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ORIGINAL RESEARCH

The Effect of Intravenous Metoclopramide on Gastric Emptying of Opium-dependent Patients based on Ultrasonographic Criteria; a Case-control Study

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Abstract: **Introduction:** Induction of anesthesia for emergency procedures, without prior gastric preparation and incomplete fasting, is associated with the risk of reflux of stomach contents and aspiration. This study aimed to evaluate the effect of intravenous (IV) metoclopramide administration on gastric emptying in opium users, candidate for procedural sedation and analgesia (PSA). **Methods:** In the present case-control study, opium-dependent (case) and non-dependent (control) patients in need of PSA were administered with 10 mg IV metoclopramide after undergoing gastric ultrasonography for determination of its area and contents. Then, 30 minutes after the administration of metoclopramide, the area and contents of the stomach were measured again and compared with the measures obtained before the intervention. **Results:** 135 patients were evaluated in three groups of 45, including the case, control, and placebo groups. The three groups were similar regarding mean age ($p = 0.068$), sex ($p = 0.067$), weight ($p = 0.596$), height ($p = 0.671$), body mass index (BMI) ($p = 0.877$), duration of fasting ($p = 0.596$), and type of gastric contents ($p = 0.124$). Mean antral cross-sectional area (CSA) of the study participants in the case, control, and placebo groups before the administration of the drug was 8.49 ± 1.40, 8.31 ± 2.56, and 6.56 ± 1.72 cm^2, respectively. Mean gastric area in the case ($p < 0.001$) and control ($p < 0.001$) groups had significantly decreased after the intervention. Mean antral gastric grade of gastric contents in the case ($p < 0.001$) and control ($p < 0.001$) groups had significantly decreased after the intervention. **Conclusion:** It seems that metoclopramide administration in opium users in need of PSA leads to a significant decrease in mean gastric area and increases gastric emptying.

Keywords: Deep Sedation; Emergency Treatment; Anesthesia; Respiratory Aspiration; Ultrasonography; Clinical Trial

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1. Introduction

Incomplete fasting at the time of anesthesia induction or administration of sedative-hypnotic drugs, which are associated with loss of protective reflexes such as cough and swallowing, is associated with the risk of reflux of stomach contents and aspiration. Therefore, in contrast to candidate patients for elective surgery, in emergency situations, when delaying the intended procedure or surgery for increasing fast-

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ing time is not possible, there is a higher risk of pulmonary aspiration (1-3). Considering that this event is a very serious and dangerous side effect of anesthesia induction and can be associated with substantial morbidity and mortality, taking proper measures for its prevention is essential (4, 5).

Conditions such as pregnancy, drug abuse, diabetes, and renal failure, which are associated with decrease in gastric movement, as well as conditions leading to increase in intraabdominal pressure, including obesity, ascites, and abdominal tumors are among known risk factors for aspiration during anesthesia induction. Gastric volume and acidity of its contents are among other factors that are known to increase the probability of aspiration and its severity and many interventions have been tested with the aim of affecting these variables (5).

Various medications, like antacids, prokinetics, antiemetics, and anticholinergics or a combination of them have been used for decreasing the risk of aspiration before induction of anesthesia in emergency situations. Additionally, measures such as inserting nasogastric (NG) tube, and gastric emptying, placing the head in a downward 15- 20° angle and Sellick maneuver are among the non-drug interventions used in this regard (6). To evaluate the efficacy of these interventions various methods have been introduced. In recent years, ultrasonography has been used for qualitative and quantitative evaluation of gastric contents as well as assessing the effect of different interventions, some of which were mentioned (7).

The effect of prescribing metoclopramide on gastric motility based on ultrasonographic criteria has been evaluated in different studies (7-11). However, its efficiency in patients with drug abuse has rarely been assessed. Meanwhile, considering the effect of drugs on gastrointestinal tract movements, there is more concern regarding decrease in gastrointestinal tract movements and lowered response to prescription of prokinetic drugs, including metoclopramide, in these patients (12-14). Considering the afore-mentioned points, the present study was designed and performed with the aim of evaluating the effect of IV metoclopramide on gastric emptying in patients with drug abuse, who were candidates for undergoing procedural sedation and analgesia (PSA).

2. Methods

2.1. Study design and settings

The present case-control study was performed on opium-dependent (case) and non-dependent (control) patients in need of PSA in the emergency department of Imam Hossein Hospital, Tehran, Iran, between 2021 and 2022. After undergoing gastric ultrasonography for determination of its area and contents, the patients were divided into 3 groups of case (opium-dependent patients who received 10 mg IV metoclopramide), control (non-opium-dependent patients who received 10 mg IV metoclopramide) and placebo (non-opium-dependent patients who received 2cc distilled water). Then, 30 minutes later, the area and quality of gastric contents were measured and compared with measures before the intervention. The proposal of this study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1399.154). In addition, the protocol of this study was registered on the Iranian registry of clinical trials under the code IRCT20210406050864N1. After providing explanations regarding the protocol of the study, informed written consent was obtained from the patients for participation in the present study. No additional costs were inflicted on the patients or the health care system as a result of this study and the researchers adhered to the confidentiality of patients' data and ethical principles in biomedical research based on the declaration of Helsinki.

2.2. Study population

The study population consisted of patients with a history of daily drug abuse for more than 6 weeks, using any type of opioid (derivatives of poppies or opium), who were candidates for PSA and had eaten solid food less than 8 hours before or drank liquids less than 2 hours before. Patients who were unable to assume the proper position for ultrasonography, those with body mass index (BMI) over 35, obstruction in the gastrointestinal tract, diabetes, history of gastric surgery, hiatal hernia, those who had used medications that change gastrointestinal tract movements in the previous 72 hours, and those with history of allergic or extrapyramidal reactions after receiving metoclopramide were excluded from the study. The control and placebo groups were selected from non-dependent individuals with a similar situation.

2.3. Intervention

All of the patients included in the study were under full cardiopulmonary monitoring and their vital signs were recorded. Then the patients were divided into 3 groups of case, control, and placebo. All the patients underwent ultrasonography by a radiologist in supine and right lateral positions and their gastric area and its contents' qualities were evaluated and registered.

The control group included non-dependent individuals and the case group included dependent patients, all of whom received 10 mg (2cc) IV metoclopramide. The placebo group consisted of non-dependent patients who received 2cc distilled water instead of metoclopramide. The onset of action of IV metoclopramide is 1-3 minutes and it reaches the peak of action in 15-20 minutes. Therefore, the second measurement was done 30 minutes after the prescription of the drug or placebo. The person prescribing the drug was aware of the groupings, but the patients and the radiologist in charge of performing the ultrasonography were blind to the groupings.

Table 1: Comparing the baseline characteristics of participants between the three study groups

Variable	Placebo (n = 45)	Control (n = 45)	Case (n = 45)	P-value
Age (year)				
Mean ± SD	50.8 ± 15.9	43.1 ± 18.0	49.3 ±15.8	0.068
Sex				
Male	25 (55.6)	16 (35.6)	26 (57.8)	0.067
Female	20 (44.4)	29 (64.4)	19 (42.2)	
Weight (Kg)				
Mean ± SD	69.5 ± 14.7	66.7 ± 9.3	67.2 ±14.5	0.596
Height (m)				
Mean ± SD	1.7 ± 0.05	1.6 ± 0.07	1.7 ± 0.04	0.671
BMI				
Mean ± SD	23.7 ± 3.9	24.3 ± 4.4	23.9 ± 3.8	0.877
Fasting time (hour)				
Mean ± SD	3.3 ± 1.4	3.6 ± 2.1	3.6 ± 1.4	0.596
Type of food consumed				
Liquid	32 (71.1)	39 (86.6)	36 (80.0)	0.124
Solid	13 (28.9)	6 (13.4)	9 (20.0)	

Data are presented as mean ± standard deviation (SD) or frequency (%). BMI: Body Mass Index.
The control group included non- opium dependent individuals and the case group included opium dependent patients, all of whom received 10 mg (2cc) IV metoclopramide. The placebo group consisted of non- opium dependent patients who received 2cc distilled water instead of metoclopramide.

Table 2: Comparing gastric ultrasonography findings in the three study groups before and after the intervention

Group	Before intervention	After intervention	p-value
Antral cross-sectional area (cm^2)			
Case	8.49 ± 4.34	4.34 ± 1.52	< 0.001
Control	8.31 ± 2.56	4.44 ± 1.37	< 0.001
Placebo	6.59 ± 1.72	6.34 ± 1.92	0.140
Antral gastric grade			
Case	1.56 ± 0.50	0.76 ± 0.68	< 0.001
Control	1.60 ± 0.49	0.87 ± 0.66	< 0.001
Placebo	1.42 ± 0.50	1.33 ± 0.94	0.486

Data are presented as mean ± standard deviation (SD).

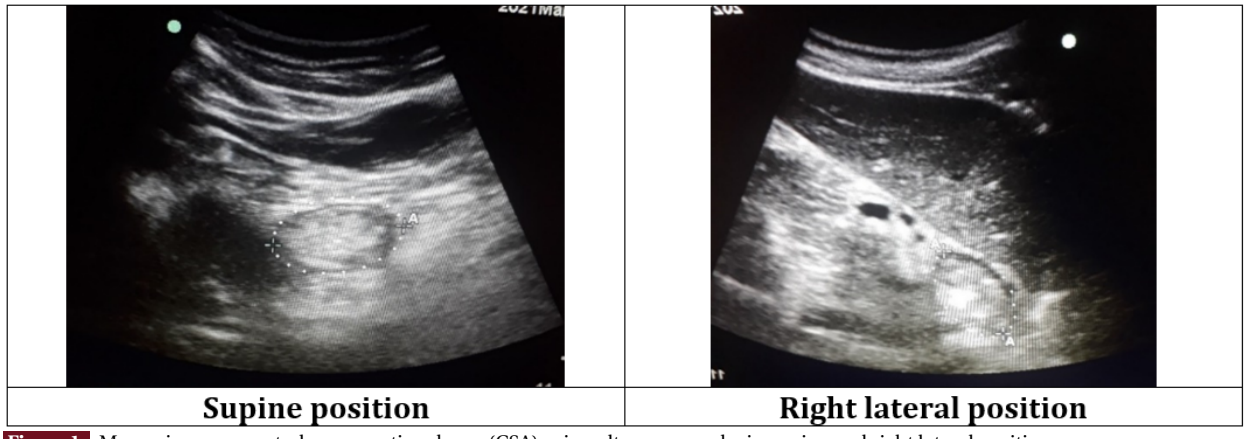

Figure 1: Measuring mean antral cross-sectional area (CSA) using ultrasonography in supine and right lateral positions.

2.4. Ultrasonographic evaluation

Patients in all three groups underwent ultrasonography in supine and right lateral positions by a radiologist. Mean antral cross-sectional area (CSA) was measured and antral gastric grade (AGG) was also evaluated.
- Mean antral cross-sectional area (CSA)

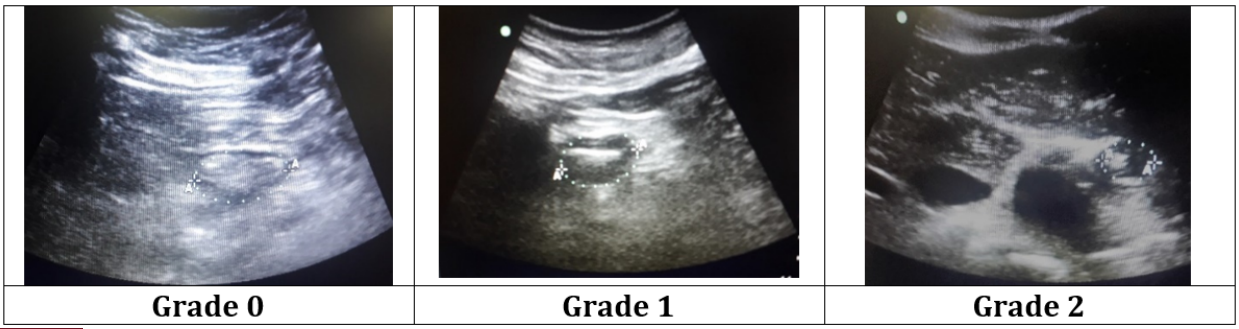

Figure 2: Evaluating antral gastric grade (AGG) using gastric ultrasonography findings.

Table 3: Changes in antral gastric grade (AGG) of patients after the intervention based on group

Variable	Placebo (n = 45)	Control (n = 45)	Case (n = 45)	P value
1 grade increase	11 (24.4)	2 (4.4)	1 (2.2)	< 0.001
No change	22 (48.9)	15 (33.3)	14 (31.1)	
1 grade decrease	9 (20.0)	21 (46.6)	23 (51.1)	
2 grades decrease	3 (6.7)	7 (15.6)	7 (15.6)	

Data are presented as frequency (%). The control group included non- opium dependent individuals and the case group included opium dependent patients, all of whom received 10 mg (2cc) IV metoclopramide. The placebo group consisted of non- opium dependent patients who received 2cc distilled water instead of metoclopramide.

In all patients, CSA was determined by an experienced radiologist using sonosite2 device and rC60xi 2-5 MHz probe in supine and right lateral positions and in sagittal view of antrum, based on anatomical landmarks of the stomach. CSA and antral volume were calculated. Measurement of CSA was done using measures of vertical thickness in longitudinal d1 and posterior d2 planes in centimeters and from the serosa of one side to the serosa of the other side. For measuring the cross-section of the antrum, the following formula was used: [CSA = 3.14 (d1×d2) ×0.4]. Based on previous studies, the cut-off for determining the volume of the stomach was considered to be > 1.5cc, and for determining the presence of solid or liquid contents, it was considered to be 3.01 cm^2 (figure 1).

- Evaluating antral gastric grade (AGG)

Qualitative evaluations of AGG for determining the presence or absence of solid and liquid contents were performed in 3 grades (0, 1, 2) as follows (figure 2): Grade 0: absence of contents; Grade 1: presence of evidence of contents only in right lateral position; and grade 2: presence of evidence of contents in both supine and right lateral positions. The mathematical model used for calculating the volume of contents and determining antral volume in this study was: VOLUME=27+(14.6*RL CSA)-(1.28*age)

2.5. Statistical analysis

Based on the study by Sayyadi et al. (8), the number of samples in each group was determined to be 45 and sampling was continued until reaching the intended sample size in all 3 groups. To analyze the data, SPSS software version 26 was used and findings were reported as mean ± standard deviation or frequency (%). To evaluate the normality of data, Kolmogorov–Smirnov test was applied. To compare the quantitative variables in the 2 groups, independent samples t-test or one-way analysis of variance, and for categorized variables, chi square and Fisher's exact test, and for normal quantitative variables in each group (before and after intervention), dependent t-test or paired t-test was used. To compare the gradings of the patient's stomach before and after the intervention, Mantel–Haenszel test was applied. In all tests, the significance level was considered to be less than 0.05.

3. Results

3.1. Baseline characteristics of the studied patients

In this study, 135 patients were studied in 3 groups of 45 including case, control, and placebo groups. The baseline characteristics of the patients has been compared between the 3 study groups in table 1.

The 3 groups were similar regarding mean age (p = 0.068), sex (p = 0.067), weight (p = 0.596), height (p = 0.671), body mass index (BMI) (p = 0.877), duration of fasting (p = 0.596), and type of food consumed instead of type of gastric content (p = 0.124). The participants in the case group were opium-dependent, and would usually use it once a day, and most of them had a history of using opium for more than 7 years; their most common route of consumption was the oral route.

3.2. Ultrasonographic findings

Mean CSA

Mean CSA of the patients participating in the study in case, control, and placebo groups before the administration of the drug was 8.49 ± 1.40, 8.31 ± 2.56, and 6.56 ± 1.72 cm^2, respectively. Table 2 compares the mean CSA before and after the administration of the drug in the 3 studied groups. In contrast to the placebo group, mean CSA had significantly decreased in the case ($p < 0.001$) and control ($p < 0.001$) groups after the intervention. Mean CSA of the patients after the administration of the drug in the case group was lower that the control group, and in the control group it was less than the placebo group ($p < 0.001$).

Evaluating AGG

Table 2 compares the mean qualitative score of gastric contents in the 3 studied groups before and after the intervention. In contrast to the placebo group, mean AGG had significantly decreased in the case ($p < 0.001$) and control ($p < 0.001$) groups after the intervention. Mean AGG of the patients after the administration of the drug in the case group was lower that the control group, and in the control group it was less than the placebo group ($p < 0.001$). Table 3 compares AGGs of the 3 studied groups after the intervention.

4. Discussion

Based on the results of the present study and considering the ultrasonographic findings, it seems that prescription of metoclopramide in opium users in need of PSA can significantly decrease mean CSA and increase gastric emptying.

The effect of metoclopramide on acceleration of gastric emptying and decreasing gastric volume in patients in need of PSA, who have not had enough fasting time, has been confirmed in previous studies using different measuring methods, including use of ultrasonographic indices. Yet, the effectiveness of this intervention in opium users has been a matter of question.

Most opiate agonists, including morphine, lead to less motility in the gastrointestinal tract through stimulation of mu receptors.

Decrease in gastric motility, increase in tonicity of the sphincter, change in motility patterns, and peristaltism are commonly seen following use of opiates. In fact, these compounds lead to increase in contraction of gastric antrum and pylorus and the upper parts of the duodenum, as well as decrease in tonicity in the relaxed state of the gastric muscles (12-14). On the other hand, metoclopramide is an antagonist of D2 receptor, which can inhibit the effects of the endogenous dopamine transmitter on the gastrointestinal tract. Endogenous dopamine leads to decreased motility of the stomach and proximal small intestine by inhibiting the release of acetylcholine, and its effects are neutralized with the injection of metoclopramide (15).

In a study by Sayyadi et al., qualitative and quantitative ultrasonographic evaluation of the stomach before surgery was done in candidate patients in need of emergency surgery, who received 10 mg metoclopramide. In that study, drug-dependent patients and those using opiates were excluded from the study. The results of that study showed that although AGG and CSA of the 2 groups were not significantly different after intervention, mean decrease in CSA in the metoclopramide group was higher than the control group, and the decrease observed in AGG after the intervention in the metoclopramide group was higher than the control group (8). Comparing the results of the present study with that study can lead to the hypothesis that metoclopramide has even higher effectiveness in opium users; as in the present study, those in the case group showed a significant decrease in CSA and AGG compared to control and placebo groups.

In the systematic review by Priya Vijayvargiya et al. performed in 2019, there were 899 included articles, in 22 of which gastric emptying (GE) was studied, in 23 studies upper gastrointestinal tract symptoms (UGI Sx), and in 14 studies both GE and UGI Sx were evaluated. In 18 of the studies the effects of D2 receptor antagonists, including metoclopramide and domperidone, on both UGI Sx and GE were evaluated. In 6 studies, these medications were associated with 20 to 50% improvement in GE, in 4 studies no difference was found in GE, in 13 studies there was 20 to 50% improvement in UGI Sx, and in 2 studies no difference was found in UGI Sx. Of course, in these studies the patients were mainly divided into 2 groups of patients with gastroparesis (GP) and functional dyspepsia (FD), both of which showed similar improvement in GE. The study also showed that there was a significant correlation between improvement in GE and changes related to UGI Sx. In that study, opioid users were not evaluated and analyzed, and thus, in the conclusion of the study, it was suggested to perform further studies in similar populations using optimal tests and more proper evaluations for GE and UGI Sx (16). It seems that considering the risk of aspiration of gastric contents in emergency procedures without gastric preparation, using medications such as metoclopramide, which accelerate GE, can help reduce the probability of this event.

5. Limitation

The 3 studied groups were not homogenous regarding ultrasonographic indices before the intervention. Additionally, considering the absence of aspiration in all of the groups following induction of anesthesia, nothing can be said regarding the effect of this medication on the prevalence of aspiration. Also, there is the possibility of wrong and inaccurate self-declaration of opium users regarding the type of sub-

stance used and the last time using it and even the duration of fasting. Of course, we tried to minimize its probability by fully explaining the importance of receiving correct information.

6. Conclusion

It seems that metoclopramide administration in opium users in need of sedation for emergency procedures leads to significant decrease in ACS and increase in gastric emptying.

7. Declarations

7.1. Acknowledgments

Not applicable.

7.2. Conflict of interest

There is not to declare.

7.3. Funding and supports

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7.4. Authors' contribution

Study Design: AAD, SS; Data gathering: SJY, MR, EM; Analysis: SS; Interpretation of results: SS, AAD, SJY, MR; Drafting: SS, SJY; Critically revised: All authors.

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