in these patients. Therefore, we hypothesized that co-treatment of ultra-low-dose IV naloxone with morphine could ameliorate acute renal colic pain intensity and morphine-induced side effects in patients suffering an acute stone episode. The current study was designed to evaluate the efficacy of ultra-low-dose IV naloxone combined with IV morphine, as compared to IV morphine plus placebo, in terms of pain management and morphine-induced side effects in patients with renal colic who presented in the emergency department (ED).

2. Methods

2.1. Patients and study design

This double-blind clinical trial was performed in the ED on 150 patients with renal colic. Patients ranged in age from 34 to 60 years old and all presented with acute and severe pain between May 2017 and February 2018. The inclusion criteria were renal colic and a pain score of 7–10 based on the Numeric Rating Scale (NRS). Patients were excluded if there were morphine contraindications, or if they had a history of drug dependence, had received sedative medications before the study, had peritoneal symptoms in an abdominal examination, or had psychosis, pregnancy, or acute ischemic disease. They were also excluded if their renal colic diagnosis was changed in further assessments or if they withdrew their consent to participate in the study.

Diagnosis of acute renal colic was performed based on urinary symptoms (such as hematuria), clinical signs (flank colic pain, dysuria, urinary frequency), and paraclinical assessments of urinary stones, such as urine analysis; kidney, ureter, bladder (KUB) radiography; sonography; and computed tomography (CT) scans [28]. In the absence of patients' self-reported pain improvement (no pain control), abdominal and pelvic CT scans were performed even given normal sonography and the absence of hematuria. Renal colic was confirmed following observation of stones in the urinary system in KUB radiography or abdominal and pelvic CT scans and/or unilateral hydronephrosis in sonography. The location of pain and any family history of renal stones were questioned.

2.2. Ethical approval

After explaining the purpose and method of study and also obtaining informed consent, patients were randomly assigned to intervention or control groups. The study was performed in accordance with the Helsinki Declaration. The study design and protocol were approved by the Ethics Committee of Mazandaran University of Medical Sciences (IR. MAZUMS.IMAMHOSPITA.REC95.2627). This trial has been registered at http://www.irct.ir under identifier IRCT2017031923696N5.

2.3. Analgesia protocol

In the intervention group, patients received IV morphine (0.1 mg kg^{-1}) plus a single ultra-low dose of IV naloxone (0.001 mg kg^{-1} − alternatively, 1 μg kg^{-1}). In the control group, patients received 0.1 mg kg^{-1} of IV morphine and a placebo (sterile water). Medications were injected over 1 to 2 min. If needed, additional bolus doses of IV morphine (0.05 mg kg^{-1}) were given to patients in both groups after 20 min during study (no pain control: NRS pain >4) [29]. Patients who were unable to tolerate the pain within 30 min after administration of IV drugs were treated with other analgesic drugs. Other common pain-relieving and antispasmodic agents such as diclofenac, fentanyl and diazepam were administered to decrease the severity of a patient's pain, according to the patient's status and if there were no contraindications for usage of these drugs. In the case of sustained vomiting or nausea with NRS > 4, IV metoclopramide 10 mg was prescribed.

2.4. Randomization and bias-controlling

The patients referred to the ED were enrolled randomly by an emergency medicine specialist physician. Block randomization was conducted with a random-plan generator (https://www.sealedenvelope.com) to generate a random list, according to which patients were allocated into either the control group of monotherapy with morphine (morphine group) or the intervention group of combination therapy with morphine and naloxone (naloxone group). The preparation of drugs (~10 ml) were performed by two nurses, not involved in the care of patients. The nurses who injected patients did not know which medication they were using. All of the syringes used in both groups were similar. Outcomes were evaluated by an emergency medical resident who did not know which group the patients belonged to. During the study, the patients, nurses and physicians were unaware of which group patients belonged to. Only the nurses who had prepared drugs and the supervisor of the study were aware of the random list assignments. The study supervisor was not involved during the intervention.

2.5. Outcomes measurement and data handling

The primary outcome was reducing pain intensity. Secondary outcomes were sedation status, nausea intensity, respiratory rate (RR), systolic and diastolic blood pressure (SBP and DBP respectively), the amount of additional morphine prescribed and the rate of IV metoclopramide administration. A numbering system was used to determine the severity of pain, morphine-induced sedation, and nausea in patients.

The assessment of analgesia and nausea intensity were performed with the NRS [30,31], a 0–10 verbal numeric scale. A score of 0 represents no pain/nausea and 10 represents the maximum pain/nausea level. We graded the intensity of pain according to NRS as mild (score, 1–3), moderate (score, 4–6), and severe (score, 7–10) [30]. The evaluation of sedation intensity was performed with the Ramsay Sedation Scale (RSS) [31], which is scored from 1 to 6. At Score 1, a patient is anxious and agitated or restless, or both; at score 2, a patient is cooperative, oriented, and tranquil (normal state). The intensity of sedation increases up to 6 [32].

The severity of baseline pain, sedation, and nausea were assessed and recorded for all patients at the time of their entrance to the ED before prescribing the drugs (T1), then at 20 (T2), 40 (T3), 60 (T4), 120 (T5), and 180 (T6) minutes after starting treatment. SBP and RR at all six timepoints were measured and recorded. Normal saline (100–200 cc) was infused in the cases with SBP lower than 90 mmHg. DBP was recorded at the baseline and at the end of study (T1 and T6). Data assessment and recording were done by the emergency medical resident. Throughout the 180-minute study period, the amount of additional morphine prescribed based on the study analgesia protocol, as well as bolus administration rate of metoclopramide in both groups was recorded. Other drugs administered to patients during the study, such as any antispasmodic, or analgesia medications, were also recorded. Additionally, age, sex, and body weight at baseline were also recorded as demographic data.

2.6. Statistical analysis

Using a meaningful mean group difference of 1 point on the 10-point scale, an expected common (standard deviation [SD]) of 1.75 points [17], 90% power, and 2-tailed level of significance at $p < 0.05$, the predicted minimum required sample size was 65 per group. Categorical variables were reported using percentages. Quantitative data was reported using mean (SD) or median [first quartile, third quartile], respectively. We used the Shapiro–Wilk test to determine whether data were normally distributed. To compare the quantitative data between groups, an independent sample t-test or Mann–Whitney U test were used, and for the qualitative data a Fisher's exact test was used. Intergroup changes were evaluated by the Friedman test for quantitative data with non-normal distribution and were evaluated with a repeated measures ANOVA or a paired t-test for quantitative data with normal distribution (evaluating intergroup changes). Additionally, the estimation of differences in values of pain, sedation, and nausea scores between baseline and the follow up points were tested using generalized estimating equation (GEE) models, which also were adjusted with added covariates (antispasmodic and/or other analgesic drugs). Data were analyzed using intention-to-treat analysis (ITT).

A repeated measures ANOVA with both between-groups and within-subjects factors was applied to analyze the RSS score, RR, and SBP values across time with antispasmodic and/or other analgesic drugs as covariates. The primary and interaction effects of time and group on these values were determined by repeated measure ANOVA. We used Mauchley's Sphericity test to test for compound symmetry assumption. The Greenhouse-Geisser correction was used for violations of sphericity. A p value of 0.05 or less was considered statistically significant. However, the threshold for clinical significance was adjusted from 0.05 to 0.05 divided by six ($0.05 \div 6 = 0.0083$, $p < 0.0083$) based on the results of the multivariable models because of evaluating pain as the primary outcome at six timepoints (T1 to T6). Data were analyzed using IBM SPSS. statistics version 24.

3. Results

3.1. Participants

A total of 180 patients with renal colic who were referred to our hospital were screened during the study period. Of these, 16 patients did not meet the inclusion criteria and 4 patients declined to participate in the study (Fig. 1). From 150 patients who allocated in the two groups, 10 and 13 patients were dropped during sturdy period in intervention and control group, respectively. In total, 127 patients completed the
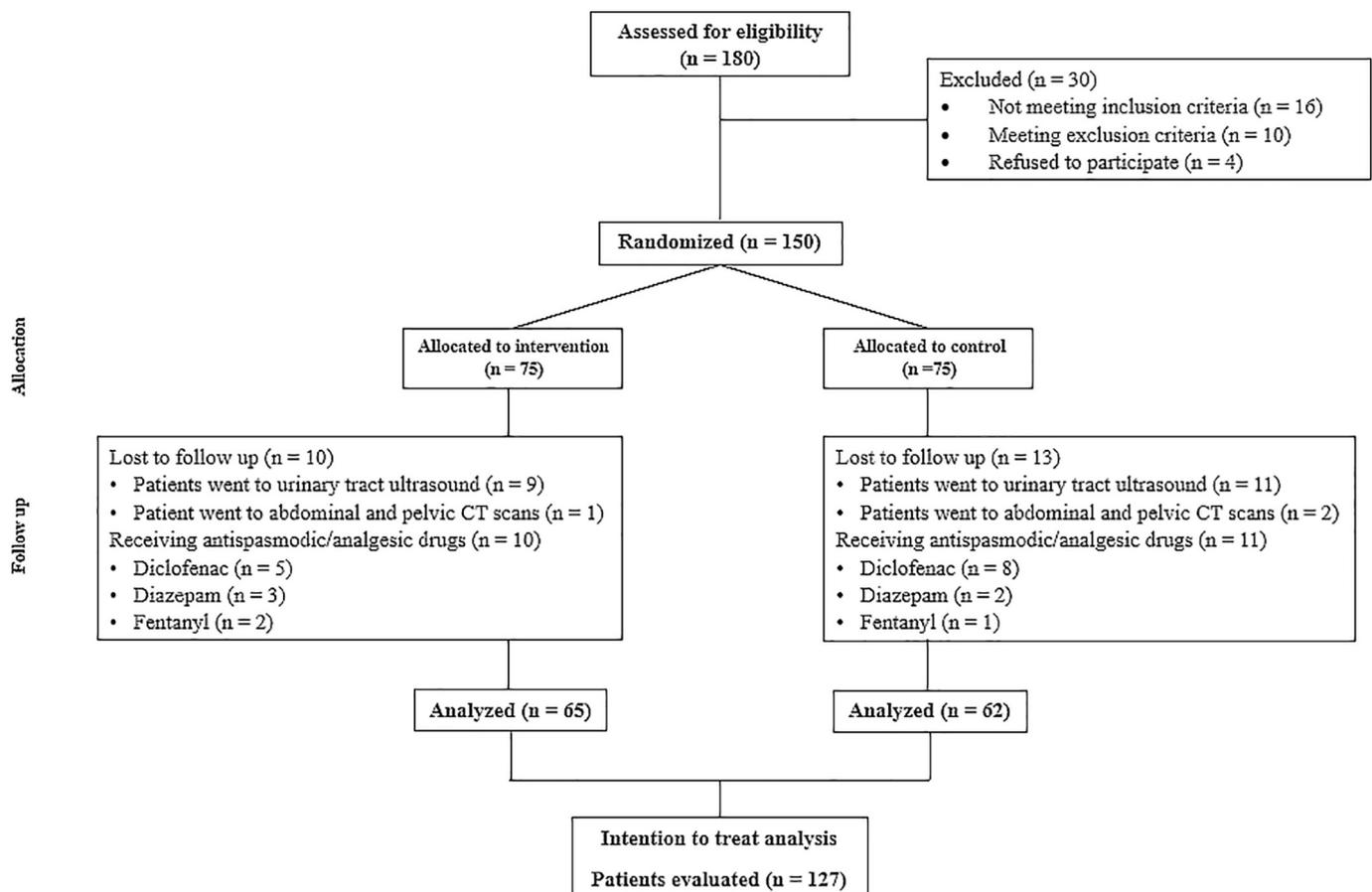

Fig. 1. Consort flowchart.

Table 1
Demographic data of patients in both groups.

	Group		p value
	Naloxone (n = 65)	Morphine (n = 62)	
Sex			
Male	19 (29.2%)	20 (32.2%)	0.57[a]
Female	46 (70.8%)	42 (67.8%)	
Age, year	41.83 (12.01)	41.66 (12.93)	0.93[b]
Weight, kg	72.15 (17.94)	71.32 (14.02)	0.76[b]

Data are presented as mean (standard deviation) or number (percentage).
[a] p-value was obtained with chi-square test.
[b] p-value was obtained with t-test.

Table 2
Pain scores at T1 to T6 in both groups.

	Group		p-value	Mean difference
	Naloxone (n = 65)	Morphine (n = 62)		
T1	9.72 (0.99)	9.55 (1.07)	0.35[a]	0.17 (−0.008)
T2	5.81 (3.42)	4.80 (3.15)	0.08[a]	**1.01 (0.27)**[d]
T3	3.29 (3.01)	3.58 (3.24)	0.59[b]	−0.29 (−0.23)
T4	1.83 (2.19)	2.57 (2.69)	0.08[b]	−0.74 (−0.5)
T5	1.08 (1.31)	2.02 (2.11)	**0.008**[b]	−0.94 (−0.8)
T6	1.05 (1.31)	1.72 (1.96)	**0.02**[b]	−0.67 (−0.65)
p-value[c]	<**0.001**	<**0.001**		

Data are presented as mean (standard deviation).
T1: baseline, T2: 20 min after injection, T3: 40 min after injection, T4: 60 min after injection, T5: 120 min after injection, T6: 180 min after injection.
[a] p-value was obtained with t-test.
[b] p-value was obtained with U-Mann Whitney test.
[c] p-value was obtained with Friedman test.
[d] Mean group difference >1 point was considered as clinically meaningful difference.

present study and data from all of these patients were analyzed. Demographic data of the patients in both groups are presented in Table 1.

3.2. Primary outcome: pain scores

All patients experienced severe pain in both groups. As the findings revealed, 90.8% of patients in the naloxone group and 78.5% of patients in the morphine group had a pain intensity of 10 (maximum pain) at baseline (Fisher's exact test, p = 0.11). Moderate to severe pain intensity had a downward trend in the naloxone and morphine groups from 100% at T1 to the end of the study (63.1% vs. 61.6% at T2, p = 1;

35.4% vs. 36.9% at T3, p = 1; 13.8% vs. 30.8% at T4, p = 0.03; 6.2% vs. 24.6% at T5, p = 0.006; and 7.7% vs. 16.9% at T6, p = 0.18).

A decreasing trend happened for NRS-measured pain in both groups over time, but the downward trend was greater in the naloxone group than in the morphine group, especially after 40 min (T3). Statistically significant differences between the two groups were found at 120 min (T5) and 180 min (T6) (Table 2 and Fig. 2). At T5 and T6, patients with a pain score of 0 (without pain) in the naloxone group versus in the morphine group were 30.8% vs 24.6%, and 32.3% vs 24.6%, respectively (Fisher's exact test, p = 0.55 and p = 0.43, respectively). A GEE model revealed that patients in the naloxone group had non-significantly reduced pain scores compared to those in the morphine group (coefficient = −0.68; 95% CI: −1.24 to −0.11, Wald X^2 (1) = 5.41, p = 0.02).

3.3. Secondary outcomes: sedation

No patients obtained RSS scores of 4–6 at different intervals of the study. At baseline, 93.8% and 95.4% of subjects from the naloxone and morphine groups obtained RSS scores equal to 1 (agitated cases), respectively (Fisher's exact test, p = 1). At T2, the frequency of RSS scores equal to 1 dropped to 50.8% in the naloxone group and 64.6% in the morphine group (p = 0.04). On the other hand, 44% and 56% of subjects from the naloxone and morphine groups obtained RSS scores equal to 2 (normal score), respectively at T2 (Fisher's exact test, p = 0.15).

At T3, 3.1% of subjects from the morphine group obtained RSS scores equal to 3, while there were no sedated patients (RSS score of 3) in the naloxone group (Fisher's exact test, p = 0.24). At T4, 1.5% and 4.5% of subjects from the naloxone and morphine groups obtained RSS scores equal to 3, respectively (Fisher's exact test, p = 0.61). At T5 and T6, 86.2% vs. 72.3% and 84.6% vs. 70.8% of subjects from the naloxone group versus the morphine group obtained RSS scores equal to 2, respectively (Fisher's exact test, p = 0.08 and p = 0.09, respectively). Also, at T5 and T6, 1.5% vs. 20% and 1.5% vs. 16.9% of subjects from the naloxone group versus the morphine group obtained RSS scores equal to 3, respectively (Fisher's exact test, p = 0.001 and p = 0.004, respectively).

3.4. Nausea score

The percentage of patients without nausea at T1 in the naloxone group versus the morphine group were 7.7% vs 16.9%, respectively (Fisher's exact test, p = 0.18). As shown in Table 3 and Fig. 3, a non-significant decrease was observed at each timepoint between the two
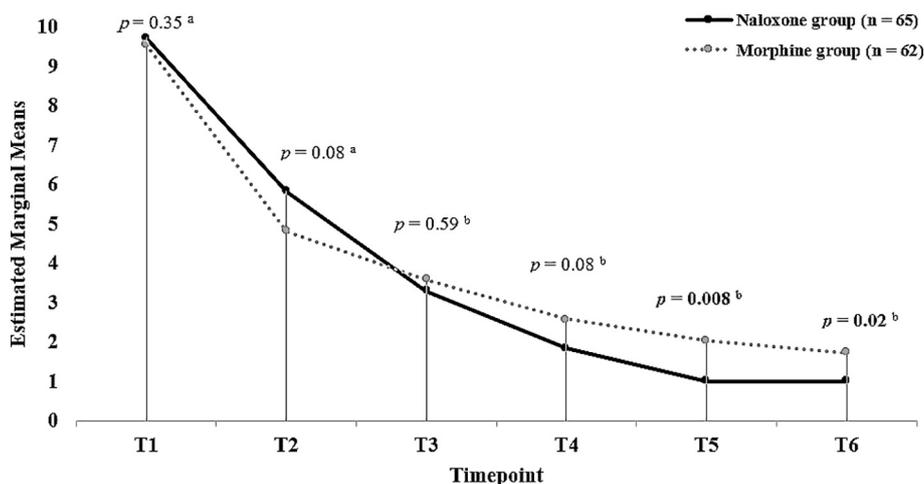

Fig. 2. Trend of pain score (according to NRS) at T1 to T6 follow-up times in both the groups in patients with renal colic. T1: baseline, T2: 20 min after injection, T3: 40 min after injection, T4: 60 min after injection, T5: 120 min after injection, T6: 180 min after injection NRS: Numeric Rating Scale. [a] p-value was obtained with t-test. [b] p-value was obtained with U-Mann Whitney test. [c] p-value was obtained with Friedman test.

Table 3
Nausea scores at T1 to T6 in both groups.

	Group		p-value[a]
	Naloxone ($n = 65$)	Morphine ($n = 62$)	
T1	5 [2, 10]	5 [2, 10]	0.13
T2	2 [1, 8]	1 [0, 2]	0.06
T3	1 [0, 2.5]	1 [0, 2]	0.36
T4	1 [0, 1]	1 [0, 2]	0.75
T5	1 [0, 1]	0 [0, 1]	0.16
T6	0 [0, 1]	0 [0, 1]	0.13
p-value[b]	<0.001	<0.001	

Data are presented as median [first quartile, third quartile].
T1: baseline, T2: 20 min after injection, T3: 40 min after injection, T4: 60 min after injection, T5: 120 min after injection, T6: 180 min after injection.
  [a] p-values obtained with U-Mann Whitney test.
  [b] p-values obtained with Friedman test.

groups ($p > 0.05$). According to the GEE model, there was no significant difference in nausea scores between the two groups (Wald X^2 (1) = 0.49, $p = 0.48$).

3.5. Respiratory rate

The trends of change regarding RR within the naloxone group and the morphine group were significant ($p < 0.001$ and $p < 0.001$, respectively). The results showed no significant difference between the two groups in the rate of breathing at all timepoints ($p > 0.05$). A repeated measures ANOVA revealed a significant time effect for RR ($F_{1, 5}$ = 24.57, $p < 0.001$, effect size = 0.16) with no significant group or group × time interactions ($F_{1, 128}$ = 15.51, $p = 0.56$ and $F_{1, 5}$ = 2.09, $p =$ 0.12, respectively) (Fig. 4).

3.6. Systolic blood pressure

The trends of change regarding SBP within the naloxone group and the morphine group were significant ($p < 0.001$, $p = 0.009$, respectively). The results showed that there was no significant difference in SBPs between the two groups at all timepoints ($p > 0.05$). A repeated measures ANOVA also yielded a significant time effect for SBP ($F_{1, 5}$ = 16.61, $p < 0.001$, effect size = 0.11) with no significant group or group × time interactions ($F_{1, 128}$ = 1.16, $p = 0.28$ and $F_{1, 5}$ = 0.38, $p = 0.86$, respectively) (Fig. 5).

3.7. Diastolic blood pressure

Mean (SD) for DBP in the naloxone group versus the morphine group were equal to 80.54 (8.48) vs 81.08 (9.82) mmHg at T1 ($p = 0.73$), respectively, and to 79.14 (12.54) vs 80.31 (9.79) mmHg at T6 ($p = 0.55$), respectively. Paired t-test results presented no significant difference in DBP changes in both the naloxone group and morphine group ($p = 0.37$, $p = 0.44$, respectively).

3.8. Morphine and metoclopramide bolus rate

Mean (SD) for the amount of additional morphine in the naloxone group and the morphine group were 4.82 (1.33) mg and 4.56 (0.84) mg, respectively ($p = 0.42$). Median [first quartile, third quartile] values of metoclopramide prescription in the naloxone and morphine groups were 10 (0, 20) mg and 10 (0, 10) mg, respectively ($p = 0.25$).

4. Discussion

We evaluated whether ultra-low-dose IV naloxone in combination with IV morphine can enhance the analgesic effect of morphine on acute pain in emergency patients with renal colic, as well as help to control morphine-induced side effects such as sedation, nausea and depressant effects on RR and BP, compared to monotherapy with morphine in the same population. The major finding of this study was that patients who received the combined naloxone therapy had non-significantly lower pain intensity associated with the same morphine consumption in comparison to the morphine-only control group. We did not find any mean difference of >1 point in the pain score between groups after the intervention as a clinically meaningful difference to show the superiority of adding naloxone to morphine over morphine monotherapy. Patients in the naloxone group also did not have significantly lower morphine-induced sedation than patients in the morphine group. Serious adverse effects were not observed regarding naloxone administration in this study.

The severity of pain was reduced in both groups. Patients who received naloxone did not experience better analgesia in comparison to patients who received morphine alone. Based on NRS pain scores, patients in the morphine group had lower pain intensity than in the naloxone group until about 40 min after treatment (T3). The descending trend in the naloxone group increased especially after T3, while 120 min after treatment (T5) was the peak of the antinociceptive effect of the co-treatment. However, there was no clinical significant differences regarding NRS pain scores between two groups throughout the
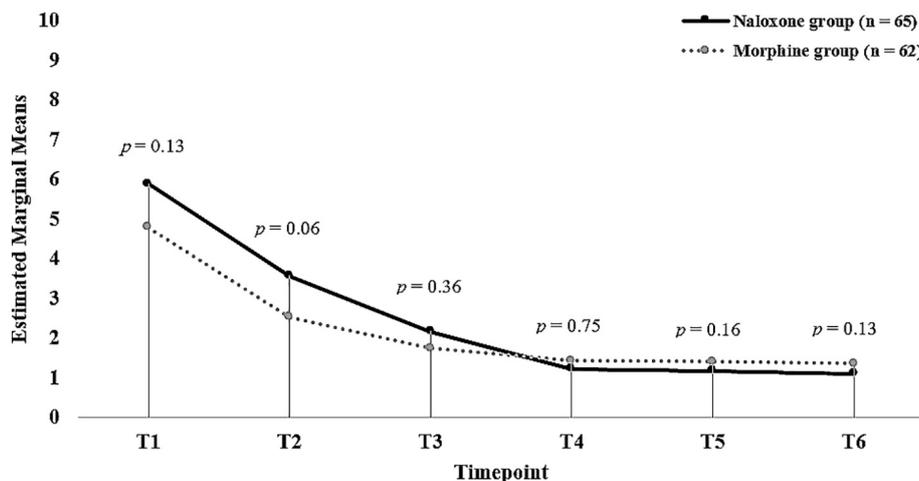

Fig. 3. Trend of nausea score (according to NRS) at T1 to T6 follow-up times in both the groups in patients with renal colic. T1: baseline, T2: 20 min after injection, T3: 40 min after injection, T4: 60 min after injection, T5: 120 min after injection, T6: 180 min after injection. NRS: Numeric Rating Scale. p-values obtained with U-Mann Whitney test.
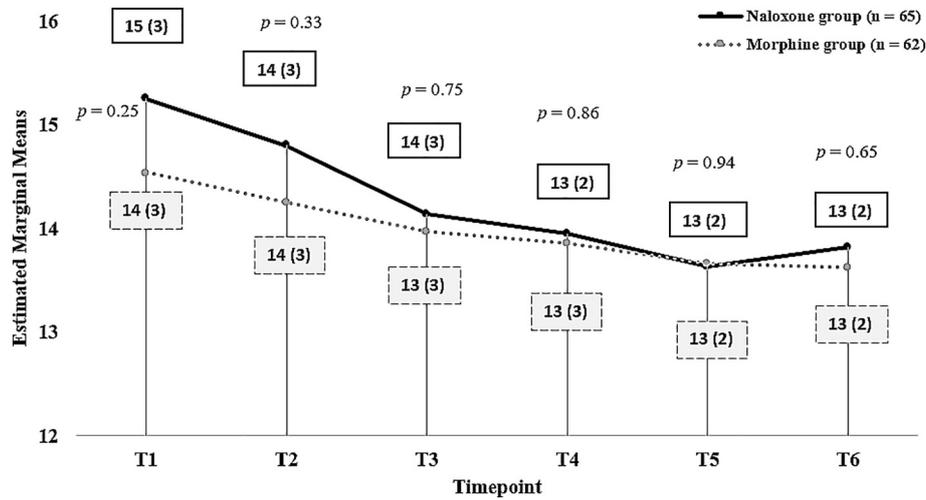
Fig. 4. Trend of respiratory rate (pulse per minute) at T1 to T6 follow-up times in both the groups in patients with renal colic. Data are presented as mean (standard deviation). T1: baseline, T2: 20 min after injection, T3: 40 min after injection, T4: 60 min after injection, T5: 120 min after injection, T6: 180 min after injection,

study. In comparison with monotherapy with morphine, the current study results showed that adding to morphine cannot act better results.

Naloxone is a fast onset of action drug (1 to 2 min) with an approximate half-life of 45 to 90 min [33]. Therefore, we expected to see a significant difference in the pain intensity at earlier timepoints between combined therapy with naloxone and monotherapy with morphine. We speculate that the analgesic effect of naloxone in the case of acute pain with maximum intensity is not efficient and obvious. After passing time and reaching mild to moderate pain intensity in the patients, the efficacy of adding naloxone to morphine in pain severity was distinctive and noticeable. However, the current study is the first clinical trial of co-treatment of ultra-low-dose naloxone with morphine in renal colic patients and further studies are necessary to confirm the findings.

Several mechanism of action have been suggested to explain the possible analgesic effects of ultra-low-dose naltrexone when combined to opioids in literature. Ultra-low-dose naloxone selectively blocks the excitatory effects elicited by morphine [20]. Moreover, naloxone at an ultra-low dose enhances opioid analgesia through (a) the prevention of a switch in G protein coupling [34]; (b) the prevention of such excitatory signaling of opioid receptors [35]; (c) a change in the signaling profile of μ opioid receptor (MOR) [34]; (d) an attenuation of morphine-induced Gβγ-adenylyl cyclase interaction [34]; and (e) reverse hyperalgesia caused by acute and low-dose opioids [35].

Another potential analgesia mechanism with ultra-low-dose naloxone could be the release of extensive amounts of endogenous opioids in the body, which reduces the analgesia requirements and increases the effects of the prescribed opioid [17,36]. However, in our study, the combination of ultra-low-dose IV naloxone and morphine did not decrease opioid requirements in our sample.

Importantly, it should be noted that naloxone may have dose-dependent effects on pain intensity; this may help to explain why the results of other studies about the effect of co-treatment of pain with morphine and naloxone have been so varied and inconclusive [22,37]. Animal studies have shown that co-treatment with morphine (1–3 mg kg^{-1}) and an ultra-low dose of naloxone markedly enhances the magnitude and duration of the analgesic effect of morphine [34,38]. On the other hand, doses of naloxone that are relatively low but nonetheless higher than the ultra-low doses in our study have been shown to increase opioid requirements and reverse analgesia [37].

Several clinical studies [20-22,37] have reported that IV ultra-low-dose naloxone added to morphine did not enhance analgesia. Cepeda et al. conducted two clinical trial in patients undergoing surgery [22,37]. In their first study [37], patients postoperatively received morphine plus normal saline or morphine plus naloxone by patient-controlled analgesia (PCA). Naloxone was infused at a rate of 0.57 μg kg^{-1} h^{-1} in the first 2 h and then 0.19 μg kg^{-1} h^{-1} until 24 h. The
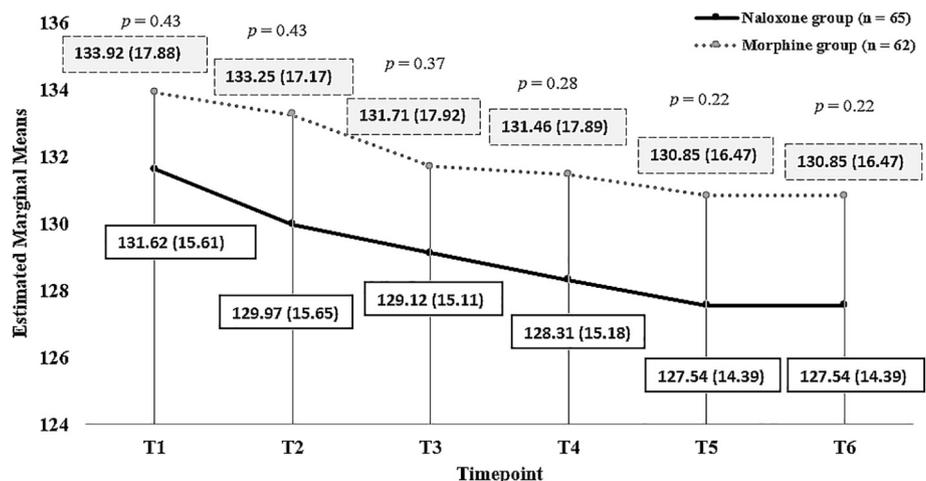

Fig. 5. Trend of systolic blood pressure values at T1 to T6 follow-up times in both the groups in patients with renal colic. Data are presented as mean (standard deviation). T1: baseline, T2: 20 min after injection, T3: 40 min after injection, T4: 60 min after injection, T5: 120 min after injection, T6: 180 min after injection.

study found that adding ultra-low doses of naloxone to morphine increased pain and subsequently opioid consumption. In Cepeda et al.'s second study [22], patients received either PCA morphine alone or PCA morphine plus naloxone as 0.05 μg/kg/h in the first 2 h and then 0.006 μg kg^{-1} h^{-1} until 24 h. The authors concluded that the combination of naloxone and morphine does not affect analgesia and opioid consumption.

Consequently, Bijur et al. [20] conducted a clinical trial to assess the analgesic effect of morphine administered with three different doses of naloxone (0.1 ng kg^{-1}, 0.01 ng kg^{-1}, or 0.001 ng kg^{-1}) added to morphine (0.1 mg kg^{-1}) versus morphine without naloxone in patients with moderate to severe pain intensity who needed morphine injections. Their results showed that pain intensity decreased in all patients; however, patients who received naloxone experienced non-significantly lower pain intensity than those had received morphine without naloxone. Moreover, the analgesia effect of naloxone non-significantly increased in association with the increase in naloxone dose. Although all three doses of naloxone in the study were too low to show statistically significant effects, the pain management was slightly better with co-administration of naloxone and morphine in emergency patients with severe pain.

Recently, Firouzian et al. [17] reported that infusion of ultra-low-dose naloxone at a dose of 0.25 μg kg^{-1} h^{-1} for 24 h along with PCA morphine significantly relieved pain intensity, as well as reducing overall morphine consumption after lumbar discectomy surgery (morphine rate: near 0.96 mg h^{-1}). The naloxone used in the Firouzian study was applied with a constant infusion rate for 24 h. We chose an IV single-dose of naloxone in combination with morphine because of its rapid onset in ED patients with renal colic.

The rate of morphine injection in patients with renal colic is high because they experience the highest levels of acute pain [26,27]. Receiving such high amounts of morphine (or other analgesic agents) results in increasing sedation in these patients. Ultra-low-dose naloxone can reduce opioid-induced side effects as well as analgesic tolerance and dependence [17,35]. Our study results indicated that decreased pain intensity was generally associated with increased sedation. Importantly, however, patients in the naloxone group did not display either greater agitation or sedation in comparison to the control group, despite reporting non-significant slightly lower pain level and receiving a relatively similar amount of morphine.

Although, there were meaningful differences in the sedated patients between the monotherapy with morphine and naloxone group at T5 and T6, the majority of the sedation outcomes revealed no significant differences between the two groups. It seems that the ultra-low dose naloxone added to morphine did not improve sedation outcome in these papulation. There is no biologically plausible mechanism to justify the reason of this happening.

Nausea intensity, similar to pain intensity, significantly decreased at the end of study in both groups. It is possible that nausea improvement resulted from successful pain relief in both the naloxone and control groups. Although nausea intensity until 60 min after treatment (T4) was a little higher in the naloxone group than in the control group, after this timepoint the trend reversed and nausea was slightly lower in the naloxone group; however, the difference between two groups was not significant at any point. The literature about the effectiveness of ultra-low-dose naloxone on nausea intensity reports divergent results [14,39,40]. There are a few studies that suggest a positive effect of naloxone in the treatment of nausea [14,17]. More studies have shown no advantage of naloxone injection for prophylaxis of nausea and vomiting after cesarean surgery [39,40]. However, additional studies about the effectiveness of ultra-low-dose IV naloxone combined with morphine on opioid-induced nausea are needed.

Our results found that RR and BP had a decreasing trend with time passage in both groups; however, we did not find significant differences between the two groups. RR and BP appeared to reach normal ranges following the amelioration in pain intensity. In other words, the normalization of RR and BP was related to successful pain control in both groups.

Our data suggest that ultra-low-dose IV naloxone in combination with morphine is a safe and ineffective method for renal colic pain control. Similar to the results of previous studies [17,19,21], we also found no side effects in patients following IV administration of ultra-low-dose naloxone along with morphine. Limitations of our study include the fact that clinical items such as heart rate, pulse oximetry saturation (Spo2), vomiting frequency, length of hospital stay, and patient satisfaction were not recorded.

5. Conclusion

Our data suggest that concurrent use of single ultra-low-dose IV naloxone and morphine would not provide better analgesia in patients with renal colic. In addition to non-significant reducing acute pain in this population, naloxone failed to act as a co-treatment with morphine to improve sedation/agitation states. However, more robust randomized, controlled studies with large sample sizes are needed, with regards to the safety and effectiveness of the co-treatment of naloxone with morphine or other opioids.

Conflict of interest

Acknowledgment

Appendix A. The Ramsey sedation scale (RSS)

RSS scores	Describe
1	Awake, anxious, agitated, restless
2	Cooperative, oriented, tranquil
3	Responsive to commands only
4	If asleep: brisk response to light glabellar tap or loud auditory stimulus
5	Sluggish response to light glabellar tap or loud auditory stimulus
6	No response to light glabellar tap or loud auditory stimulus

References

[1] Hosseininejad SM, Zeydi AE. Can intracutaneous sterile water injection be used as a possible treatment for acute renal colic pain in the emergency department? A short literature review. Urol Ann 2015;7(1):130–2.

[2] Roughley MJ, Belcher J, Mallen CD, Roddy E. Gout and risk of chronic kidney disease and nephrolithiasis: meta-analysis of observational studies. Arthritis Res Ther 2015; 17(1):90.

[3] Sin B, Cao J, Yang D, Ambert K, Punnapuzha S. Intravenous lidocaine for intractable renal colic unresponsive to standard therapy. Am J Ther 2018. https://doi.org/10.1097/MJT.0000000000000729 [Epub ahead of print], PMID: 29443696. 23 Jan

2018. https://journals.lww.com/americantherapeutics/Abstract/publishahead/Intravenous_Lidocaine_for_Intractable_Renal.

[4] Kan W-C, Chou Y-H, Chiu S-J, Hsu Y-W, Lu H-F, Hsu W, et al. Study of the association between ITPKC genetic polymorphisms and calcium nephrolithiasis. Biomed Res Int 2014;2014:397826.

[5] Ziapor B, Motamed H, Verki MM, Norani H. Comparison of effect of morphine-chlorpheniramine combined versus morphine alone in alleviating acute renal colic pain: a randomized clinical trial. Jundishapur J Nat Pharm Prod 2017;12(3):e15585.

[6] García-Perdomo H, Echeverría-García F, López H, Fernández N, Manzano-Nunez R. Pharmacologic interventions to treat renal colic pain in acute stone episodes: systematic review and meta-analysis. Prog Urol 2017;27(12):654–65.

[7] Cervenakov I, Fillo J, Mardiak J, Kopečnú M, Šmirala J, Labaš P. Speedy elimination of ureterolithiasis in the lower part of ureters with the alpha 1-blocker–Tamsulosin. Int Urol Nephrol 2002;34(1):25–9.

[8] Firouzian A, Alipour A, Dezfouli HR, Kiasari AZ, Baradari AG, Zeydi AE, et al. Does lidocaine as an adjuvant to morphine improve pain relief in patients presenting to the ED with acute renal colic? A double-blind, randomized controlled trial. Am J Emerg Med 2016;34(3):443–8.

[9] Morteza-Bagi HR, Amjadi M, Mirzaii-Sousefidi R. The comparison of apotel plus low dose of morphine and full dose of morphine in pain relief in patients with acute renal colic. Addict Health 2015;7(1–2):66.

[10] Karamese M, Akdağ O, Kara I, Yıldıran GU, Tosun Z. The comparison of intrathecal morphine and IV morphine PCA on pain control, patient satisfaction, morphine consumption, and adverse effects in patients undergoing reduction mammoplasty. Eplasty 2015;15:e15.

[11] Rebel A, Sloan P, Andrykowski M. Postoperative analgesia after radical prostatectomy with high-dose intrathecal morphine and intravenous naloxone: a retrospective review. J Opioid Manag 2009;5(6):331–9.

[12] Kosiński S, Siudut B. Pain treatment in the emergency department: what do patients think? Anestezjol Intens Ter 2011;43(4):234–8.

[13] Tsai R-Y, Jang F-L, Tai Y-H, Lin S-L, Shen C-H, Wong C-S. Ultra-low-dose naloxone restores the antinociceptive effect of morphine and suppresses spinal neuroinflammation in PTX-treated rats. Neuropsychopharmacology 2008;33(11):2772.

[14] Movafegh A, Shoeibi G, Ansari M, Sadeghi M, Azimaraghi O, Aghajani Y. Naloxone infusion and post-hysterectomy morphine consumption: a double-blind, placebo-controlled study. Acta Anaesthesiol Scand 2012;56(10):1241–9.

[15] Hayl J, Vincentel S, Somogyil A, Chapleol C, Whitel J. Potentiation of buprenorphine antinociception with ultra-low dose naltrexone in healthy subjects. Eur J Pain 2011; 15(3):293–8.

[16] Maxwell LG, Kaufmann SC, Bitzer S, Jackson Jr EV, McGready J, Kost-Byerly S, et al. The effects of a small-dose naloxone infusion on opioid-induced side effects and analgesia in children and adolescents treated with intravenous patient-controlled analgesia: a double-blind, prospective, randomized, controlled study. Anesth Analg 2005;100(4):953–8.

[17] Firouzian A, Baradari AG, Alipour A, Zeydi AE, Kiasari AZ, Emadi SA, et al. Ultra–low-dose naloxone as an adjuvant to patient controlled analgesia (PCA) with morphine for postoperative pain relief following lumber discectomy: a double-blind, randomized, placebo-controlled trial. J Neurosurg Anesthesiol 2018;30(1):26–31.

[18] Yang C-P, Cherng C-H, Wu C-T, Huang H-Y, Tao P-L, Wong C-S. Intrathecal ultra-low dose naloxone enhances the antinociceptive effect of morphine by enhancing the reuptake of excitatory amino acids from the synaptic cleft in the spinal cord of partial sciatic nerve–transected rats. Anesth Analg 2011;113(6):1490–500.

[19] Sartain JB, Barry JJ, Richardson CA, Branagan HC. Effect of combining naloxone and morphine for intravenous patient-controlled analgesia. Anesthesiology 2003;99 (1):148–51.

[20] Bijur PE, Schechter C, Esses D, Chang AK, Gallagher EJ. Intravenous bolus of ultra-low-dose naloxone added to morphine does not enhance analgesia in emergency department patients. J Pain 2006;7(2):75–81.

[21] Ling W, Hillhouse M, Jenkins J, Miotto K, Torrington M, Chapleo C. Comparisons of analgesic potency and side effects of buprenorphine and buprenorphine with ultra-low-dose naloxone. J Addict Med 2012;6(2):118–23.

[22] Cepeda MS, Alvarez H, Morales O, Carr DB. Addition of ultralow dose naloxone to postoperative morphine PCA: unchanged analgesia and opioid requirement but decreased incidence of opioid side effects. Pain 2004;107(1–2):41–6.

[23] Sadeghi M, Movafegh A, Nouralishahi B. The effect of an intravenous bolus of ultra-low-dose naloxone on intraoperative sedation, post operative pain intensity and morphine consumption in cesarean section patients under spinal anesthesia. Res J Biol Sci 2008;10:1223–6.

[24] Movafegh A, Nouralishahi B, Sadeghi M, Nabavian O. An ultra-low dose of naloxone added to lidocaine or lidocaine-fentanyl mixture prolongs axillary brachial plexus blockade. Anesth Analg 2009;109(5):1679–83.

[25] Xiao Y, Wu L, Zhou Q, Xiong W, Duan X, Huang X. A randomized clinical trial of the effects of ultra-low-dose naloxone infusion on postoperative opioid requirements and recovery. Acta Anaesthesiol Scand 2015;59(9):1194–203.

[26] Birnbaum A, Esses D, Bijur PE, Holden L, Gallagher EJ. Randomized double-blind placebo-controlled trial of two intravenous morphine dosages (0.10 mg/kg and 0.15 mg/kg) in emergency department patients with moderate to severe acute pain. Ann Emerg Med 2007;49(4):445–53 [e2].

[27] 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.

[28] Shokeir AA. Renal colic: new concepts related to pathophysiology, diagnosis and treatment. Curr Opin Urol 2002;12(4):263–9.

[29] Lee JS, Hobden E, Stiell IG, Wells GA. Clinically important change in the visual analog scale after adequate pain control. Acad Emerg Med 2003;10(10):1128–30.

[30] Shih MT, Juho YC, Meng E, Sun GH, Cha TL, Wu ST, et al. Pain severity in renal colic: a retrospective evaluation of initial visits in patients at a medical center. Int Surg J 2016;3(2):480–3.

[31] Ramsay M, Savege T, Simpson B, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J 1974;2(5920):656.

[32] Yeaman F, Meek R, Egerton-Warburton D, Rosengarten P, Graudins A. Sub-dissociative-dose intranasal ketamine for moderate to severe pain in adult emergency department patients. Emerg Med Australas 2014;26(3):237–42.

[33] Mégarbane B, Declèves X, Bloch V, Bardin C, Chast F, Baud FJ. Case report: quantification of methadone-induced respiratory depression using toxicokinetic/toxicodynamic relationships. Crit Care 2007;11(1):R5.

[34] Burns LH. Ultra-low-dose opioid antagonists enhance opioid analgesia while reducing tolerance, dependence and addictive properties. Recent developments in pain research Kerala. India: Research Signpost; 2005. p. 115–36.

[35] Wang H-Y, Frankfurt M, Burns LH. High-affinity naloxone binding to filamin A prevents mu opioid receptor–Gs coupling underlying opioid tolerance and dependence. PLoS One 2008;3(2):e1554.

[36] Sloan P, Hamann S. Ultra-low-dose opioid antagonists to enhance opioid analgesia. J Opioid Manag 2006;2(5):295–304.

[37] Cepeda MS, Africano JM, Manrique AM, Fragoso W, Carr DB. The combination of low dose of naloxone and morphine in PCA does not decrease opioid requirements in the postoperative period. Pain 2002;96(1–2):73–9.

[38] Powell KJ, Abul-Husn NS, Jhamandas A, Olmstead MC, Beninger RJ, Jhamandas K. Paradoxical effects of the opioid antagonist naltrexone on morphine analgesia, tolerance, and reward in rats. J Pharmacol Exp Ther 2002;300(2):588–96.

[39] Connelly N, Rahimi A, Parker R. Nalmefene or naloxone for preventing intrathecal opioid mediated side effects in cesarean delivery patients. Int J Obstet Anesth 1997;6(4):231–4.

[40] Dailey PA, Brookshire GL, Shnider SM, Abboud TK, Kotelko DM, Noueihid R, et al. The effects of naloxone associated with the intrathecal use of morphine in labor. Anesth Analg 1985;64(7):658–66.