Original Article DOI: 10.22114/ajem.v0i0.178

Comparing the Analgesic Effect of Aminophylline and Hyoscine with Morphine on Renal Colic: a Randomized Clinical Trial

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Published online: 2020-01-30

Abstract

Introduction: Although narcotics are effective for pain relief in these patients, they have little impact on the underlying cause. Therefore, surveys have been conducted to find more effective agents.

Objective: This study conducted to compare the analgesic effect of aminophylline and hyoscine combination with morphine on renal colic patients.

Methods: This double-blind clinical trial was conducted on patients with renal colic caused by urinary tract stones. Subjects were selected via convenience sampling method. Patients were randomly divided into two groups based on whether they received aminophylline + hyoscine or morphine. Before drug administration, one researcher was asked to measure the pain of the patients using Graduated Numbered Visual Analogue Scale (GN-VAS). Afterward, 20 mg of hyoscine along with 3 mg/kg of aminophylline in 100 cc normal saline was injected during 10 minutes into patients in the one group, whereas 0.1 mg/kg of morphine was intravenously with 100 cc normal saline to align two groups, administered to the subjects in another group. Half an hour after the administration of drugs, pain was measured for the second time. Vital signs and side effects were all recorded.

Results: In this study, 95 patients (47 patients in the aminophylline+hyoscine group and 48 patients in the morphine group) remained in the trial until the end. The difference in sex distribution($p=0.227$) and age($p=0.680$) of the two groups was not statistically significant. Median of pain intensity was not significantly different between the two study groups ($p<0.05$), neither before nor after administration of the drugs. The mean time required for pain relief in morphine group was significantly lower than aminophylline+hyoscine group (5.9±1.6 vs. 11.1±1.6 minutes; $p<0.001$).

Conclusion: Overall, our findings indicated that aminophylline + hyoscine combination was effective in reducing renal colic pain and there is no significant difference between this combination and morphine in terms of pain relief.

Key words: Aminophylline; Hyoscine N-oxide; Morphine; Pain Management; Renal Colic

Cite this article as: Akbari H, Foroughian M, Abiri S, Kalani N, Rayatdoost E, Safaei M, et al. Comparing the Analgesic Effect of Aminophylline and Hyoscine with Morphine on Renal Colic: a Randomized Clinical Trial. Adv J Emerg Med. 2020;4(4):e85.

INTRODUCTION

Generally, 50-60% of referrals to emergency department (ED) are due to pain. Renal colic is one of the most common types of pain, which is extremely severe and intolerable, and 1-5% of the general population are affected by it (1-3). The reason for feeling this type of pain is a kidney stone obstructing the urinary flow, increase in the pressure on urinary tract wall, spasms in the smooth muscle of the ureter, edema and inflammation of the tissue near the stone, increase in peristalsis, and pressure caused by the proximal stone (4, 5). Proper pain management is one of the major objectives and responsibilities of physicians in the ED. The best and most effective treatments for renal colic are treatments that lead to spontaneous passage of a urethral stone (5). Therefore, use of medications that can reduce pain and prevent spasms has affected the treatment process of patients (6-12).

Morphine is one of the most effective analgesics in renal colic patients. Although narcotics are effective for pain relief in these patients, they have little impact on the underlying cause (13). Therefore, surveys have been conducted to find more effective agents.

Aminophylline, which is a derivative of theophylline and a member of the methylxanthine family, causes smooth muscle relaxation, particularly in the cardiopulmonary system. It stimulates the central nervous system and increases urinary retention. In terms of the drug's mechanism, it could be stated that it elevates the concentration of 3',5'-cyclic adenosine monophosphate in cells via inhibition of phosphodiesterase enzyme and activates protein kinase A (PKA). In addition, aminophylline reduces inflammation by inhibiting synthesis of both tumor necrosis factor-alpha (TNFα) and leukotriene (11).

Moreover, hyoscine butylbromide is a drug that can theoretically be applied in combination with other analgesics to alleviate renal colic pain (1). It is an antimuscarinic drug that reduces smooth muscle cramps, especially in the gastrointestinal (GI) tract. It is expected that use of antimuscarinic drugs will be effective for relieving renal colic, since the ureteral activity is controlled by the autonomic nervous system (5). Furthermore, this drug can block the acetylcholine released from the parasympathetic nerve endings in the muscles and the glands and is expect to be able to alleviate renal colic pain (1).

Considering the above-mentioned points, it could be theorized that combining aminophylline and hyoscine could provide therapeutic benefits for renal colic patients in addition to having an analgesic effect. With this background in mind, this study conducted to compare the analgesic effect of aminophylline and hyoscine combination with morphine on renal colic patients.

Methods

Study design

This double-blind clinical trial (registered as IRCT20180805040712N1) was performed from May 2016 to March 2017 on patients with renal colic caused by urinary tract stones, who presented to the ED of a hospital in Jahrom, Iran. It should be noted that the study was approved by the ethics committee of Jahrom University of Medical Sciences (IR.JUMS.REC.1396.054). Informed consent was obtained from the patients. All authors adhered to the principles of Helsinki declaration throughout the study.

Study population

Patients with moderate or severe pain (based on vertical Graduated Numbered Visual Analogue Scale (VAS)) in the age range of 18-55 years with diagnosis of renal colic caused by urinary tract stones were eligible. The exclusion criteria consisted of pregnancy, history of addiction, hypertension, previous urinary tract surgery, parenteral pain management before hospitalization, known allergy to aminophylline or hyoscine or morphine, excessive hypersensitivity to xanthines, arrhythmias, and hypothyroidism. Considering mean difference of pain score to be 0.5 in the two groups, standard deviation=0.7 for zero to three pain score, α=0.05 and β=0.1 sample size was calculated as 42 patients in each group and then considering 10% loss to follow-up, the sample size required was 47 individuals in each group. Subjects were selected via convenience sampling method. Patients were randomly divided into two groups based on whether they received aminophylline + hyoscine or morphine. Randomization was carried out using the table derived from the following website: https://www.randomizer.org/.

Definition

Vertical Graduated Numbered VAS was the scaling for our patients. This scale was 100 mm long with the extreme limits from "not at all" (no symptom or no pain) to "enormously" or "hugely" (the worst possible level of the symptom) and patients were categorized in 4 groups (no pain, mild, moderate and severe). The patients were trained to put a mark on the scale according to the intensity of their symptoms. Results were uttered in millimeters from zero (no symptom) to 100 (worst possible level of the symptom) (14).

Intervention

Before drug administration, one researcher who was unaware of the treatment group, was asked to measure the pain of the patients (who themselves were also unaware of their group) using Vertical Graduated Numbered VAS. Heart rate, systolic and diastolic blood pressure, and presence of dry mouth, nausea and vomiting were all recorded. Afterward, 20 mg of hyoscine along with 3 mg/kg of aminophylline in 100 cc normal saline was injected during 10 minutes into patients in the first group, whereas 0.1 mg/kg of morphine was intravenously with 100 cc normal saline to align two groups, administered to the subjects in the second group (11, 15). Half an hour after the administration of drugs, pain and other mentioned variables were measured for the second time with the same researcher performed the primary evaluations. On this step, the patients were categorized into four groups of no pain, mild, moderate and severe in terms of severity of pain.

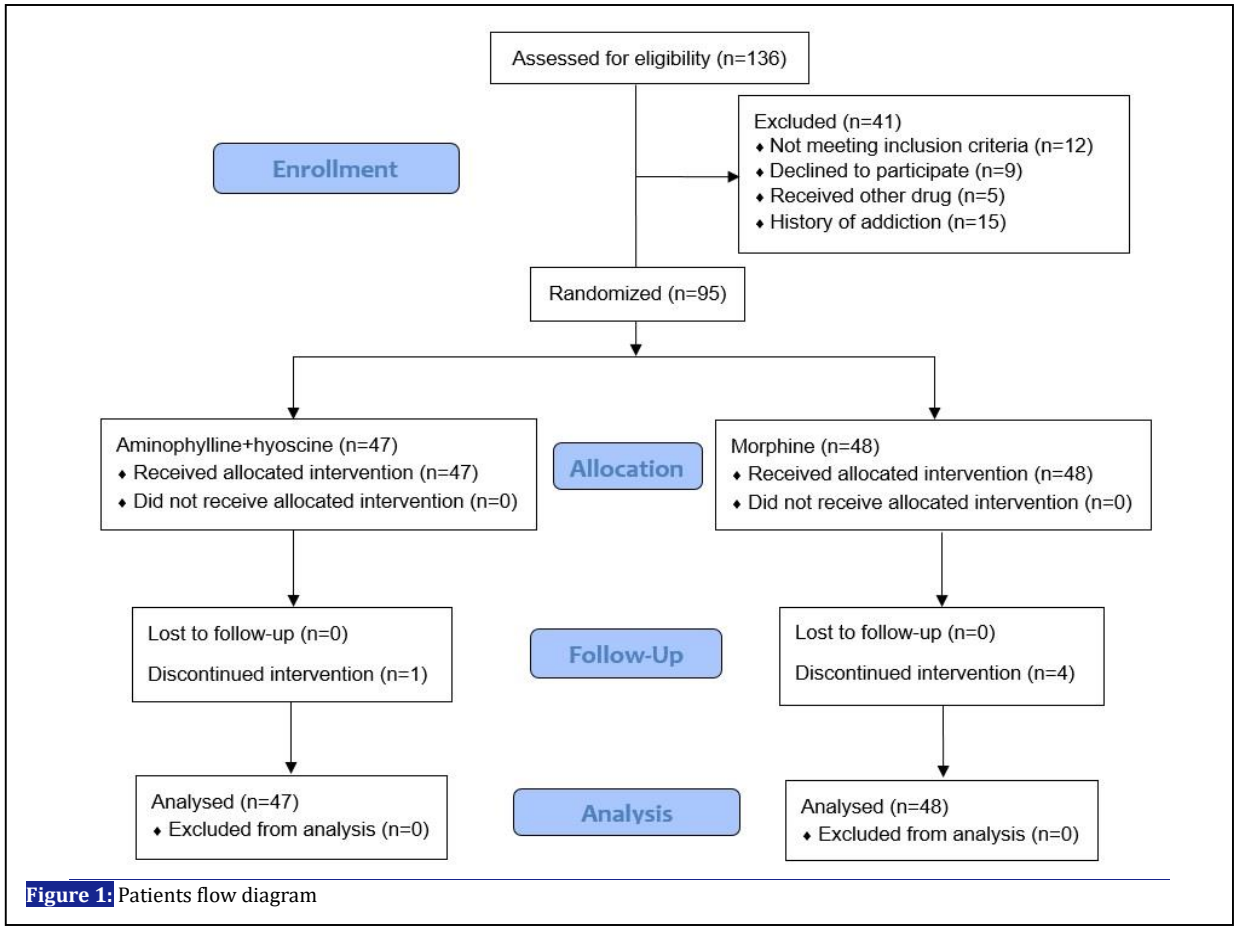

Figure 1: Patients flow diagram

Statistical analysis

We presented data as frequency, mean with standard deviation, and median with interquartile range (IQR, presented as range with 75th–25th percentiles), as appropriate. Fisher's exact and Chi-square tests were used for comparison of categorical variables. In this study, pain score was presented categorically (no pain, mild, moderate and severe) and analysed based on numerical scale from pain score of zero to three for each person. We used graphical approaches and Shapiro-Wilk Test for assessing normality. We calculated percentage of changes after the injection of drugs in each group and then compared the amount of change between the two groups. We used the independent t-test or Univariate analysis, with before value as covariate, for assessment of the difference between mean values in the two drug groups. Additionally, we used paired t-test for assessing mean values before and after drug administration. For non-normal data non-parametric equivalents of these tests were used to compare numerical variables. Statistical tests were performed as two-tailed tests with a significance level of $p<0.05$. Data were analyzed using SPSS software (IBM Corporation, Armonk, USA).

RESULTS

Baseline findings

In this study, 95 patients (47 patients in the aminophylline+hyoscine group and 48 patients in the morphine group) remained in the trial until the end. CONSORT flowchart of this study is seen in figure 1. In total, 23 participants (70.2%) of the aminophylline + hyoscine group were male and the rest were female. In the morphine group, 28 subjects (58.3%) were male and the rest were female. The difference in sex distribution of the two groups was not statistically significant (p=0.227). In addition, the mean age of patients in aminophylline + hyoscine and morphine groups was 29.21±5.40 and 28.72±5.96 years, respectively (p=0.680).

Pivotal findings

Figure 2 presents distribution of patients in pain categories before and after the administration of drugs in the two study groups. Before intervention, about 90% of the patients had severe pain in both study groups and difference between pain severity of the groups was not significant (p=0.714). After intervention, 12.5% and 8.5% of patient had severe pain in morphine and aminophylline group,

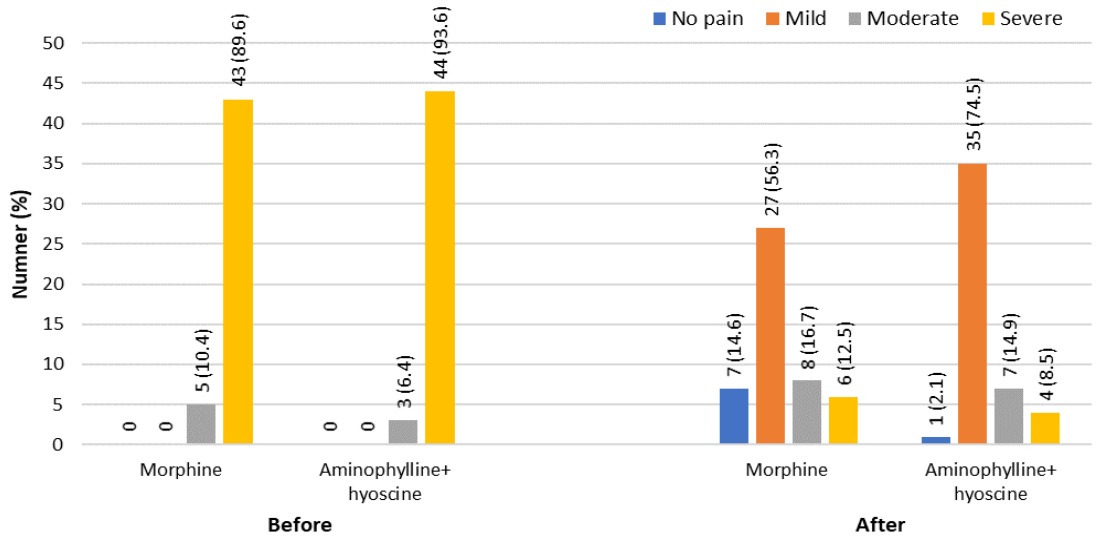

Figure 2: Frequency of patients in each pain category, before and after the administration of drugs in the two study groups (Morphine or Aminophylline+ Hyoscine).

respectively. However, the difference between pain severity of the two groups after intervention was not significant (p=0.109). Based on the findings, median of pain intensity was not significantly different between the two study groups (p<0.05) neither before nor after administration of the drugs. Mean pain score reduced significantly in both groups (p <0.001) after the injection of the drugs. Nonetheless, no significant difference was observed between the groups in terms of the percentage of pain score changes after the injection of drugs (p=0.678).

Table 1 shows the details of pain intensity changes after drug administrations in the two study groups. Based on the findings, 6 (12.5%) patients in morphine group had severe pain after injection, whereas for the aminophylline group this occurred in 4 (8.5%) patients. In morphine group, the severity of pain in 3 (6.3%) patients changed from severe pain to no pain after injection, whereas this did not occur for any of the patients in the aminophylline+hyoscine group. In the morphine group, the severity of pain in 7 patients reduced to no pain after the injection, but in the aminophylline group only one patient had no pain. The mean time required for pain relief in morphine group was significantly lower than aminophylline+hyoscine group (5.9±1.6 vs. 11.1±1.6 minutes; p<0.001).

Other findings

Vital signs alterations in the two study groups are reported in table 2. Systolic blood pressure had significantly decreased in both group (p<0.001) and percentage of change after the injection of drug in morphine group was significantly higher than aminophylline+hyoscine group [Median (IQR): -7.7 (10.6) vs -7.1 (7.1); P=0.017]. Diastolic blood pressure and heart rate significantly decreased in morphine group, but increased in aminophylline+hyoscine group. So, Percentage of changes in diastolic blood pressure and heart rate were statistically significant between the two groups (p<0.05).

The results of assessing side effects are presented in table 3. None of the patients had dry mouth or shivering before drug administration. After drug administration, prevalence of dry mouth was significantly lower in morphine group compared to aminophylline+hyoscine group (22.9% vs 85.1%;

Table 1: Pain intensity changes after drug administration in the two study groups

Change in pain category (pre → post)	Morphine (n=48)	Aminophylline + Hyoscine (n=47)
	Frequency (%)	
Moderate pain→ No pain	4 (8.3)	1 (2.1)
Moderate pain→ Mild pain	1 (2.1)	2 (4.3)
Severe pain → No pain	3 (6.3)	0 (0.0)
Severe pain → Mild pain	26 (54.2)	33 (70.2)
Severe pain → Moderate pain	8 (16.7)	7 (14.9)
Severe pain → Severe pain	6 (12.5)	4 (8.5)

Table 2: Pain and vital signs differences before and after drug administration as well as percentage of change in the two drug groups

Vital sign	Time based on drug admission	Morphine (n=48)		Aminophylline + Hyoscine (n=47)		P-Value
		Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Systolic Blood Pressure	Before	127.6 (9.6)	130.0 (130.0, 120.0)	137.0 (4.6)	140.0 (140.0, 130.0)	<0.001
	After	119.0 (9.2)	120.0 (120.0, 112.5)	130.4 (6.6)	130.0 (130.0, 130.0)	<0.001^
	P-Value	<0.001		<0.001		
	Percent of change	-6.6 (6.5)	-7.7 (0.0, -10.6)	-4.7 (5.3)	-7.1 (0.0, -7.1)	0.017
Diastolic Blood Pressure	Before	81.1 (3.7)	80.0 (80.0, 80.0)	80.0 (2.1)	80.0 (80.0, 80.0)	0.069
	After	79.4 (4.2)	80.0 (80.0, 80.0)	80.6 (2.5)	80.0 (80.0, 80.0)	0.078
	P-Value	0.008		0.003		
	Percent of change	-2.1 (5.3)	0.0 (0, 0)	0.84 (3.2)	0.0 (0, 0)	0.002
Heart rate	Before	89.5 (8.5)	90.0 (100.0, 80.0)	85.4 (5.0)	90.0 (90.0, 80.0)	0.005
	After	78.6 (7.3)	80.0 (80.0, 70.0)	94.0 (6.1)	90.0 (100.0, 90.0)	<0.001^
	P-Value	<0.001		<0.001		
	Percent of change	-11.8 (7.5)	-11.1 (-10.0, -12.5)	10.1 (4.8)	11.1 (12.5, 11.1)	<0.001

^ Univariate analysis, with before value as covariate
SD: Standard Deviation; IQR: Interquartile Range, presented as range with 75th–25th percentiles

Table 3: Dry mouth, Shivering and Nausea in the two drug groups (Morphine or Aminophylline+ Hyoscine)

Adverse effect	Morphine (n=48)	Aminophylline + Hyoscine (n=47)	P-Value
Dry mouth			
Yes	11 (22.9)	40 (85.1)	<0.001
No	37 (77.1)	7 (14.9)	
Shivering			
Yes	4 (8.3)	1 (2.1)	0.362
No	44 (91.7)	46 (97.9)	
Nausea*			
Yes	4 (9.3)	15 (32.6)	0.009
No	39 (90.7)	31 (67.4)	

* After drug administration for patients who had not nausea before

P<0.001). However, after drug administration prevalence of shivering in morphine group was higher than aminophylline+hyoscine group (8.3% vs 2.1%), but this difference was not significant (p=0.362). Before administration of the drugs, nausea frequency was not significantly different between the two groups (p=0.204), and only six patients (6.3%) did not have nausea, five of which were in the morphine group. Additionally, four patients had nausea both before and after injection. 89 patients (93.7%) had nausea before drug administration, prevalence of nausea after drug administration was 9.3% and 32.6% in morphine and aminophylline + hyoscine group, respectively. In other words, it was determined that the injection of morphine had a greater effect on reducing nausea, compared to aminophylline + hyoscine injection (90.7% vs 67.4%; p=0.009).

Discussion

Our findings in current study showed the similar impact of aminophylline + hyoscine versus morphine injection in terms of reducing the level of pain in renal colic patients. However, the time required for pain relief after aminophylline + hyoscine injection was significantly longer compared to morphine administration.

Aminophylline is one of these drugs, which increases intracellular cyclic Adenosine Mono Phosphate (cAMP) because it is a phosphodiesterase inhibitor. On the other hand, it decreases the concentration of calcium ions in smooth muscle. In addition, it inhibits the effects of prostaglandins on them/smooth muscles and leads to the inhibition of the release of histamine and leukotrienes. When aminophylline is absorbed in the body, theophylline is released and metabolized in the liver and gets converted into caffeine (16). In a study by Djaladat et al. in Bandar Abbas, Iran (2005) on the effects of aminophylline on renal colic pain, it was concluded that aminophylline reduced renal colic pain and decreased their need

to use narcotic analgesics (17). Kheirollahi et al., (2010) compared the combination of muscle hyoscine and desmopressin inhalation with hyoscine alone, reporting that the use of both intramuscular hyoscine and inhaled desmopressin and hyoscine alone were effective in relieving pain in patients. However, the combination of hyoscine and desmopressin together was more effective than hyoscine alone in terms of relief of renal colic pain (15). On the other hand, Holdgate et al. conducted a research on the effect of anti-muscarinic drugs in reducing renal colic pain during September 2002-March 2004, remarking that the use of hyoscine had no effect on reduction of renal colic pain (1). Therefore, the combination of both aminophylline and hyoscine on pain relief was assessed in the present study. According to the literature, aminophylline and hyoscine are safe and inexpensive and have the least complications. Considering the complications of narcotic drugs, such as nausea and vomiting, constipation, urinary retention, hypotension, respiratory depression, creating sedation in patients and possibility of addiction, the mentioned drugs can be used as complementary treatments to control renal colic.

Unfortunately, the complications of using the two treatments were not broadly assessed in the present study. Considering the similar analgesic effects of the combination of aminophylline + hyoscine and morphine alone, it is suggested to conduct further studies in the future to evaluate the complications of these drugs on patients. However, regarding hypotension, as one of the complications of the use of narcotic drugs, we found that the reduction in systolic blood pressure was higher in the morphine group, compared to the aminophylline + hyoscine group. Additionally, in terms of heart rate, the results demonstrated that the injection of morphine significantly reduced heart rate; whereas, aminophylline + hyoscine injection significantly increased heart rate in patients. Nonetheless, other results indicated that morphine had a greater effect on reducing nausea in patients compared to aminophylline + hyoscine. On the other hand, the administration of aminophylline + hyoscine caused dry mouth in a higher number of patients, compared to morphine.

Limitations

Our study did not have enough power to allow subgroup analysis. Another limitation was that we did not follow up our participants for longer periods of time such as 1 or 2 hour(s) after injection; Therefore, we cannot reach any conclusions in this regard.

Conclusions

Overall, our findings indicated that aminophylline + hyoscine combination was effective in reducing renal colic pain and there is no significant difference between this combination and morphine in terms of pain relief. However, since the combination of aminophylline and hyoscine drugs causes smooth muscle relaxation due to vasodilation and a proliferative effect, it could effectively move the renal stone as well as controlling the pain of patients and reducing inflammation caused by the renal stone.

Acknowledgements

This article was derived from a thesis performed by Dr. Safaei as general physician course at Jahrom University of Medical Sciences. Hereby, we extend our gratitude to the staff of the hospital in Jahrom for assisting us in performing the research. We would like to thank the Clinical Research Development Unit of Peymanieh Educational and Research and Therapeutic Center of Jahrom University of Medical Sciences for providing facilities to this work

Authors' contribution

All the authors met the standards of authorship based on the recommendations of the International Committee of Medical Journal Editors.

Conflict of interest

None declared.

Funding

The study was financially supported by the vice-chancellor for research of Jahrom University of Medical Sciences..

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