ORIGINAL ARTICLE

Comparison of penthrox (methoxyflurane) inhalation and intravenous morphine for acute limb fracture pain management in the emergency department: a randomized controlled trial

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Abstract

Objective:

Effective pain management is crucial in emergency settings, and both penthrox (methoxyflurane) inhalation and intravenous morphine are commonly used analgesics. This study aimed to compare the analgesic efficacy, adverse effects, and patient satisfaction associated with penthrox spray and morphine for acute limb fracture pain management in the emergency department.

Methods:

This prospective, double-blinded, randomized controlled trial included 50 patients aged 20-55 years with acute limb fracture pain, randomly assigned to receive either penthrox spray or intravenous morphine. The primary outcome was pain intensity assessed using the visual analog scale (VAS) over 60 minutes. Secondary outcomes included adverse effects, vital signs, and patient satisfaction.

Results:

Both groups experienced significant pain relief over time, with a similar reduction in VAS scores ($P<0.001$). However, the penthrox spray group showed a trend toward more rapid pain reduction, although not statistically significant. The frequency of vomiting and nausea tended to be lower in the penthrox spray group (24% vs. 40%, $P=0.225$). There were no significant differences in patient satisfaction scores between groups. While both groups experienced a decrease in blood pressure, the heart rate remained stable in the penthrox spray group but decreased significantly in the morphine group ($P<0.001$).

Conclusion:

Penthrox spray and intravenous morphine demonstrated comparable analgesic efficacy for acute limb fracture pain in the emergency department. Penthrox sprays trended toward faster pain relief and potentially lower risk of vomiting and nausea. The stable heart rate observed with penthrox may be advantageous in certain clinical scenarios. Consideration of factors such as onset of action, adverse effects, and patient preferences may guide the choice between these analgesics.

Keywords:, Acute Pain; Emergency Department; Methoxyflurane; Morphine; Penthrox

1. Introduction

Efficient pain control is crucial for patient care, especially in urgent situations like emergency departments (EDs). Insufficient pain management can result in negative physiological and psychological effects, longer hospital stays, and reduced quality of life (1). Consequently, several pharmacological treatments have been used to relieve pain, each with advantages and disadvantages (2).

Penthrox (methoxyflurane) inhalation and intravenous morphine are two commonly used analgesics in EDs (3). Penthrox is a volatile anesthetic agent that has been increasingly utilized for pain relief due to its rapid onset of action, ease of administration, and self-titration capabilities (4).

It is administered via a hand-held inhaler, allowing patients to self-titrate their dosage according to their individual pain levels. This approach offers a degree of control and personalization in pain management. Furthermore, the inhalational route of administration bypasses the need for intravenous access, which can be advantageous in certain clinical scenarios (5). Penthrox has been shown to provide effective analgesia in various acute pain conditions, such as trauma, renal colic, and musculoskeletal injuries (4).

On the other hand, morphine, an opioid analgesic, has been a longstanding choice for pain management in EDs. It offers potent analgesia and is widely used to manage moderate to severe pain (6). However, morphine is associated with potential side effects, including nausea, vomiting, respiratory depression, and sedation, which may limit its use in certain patient populations (7).

While both penthrox and morphine have been extensively studied and utilized in pain management, there is ongoing debate and research surrounding their comparative efficacy, safety profiles, and patient satisfaction. Factors such as the specific patient population, type and severity of pain, and clinical setting may influence these analgesics' relative advantages and limitations. Several clinical trial studies on limb fracture pain management highlighted the advantages of non-opioid analgesics in pain management (8-10). But to date, no clinical trial compared penthrox versus morphine on limb fracture pain management.

This study aimed to contribute to the existing body of knowledge by investigating the analgesic efficacy, adverse effects, and patient satisfaction associated with using penthrox spray and intravenous morphine to relieve closed limb fracture acute pain in the emergency department setting. By comparing these two widely used analgesics, the findings may provide valuable insights to guide clinical practice and optimize pain management strategies in acute care environments.

2. Methods

2.1.Study design and participants

This prospective, double-blinded, randomized controlled trial was conducted from 2023-04-21 to 2024-04-21 in the ED of Ayatollah Kashani Hospital in Isfahan, Iran. Patients aged 20-55 years presenting with acute traumatic closed limb fracture pain were included. Exclusion criteria included known allergy or contraindications to penthrox or morphine, significant respiratory or

cardiovascular disease, head injury, impaired cognitive function, pregnancy, and severe pain requiring immediate intervention.

2.2.Ethical Considerations

The study protocol was approved by the Isfahan Ethics Review Board (IR.MUI.MED.REC.1399.014) and the Iranian Registry for Clinical Trials (IRCT20230302057587N1). Written informed consent was obtained from all participants prior to enrollment. The study adhered to ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice guidelines.

2.3.Randomization and blinding

Eligible participants were randomly assigned in a 1:1 ratio to receive either penthrox inhalation or intravenous morphine using a balanced block randomization method with a block size of 4. The randomization sequence was computer-generated, and allocation concealment was ensured using sequentially numbered, opaque, sealed envelopes. The study medications were prepared by an independent pharmacist not involved in patient care or data collection. Both participants and ED personnel involved in patient assessment and data collection were blinded to the treatment allocation.

2.4. Interventions

Methoxyflurane, a fluorinated hydrocarbon inhalation agent available in 3 cc ampoules, is used in the pentorax inhaler (manufactured by MDI, Melbourne, Australia). Three ccs of methoxyflurane are poured into each spray. If the diluting valve is open, the spray emits 0.2-0.4%; if closed, it releases 0.5-0.7% methoxyflurane. It also has an oxygen port. To administer methoxyflurane, a pentorax inhaler with activated charcoal was used. The patient was asked to cover the diluting valve with his finger, put the nebulizer mouthpiece in his mouth, and exhale through the nose. A maximum of 1 vial (equivalent to 3 cc) was prescribed to each patient without supplemental oxygen. Each trained nurse care provider administers methoxyflurane to two patients in their shift. Each inhaler is used only for one patient. Vital signs, including pulse rate, heart rate, oxygen saturation percentage, and body temperature, are recorded with each inhalation of penthrox. All patients undergo cardiac monitoring, and if changes are made, they are recorded with an electrocardiogram. Any side effects caused by the drug, including hypotension, bradycardia, convulsions, decreased level of consciousness, itching, skin rash, and respiratory depression, are recorded. Every ten minutes, if the patient's pain level is 5/10, intravenous fentanyl with a dose of

1 microgram per kilogram of weight will be prescribed as a rescue dose. At the end of the meeting, the rescue dose of fentanyl will be recorded.

2.5. Control group

Intravenous morphine at a dose of 0.1 mg per kilogram of weight (manufactured by Daro Pakhsh Co., Tehran, Iran) was infused. Every time intravenous morphine was used, the vital signs were recorded, including pulse rate, heart rate, degree of temperature, and percentage of oxygen saturation. All patients undergo cardiac monitoring, and if changes are made, they are recorded with an electrocardiogram. Any side effects caused by the drug, including hypotension, bradycardia, convulsions, decreased level of consciousness, itching, skin rash, and respiratory depression, are recorded. Every ten minutes, if the patient's pain level is 5/10, intravenous fentanyl with a dose of 1 microgram per kilogram of weight will be prescribed as a rescue dose, and at the end of the meeting, the rescue dose of fentanyl will be recorded.

2.6. Patient satisfaction assessment

Patient satisfaction with the pain management intervention was evaluated using the validated Persian version of the patient satisfaction questionnaire (PSQ). The Persian PSQ demonstrated good construct validity. It also exhibited high internal consistency reliability, with a Cronbach's alpha of 0.92 for the total scale (11). The PSQ required patients to rate their satisfaction on a 5-point Likert scale across aspects like effectiveness, side effects, and convenience. Patients completed the Persian PSQ after the 60-minute observation period following study medication administration.

2.7. Outcome measures

The primary outcome was pain intensity, assessed using the visual analog scale (VAS), which ranged from 0 (no pain) to 10 (worst imaginable pain). Pain scores were recorded 10, 20, 30, and 60 minutes after treatment initiation.

Secondary outcomes included adverse effects (nausea, vomiting, respiratory depression), vital signs (blood pressure, heart rate, oxygen saturation), and patient satisfaction scores measured on a 5-point Likert scale.

2.8.Sample size estimation

According to a similar study (12), that compared the analgesic effect of intravenous morphine and inhaled methoxyflurane for pain relief in operationally injured patients. The average final pain

score of the patient in the group receiving inhaled methoxyflurane was 15.1 ± 9.3, and in the morphine group, it was 0.57 ± 29.1. So, d is equal to 2.61. 80% power and 10% difference coefficient were considered. (Two-sided alpha and β of 0.05 and 0.2, receptively).

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 (SD_1^2 + SD_2^2)}{d^2}$$

D= 2.61

$Z_{1-\alpha/2}$= 1.96

$Z_{1-\beta}$= 0.84

N= 25

2.9. Statistical analysis

Continuous variables were reported as mean±SE, and Categorical variables were described as numbers (percentage). Shapiro-Wilk test was used for the normality test. Two independent t-tests were used to compare between-groups means. Pearson's chi-squared test was used to compare proportions between groups. The two-way repeated measure ANOVA was done to compare the changes in the study outcomes (pain, blood pressure (systolic and diastolic), and heart rate) at different time points after treatment. The statistical significance level was determined as $P<0.05$. All analyses were carried out in SPSS version 20.0.

3. Results

In this interventional study, 50 patients were evaluated (25 patients in the penthrox spray group and 25 patients in the morphine group). There was no significant difference between the penthrox spray and morphine group in gender ($P>0.05$) (Table 1).

The frequency of vomiting and nausea was lower in the penthrox spray group than in the morphine group (24% vs. 40%), but this difference was not statistically significant (P=0.225) (Table 1). There was no considerable difference between penthrox spray and morphine groups concerning the mean of oxygen saturation (SpO2) (91.56±0.635 vs. 91.96 0.740; P=0.684), and the mean of patient's satisfaction score (69.40±3.52 vs. 70±2.71; P=0.893) over time after treatment (Table1).

Table 2 shows a significant improvement in pain relief in both groups during the follow-up time after treatment (P<0.001). The effect of time and group interaction on pain relief was not statistically significant. It means the improvement in pain relief in the penthrox spray and morphine groups was similar, though the pain decreased almost sharply in the penthrox spray (Figure 1). The difference between groups was not statistically significant (P>0.05) (Table 2). Results indicate that the levels of systolic blood pressure (SBP) and diastolic blood pressure (DBP) over the studied time after treatment were decreased (P for time <0.001) independent of the type of treatment groups (P for group >0.05) (Table2). There was no significant interaction effect of time and group on SBP and DBP (P for group >0.05) (Figures 2 and3).

The heart rate (HR) did not change considerably among patients who were on penthrox spray over time after treatment (P>0.05). Still, in the morphine group, a significant reduction in HR was observed (P<0.001) (Table 2). The interaction effect of time and group on HR change was statistically significant (P<0.001) (Figure 4). Our results indicate no significant between-group differences in HR (P>0.05) (Table 2).

4. Discussion

The key findings of this study indicate that both penthrox (methoxyflurane) spray and intravenous morphine were effective in providing significant pain relief for acute limb fracture pain in the emergency department setting. However, penthrox spray demonstrated a trend toward more rapid pain reduction, although the difference was not statistically significant compared to morphine.

These findings are consistent with previous studies that have compared the analgesic efficacy of penthrox and morphine in various acute pain conditions. A subgroup analysis of the MEDITA trial, which evaluated severe trauma pain, reported comparable analgesic efficacy between inhaled methoxyflurane and intravenous morphine (3). Similarly, the PenASAP study, which focused on trauma-related pain in emergency departments, found no significant difference in pain relief between inhaled methoxyflurane and placebo (13).

The rapid onset of action and self-titration capabilities of penthrox, as observed in this study, align with the findings of a similar study on methoxyflurane versus standard analgesic treatment for acute trauma pain in the emergency setting, which reported that inhaled methoxyflurane provided faster pain relief compared to standard analgesic treatment in the emergency setting (5). The ability

to self-titrate the dose may contribute to the more rapid pain reduction seen with penthrox, as patients can adjust the dosage based on their pain levels.

Regarding adverse effects, the lower frequency of vomiting and nausea observed with penthrox spray in this study, although not statistically significant, is consistent with the favorable side effect profile of penthrox reported in previous studies (4,14). The non-opioid nature of penthrox may contribute to its reduced risk of opioid-related adverse effects, such as nausea and vomiting.

Interestingly, while both treatment groups experienced a decrease in blood pressure over time, likely due to the analgesic effects, the heart rate remained relatively stable in the penthrox spray group but decreased significantly in the morphine group. This finding is consistent with the known effects of opioids on heart rate and respiratory depression (6,7). The lack of significant changes in heart rate with penthrox may be advantageous, particularly in certain patient populations or clinical scenarios where opioid-related respiratory depression is a concern.

The comparable patient satisfaction scores between the two treatment groups in this study are in line with previous research reporting high patient satisfaction with penthrox inhalation (5,13). The self-administration aspect of penthrox may increase patient satisfaction by providing control over pain management.

It is important to note that this study focused on a specific population (acute limb fracture pain in the emergency department), and the results may not be generalizable to other pain conditions or settings. Additionally, larger studies with diverse patient populations are warranted to further investigate the relative advantages and limitations of penthrox and morphine in pain management.

5. Conclusion

This study adds to the growing body of evidence supporting the use of penthrox (methoxyflurane) spray as an effective analgesic option for acute pain management in the emergency department setting. While its analgesic efficacy was comparable to intravenous morphine, penthrox demonstrated a trend toward more rapid pain relief and a potentially favorable side effect profile. Consideration of factors such as the onset of action, adverse effects, patient preferences, and clinical circumstances may guide the choice between penthrox and morphine in this setting.

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Table 1 Comparison of gender and treatment complications between groups

Characteristics		Group		P-value
		Penthrox spray (n=25)	Morphine (n=25)	
Gender	Female	15 (60%)	11 (44%)	0.258[a]
	Male	10 (40%)	14 (56%)	
Vomiting and nausea		6 (24%)	10 (40%)	0.225[a]
Oxygen saturation (SpO2)		91.56±0.635	91.96±0.740	0.684[b]
Satisfaction		69.40±3.52	70±2.71	0.893[b]

Data are shown as frequency (%) or mean ± SE. [a]:P-values are resulted from chi-squared test. [b]:P-values are resulted from two-independent t-test

Table2 Comparison the change of the study outcomes in penthrox spray and morphine groups over time after treatment

Variables	Group	Time after receiving the drug				P-value		
		10 min	20 min	30 min	60 min	Time	Group	Time × group
Pain	**Penthrox spray**	7.56±0.25	6.68±0.23	6.24±0.27	6.00±0.28	<0.001*	0.743	0.231
	Morphine	7.68±0.24	6.60±0.19	6.24±0.29	6.40±0.31	<0.001*		
P-value[a] (Between group comparisons)		0.733	0.807	> 0.999	0.322			
SBP	**Penthrox spray**	133.8±2.66	126.0±2.80	124.2±2.44	123.6±2.47	<0.001*	0.140	0.103
	Morphine	128.0±2.65	119.2±2.70	117.8±2.45	123.4±2.39	<0.001*		
P-value[a] (Between group comparisons)		0.130	0.092	0.070	0.955			
DBP	**Penthrox spray**	78.6±1.75	77.0±1.89	76.0±1.80	74.6 ± 1.75	<0.001*	0.431	0.385
	Morphine	77.6±1.76	73.8±1.62	73.6±1.40	75.4 ± 1.32	<0.001*		
P-value[a] (Between group comparisons)		0.688	0.205	0.298	0.717			
HR	**Penthrox spray**	84.4±2.30	84.2±2.39	85.2±2.35	86.0±2.31	0.814	0.736	<0.001*
	Morphine	90.2±1.81	84.0±1.71	81.2±1.27	81.2±1.51	<0.001*		
P-value[a] (Between group comparisons)		0.053	0.946	0.141	0.088			

*p-value<0.05 was considered as statistically significant. P-values are resulted from repeated measure ANOVA. [a]: P-values are resulted by bonferroni correction for multiple comparisons. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate

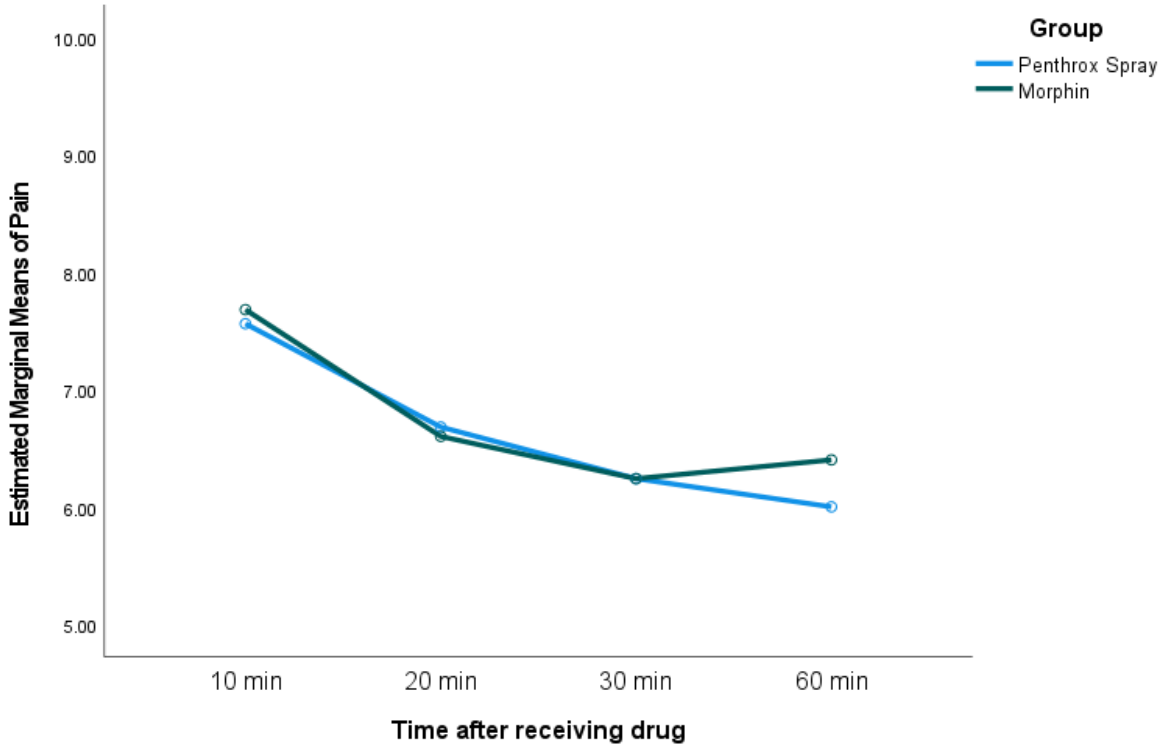

Figure 1 Trends of change in pain score in penthrox spray and morphine groups over time after treatment

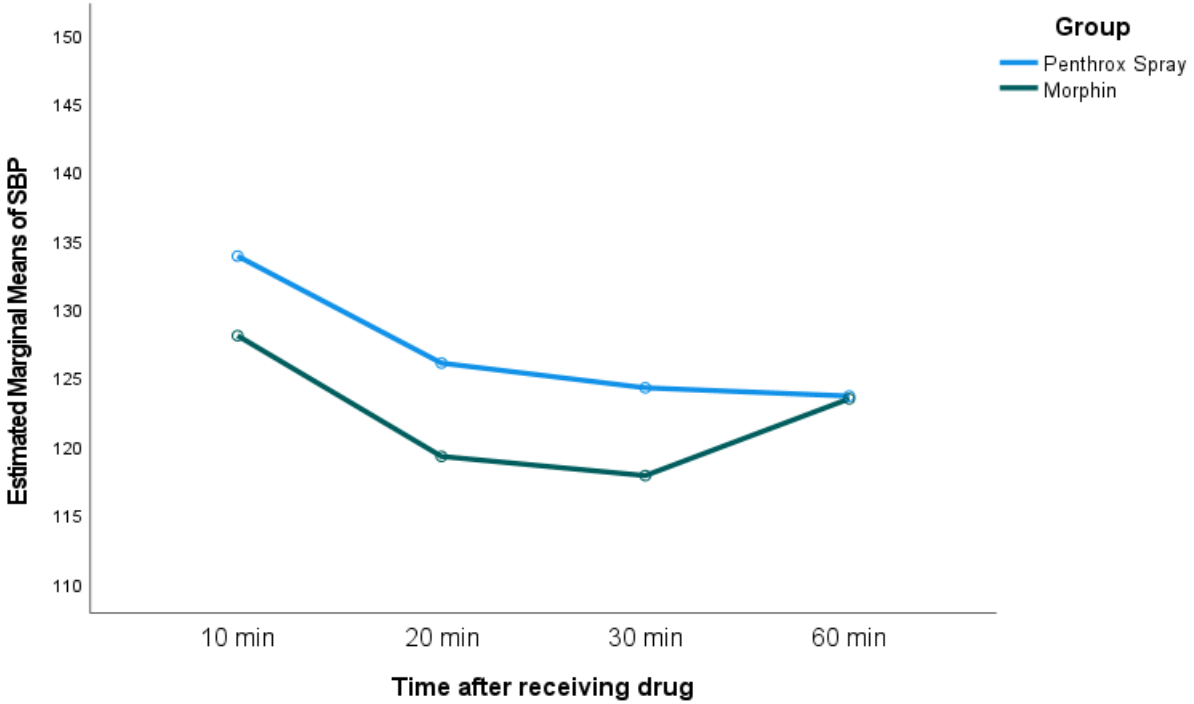

Figure 2 Trends of change in systolic blood pressure (SBP) in penthrox spray and morphine groups over time after treatment

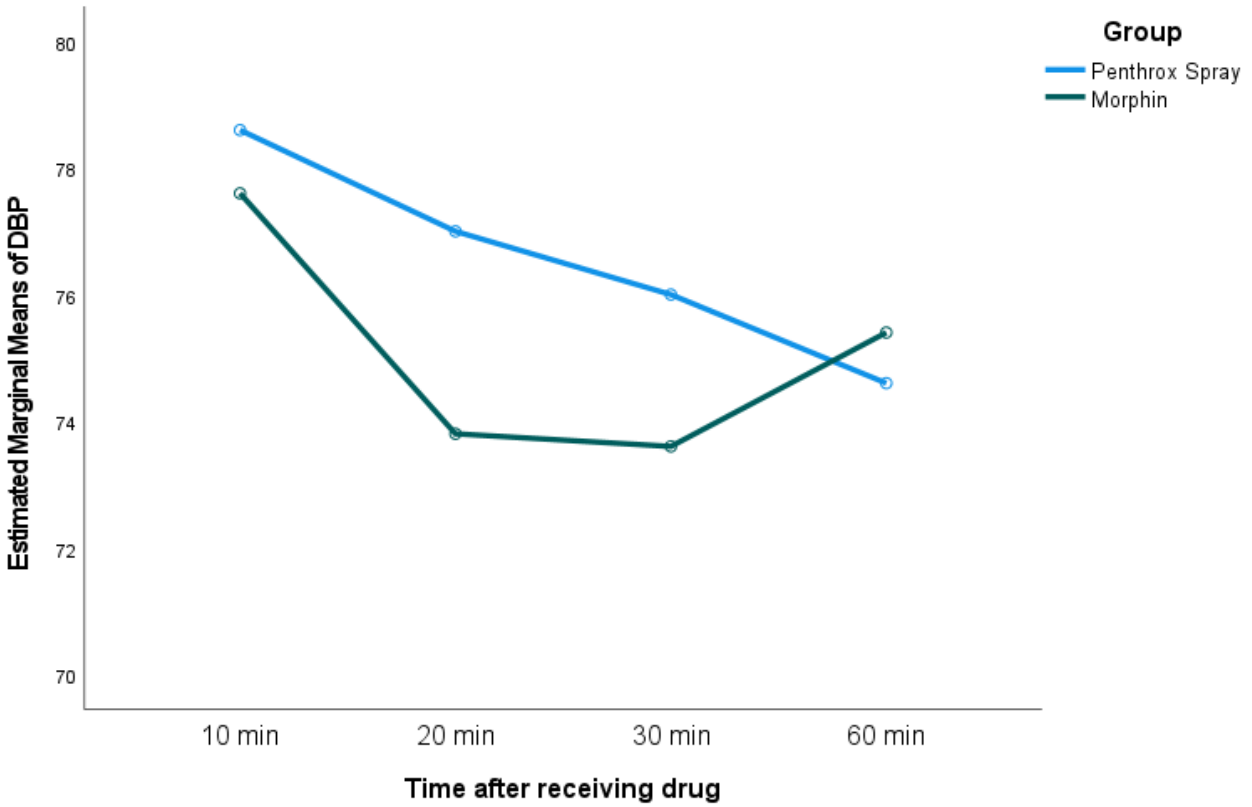

Figure 3 Trends of change in diastolic blood pressure (DBP) in penthrox spray and morphine groups over time after treatment

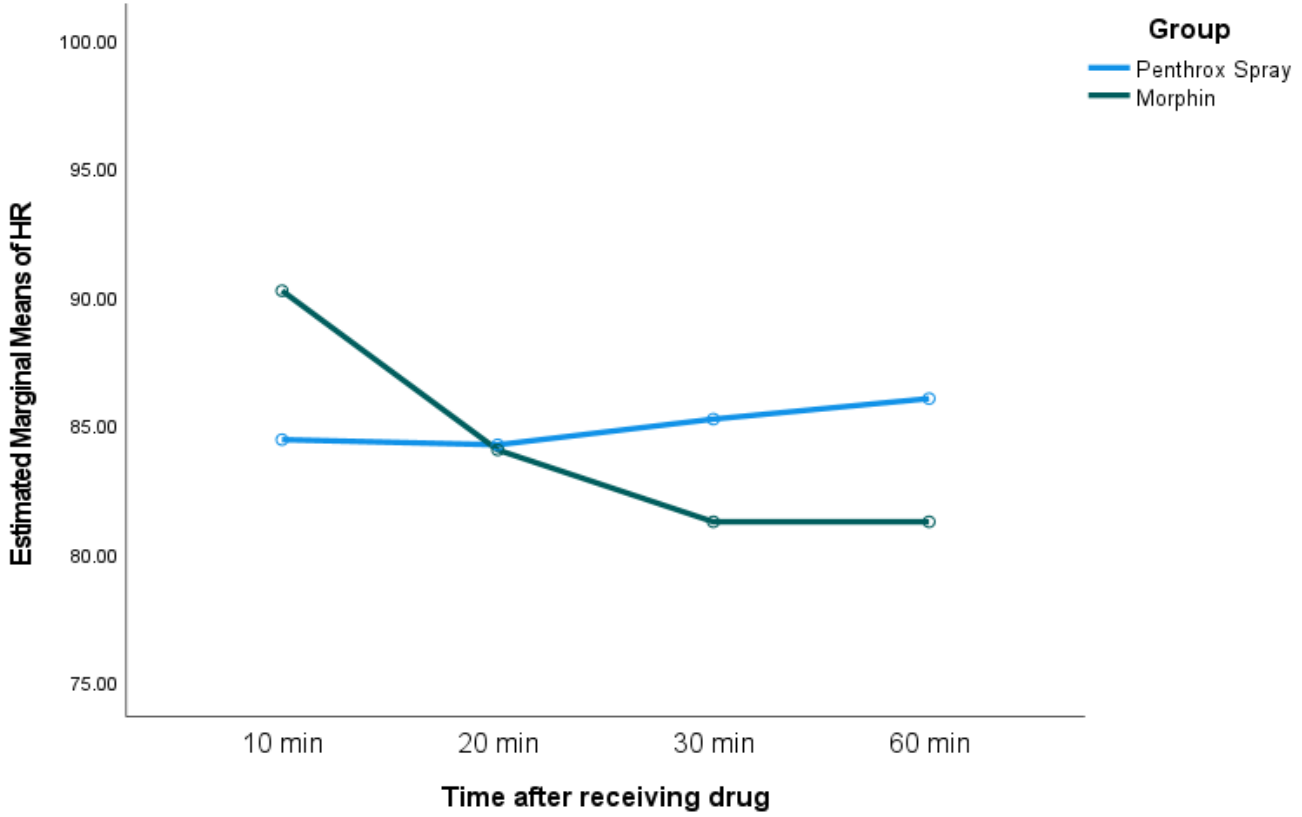

Figure 4 Trends of change in heart rate (HR) in penthrox spray and morphine groups over time after treatment