Emergency. 2018; 6 (1): e24

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ORIGINAL RESEARCH

Lidocaine-Midazolam-Fentanyl Combination in Controlling Pain for Reduction of Anterior Shoulder Dislocation; a Randomized Clinical Trial

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Received: March 2018; Accepted: April 2018; Published online: 16 April 2018

Abstract: **Introduction:** Finding a fast-acting compound with minimal side-effects to induce a safe and efficient analgesia with short or medium duration of action is of great interest in the emergency department. The present study has been designed with the aim of comparing the effect of midazolam + fentanyl + lidocaine combination with midazolam + fentanyl + placebo in pain management of anterior shoulder dislocation reduction. **Methods:** The present two-arm parallel double-blind randomized controlled trial was performed on patients who presented to emergency department with anterior shoulder dislocation. Patients were randomly allocated to the 2 treatment groups of midazolam + fentanyl + placebo (double-drug group) and midazolam + fentanyl + intravenous (IV) lidocaine (triple-drug group). Then outcomes such as treatment success rate and side-effects following prescription of drugs were compared between the 2 groups. **Results:** 100 patients were included in the present study (50 patients in each group; mean age of the studied patients 27.3±8.9 years; 93.0% male). Using the double-drug regimen led to 35 (70%) cases of complete analgesia, while this rate in the triple-drug group was 41 (82%) cases (p=0.16). The calculated number needed to treat was 9 cases. This means that about one in every 9 patients in treatment arm will benefit from the treatment. The most important side-effects observed included dysrhythmia (1 patient in double drug and 1 patient in triple-drug group), apnea (2 patients in each group) and SPO_2<90% (2 patients in triple-drug group) (p=0.78). Number needed to harm was 25 cases. In other words, for each 25 patients treated with the triple drug regimen, 1 case of SPO_2<90% is observed. **Conclusion:** Findings of the present study showed that adding IV lidocaine to IV midazolam + fentanyl drug combination does not provide additional analgesia in sedation for anterior shoulder reduction.

Keywords: Conscious Sedation; Midazolam; Fentanyl; Lidocaine; Combined Modality Therapy

Cite this article as: Arhami Dolatabadi A, Mohammadian A, Kariman H. Lidocaine-Midazolam-Fentanyl Combination in Controlling Pain for Reduction of Anterior Shoulder Dislocation; a Randomized Clinical Trial. Emergency. 2018; 6(1): e24.

1. Introduction

One of the painful treatment interventions in need of procedural sedation and analgesia (PSA) is reduction of anterior shoulder dislocation and the statistics are indicative of its 1 - 1.7% prevalence in societies. The prevalence of these dislocations is higher among those in the age range of 20 – 30 years and affects men more than women (1). Using a proper analgesia method for controlling the pain of these patients during reduction is of great interest (2-4).

For this purpose, emergency medicine specialists are constantly seeking a fast-acting compound with minimal side-effects to induce a safe and efficient analgesia with short or medium duration of action in patients. The first suggested protocols of PSA were based on single-drug strategies, which had a strong emphasis on using opioids, propofol, midazolam, or fentanyl alone (5). However, for achieving lasting sedation in these single-drug protocols, a high dose of the mentioned drugs were required, which would result in serious side-effects such as depression of the central nervous system (CNS), apnea and dangerous hypoxia (6). Sometimes, there would be cases that even by using the highest dose allowed, proper sedation would not be induced (7, 8).

Therefore, to relieve this deficiency, the researchers turned to double-drug strategies so that they could not only reduce the

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dose of consumption for each drug, but also achieve double effectiveness by using drugs that have different mechanisms of action. Among these drug combinations are propofol + midazolam, propofol + fentanyl, midazolam + fentanyl, and etc. (9-17).

However, these double-drug protocols also have limitations, among which are lack of complete effectiveness and considerable treatment failures in patients (6). Therefore, it is possible that adding another drug to these treatment protocols improves the effectiveness and reduces the side-effects. Lidocaine is an anesthetic drug, intravenous (IV) prescription of which can control pains due to cancer, post-surgery pains, and neuropathic pains (18). Lidocaine reduces pain in patients by decreasing the sensitivity and activity of neurons that transmit pain in the CNS and decreasing post-synaptic receptors of N-methyl-d-aspartate (19-21). Although the effectiveness of local prescription of lidocaine (intra-articular) in controlling the pain following shoulder reduction has been confirmed in a meta-analysis (22), its analgesic effects following IV prescription is less known. On the other hand, no study has been done with the aim of assessing the additive or synergic effects of using lidocaine along with midazolam + fentanyl combination, yet. Therefore, the present study was designed with the aim of comparing the effect of IV midazolam + fentanyl + lidocaine combination with midazolam + fentanyl + placebo as PSA for reduction of anterior shoulder dislocation in emergency department.

2. Methods

2.1. Study design and setting

The present two-arm parallel double-blind randomized controlled trial was performed on patients who presented to the emergency departments of Imam Hossein, Loghmane Hakim, and Shohadaye Tajrish Hospitals, Tehran, Iran, with anterior shoulder dislocation throughout 2016. The study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences and patients were included after obtaining informed consent from the patient or their companion. The researchers adhered to the principles indicated in the declaration of Helsinki throughout the study. It should be noted that the protocol of the present study was registered on the Iranian Registry of Clinical Trials under the number IRCT2016101730353N1.

2.2. Participants

Patients with anterior shoulder dislocation candidate for reduction were included in the study. Patients with altered level of consciousness at the time of presentation, those who had a fracture in their shoulder joint along with shoulder dislocation (apart from Lesion Sachs-Hill), patients with a history of surgery on the same shoulder joint or fracture of the shoulder joint, history of seizure, those who had received analgesic drugs before presenting, patients with history of cardiac diseases and dysrhythmia, history of taking digoxin, and patients with a history of allergy to lidocaine, midazolam, or fentanyl were excluded from the study.

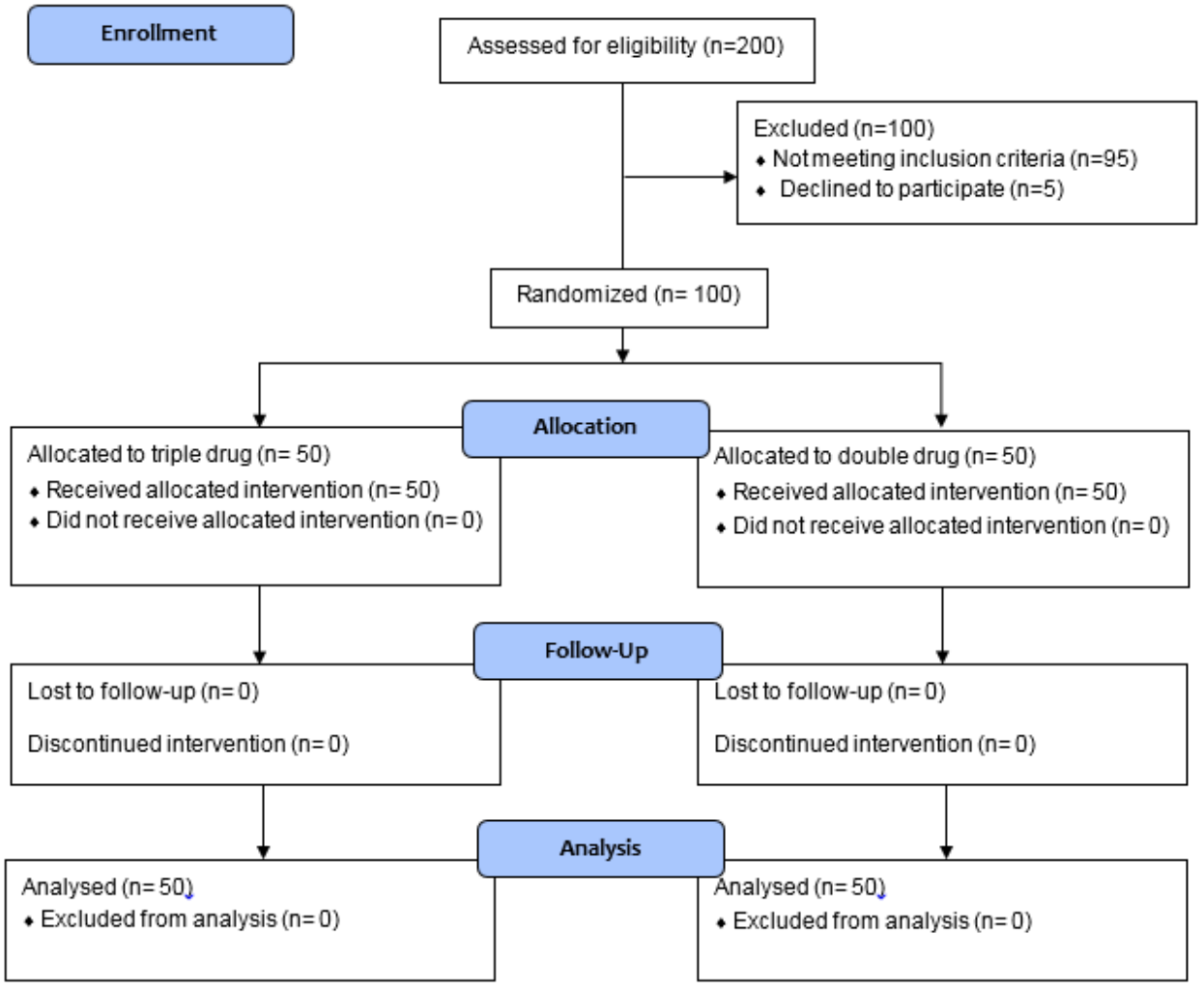
2.3. Interventions

Using a web-based program and via block randomization method (with block size of 5) without stratifying for baseline characteristics, the studied patients were allocated to the 2 treatment groups of IV midazolam + fentanyl + placebo (double-drug group) and IV midazolam + fentanyl + lidocaine (triple-drug group). Randomization was performed by a statistics expert who did not participate in the process of sampling and evaluating the outcome of the patients. Drugs were prepared as anonymous, colorless, and odorless packs by a senior researcher that played no part in the treatment process and follow-up of the patients and were given to a third year emergency medicine resident who was in charge of prescribing the drugs and evaluating the pain of the patients. Before starting therapeutic intervention, baseline characteristics of the patients including age, sex, weight, history of smoking, history of taking opium, history of alcohol consumption, and history of being affected with underlying illnesses would be recorded. Then, using Visual analog scale (VAS), pain of the patients was assessed and recorded. Before initiation of sedation, patients underwent hemodynamic evaluation and continuous pulse oximetry and 3 liters of nasal oxygen (their arterial oxygen saturation level would be maintained over 95%).

In case of no initial problem, 1 mg/kg lidocaine for patients in the triple-drug group and distilled water (as placebo) in the double-drug group were prescribed intravenously. Then both mentioned groups were given midazolam and fentanyl by injection in a titrated manner until the analgesia of the patient reached the score of 4 based on Ramsay sedation scale (23). If the patient did not reach the score of 4 despite receiving the maximum allowed dose of the drugs, the case was recorded as a case of failure in sedation and included in the analyses. After the patient reached the score of 4 based on Ramsey scale, the midazolam and fentanyl dose used was recorded for each patient and shoulder reduction was performed. After the patient became completely conscious, pain severity was evaluated and recorded based on VAS.

2.4. Evaluated outcomes

The primary outcome evaluated in this study was considered treatment success rate. For this purpose, complete analgesia (VAS=0) of the patient after reduction was defined as treatment success. The secondary outcome in the present study was considered the evaluation of side-effects following prescription of drugs including dysrhythmia, apnea, hypoxia,



flowchart 1: Flowchart of present study.

nausea and vomiting, and other side-effects. In the end, the final dose of fentanyl and midazolam used in the 2 studied groups was evaluated.

2.5. Statistical Analysis

Since in the beginning of the present research there was no similar study, a pilot study was performed on 10 patients to determine sample size based on it. Mean pain severity of patients after reduction in the pilot study was 1.33 ± 0.82 in the double-drug group and 0.82 ± 0.71 in the triple-drug group. Therefore, by considering 90% power (β=0.1) and 95% confidence interval (α=0.05), 49 patients in each group was sufficient for the present study, and in the end, 50 patients were included in each group. Data were entered to STATA 14.0 statistical software and analyzed. Quantitative data were reported as mean and standard deviation and qualitative data were reported as frequency and percentage. To compare quantitative data between the 2 studied groups, independent t-test and for comparing qualitative data, chi square or Fisher's exact test were used. In addition, based on complete analgesia, treatment success was calculated and number needed to treat, number needed to harm, absolute risk reduction and relative risk reduction were calculated based on it. In all analyses $p<0.05$ was considered as the level of significance.

3. Results

In the end, data of 100 patients were included in the present study (50 patients in each group; flowchart 1). Mean age of

Table 1: Baseline characteristics of included patients

Variable	Double-drug group (n=50)	Triple-drug group (n=50)	Total (n=100)	P
Age (year)	27.7±8.7	27.0±9.2	27.3±8.9	0.71
Sex				
Male	48 (96.0)	45 (90.0)	93 (93.0)	0.44*
Female	2 (4.0)	5 (10.0)	7 (7.0)	
Weight (kg)	75.6±9.7	72.7±10.4	74.2±10.1	0.15
Smoking status				
Non-smoker	30 (60.0)	26 (52.0)	56 (56.0)	0.42
Smoker	20 (40.0)	24 (48.0)	44 (44.0)	
Opium consumption				
No	39 (78.0)	38 (76.0)	77 (77.0)	0.81
Yes	11 (22.0)	12 (24.0)	44 (23.0)	
Alcohol use				
No	43 (86.0)	42 (84.0)	85 (85.0)	0.78
Yes	7 (14.0)	8 (16.0)	15 (15.0)	
Underlying illness				
None	45 (90.0)	43 (86.0)	88 (88.0)	0.68*
Diabetes	1 (2.0)	1 (2.0)	2 (2.0)	
Pulmonary	1 (2.0)	2 (4.0)	3 (6.0)	
Hypertension	1 (2.0)	0 (0.0)	1 (1.0)	
Liver 1 (2.0)	0 (0.0)	1 (1.0)		
Other	1 (2.0)	4 (8.0)	5 (5.0)	
Ramsay sedation scale				
4	47 (94.0)	49 (98.0)	96 (96.0)	0.62*
5	3 (6.0)	1 (2.0)	4 (4.0)	

Data were reported as mean ± standard deviation or frequency (%).
Double-drug protocol: midazolam + fentanyl + placebo; triple-drug protocol: midazolam + fentanyl + lidocaine.

Table 2: Outcome of the studied patients

Variable	Double-drug group (n=50)	Triple-drug group (n=50)	P
Visual analogue scale			
Before treatment	8.3±1.3	8.2±1.2	0.55
After treatment	0.6±0.9	0.4±0.8	0.24
Success rate*	35 (70.0)	41 (82.0)	0.16
Side effects			
None	47 (94.0)	45 (90.0)	0.78
Dysrhythmia	1 (2.0)	1 (2.0)	
Apnea	2 (4.0)	2 (4.0)	
SPO_2<90%	0 (0.0)	2 (4.0)	
Midazolam dosage (mg/kg)	5.9±2.7	5.9±2.5	0.97
Fentanyl dosage (μg/kg)	256.0±115.3	246.0±117.7	0.42

Data were reported as mean ± standard deviation or frequency (%).
*: Success rate was defined as complete analgesia (visual analogue scale=0)
Double-drug protocol: midazolam + fentanyl + placebo; Triple-drug protocol: midazolam + fentanyl + lidocaine.

the studied patients was 27.3±8.9 years (93.0% male). The 2 groups were not significantly different regarding age (p=0.71) and sex (p=0.44) distribution, smoking (0.42), drug abuse (p=0.81) and alcohol abuse (p=0.81) (table 1). Most of the patients (90% in the group with double-drug protocol and 86% in the group with triple-drug protocol) had no history of underlying illnesses (p=0.68).

Mean VAS score before the initiation of treatment in the groups under treatment with double-drug and triple-drug protocols were 8.3±1.3 and 8.2±1.2, respectively (p=0.52) and

Table 3: Number needed to treat as well as absolute and relative risk reduction of the triple-drug protocol

Variable	Value
Pain reduction	
Number needed to treat (n)	9
Absolute risk reduction	12.0%
Relative risk reduction	0.15
Adverse events	
Number needed to harm (n)	25
Absolute risk reduction	4.0%
Relative risk reduction	0.04

after treatment these measures reached 0.6±0.9 and 0.4±0.8 (p=0.24). Using the double-drug regimen led to 35 (70%) cases of complete analgesia, while this rate was 41 (82%) cases in the triple-drug group (p=0.16) (table 2). Number needed to treat calculated was 9 cases. This means that about one in every 9 patients in treatment arm will benefit from the treatment (table 3).

The most important side-effects observed included dysrhythmia (1 patient in double-drug treatment and 1 patient in triple-drug treatment), apnea (2 patients in each group) and SPO_2<90% (2 patients in triple-drug group) (p=0.78) (table 2). Number needed to harm was 25 cases. In other words, for every 25 patients treated with the triple-drug regimen, 1 case of SPO_2<90% is observed (table 3).

4. Discussion

Findings of the present study showed that adding IV lidocaine to the IV midazolam + fentanyl drug combination does not provide additional benefit in PSA for anterior shoulder reduction.

Previous studies had indicated the effectiveness of intra-articular prescription of lidocaine in decreasing the pain following shoulder reduction. In this regard, a meta-analysis in 2009 showed that using intra-articular lidocaine is a safe and effective method compared to old methods (22). In the present study, combination of midazolam + fentanyl alone has a high efficiency in sedation of patients and the pain score of the patients has reduced 7.7 points on average (between 4 and 10 points) (table 2). Therefore, using IV lidocaine prescription in combination with these drugs could not provide more effectiveness.

In a study, Kim et al. showed that prescription of 1.5 mg/kg lidocaine as a bolus and single-dose IV injection and continuing it as 2 mg/kg in each hour leads to a significant decrease in pain and reduction in the amount of fentanyl used compared with normal saline group after lumbar microdiscectomy (24). The reason for the difference between the results of that study and the present study can be the continuous infusion of lidocaine in the study by Kim et al., while in the present study only a single bolus dose was prescribed. This major difference has led to contradicting results. The evidence for this statement is hidden in the treatment mechanism of lidocaine infusion. IV infusion of the mentioned drug with 1-2 mg/kg dose per hour maintains the plasma concentration of the mentioned drug at a level that is not toxic and provides sympathomimetic and analgesic effects (25) an effect that is not seen in the single-dose strategy.

In addition to the effectiveness of a treatment regimen, its adverse side-effects are also of special importance. The findings of the present study indicate that the prevalence of side-effects after prescription of midazolam + fentanyl is not significantly different from midazolam + fentanyl + lidocaine group. In addition, number needed to harm calculated for triple-drug regimen was 25 patients. However, the major difference between the 2 drug regimens in manifestation of side-effects was observed regarding SPO_2<90%. Since simultaneous prescription of IV lidocaine and fentanyl leads to intensification of fentanyl side-effects, especially depression of central nervous system, the reason for the difference observed regarding hypoxia between the 2 groups can be sought in the interference of lidocaine with the effects of fentanyl. However, hypoxia is a common side-effect in procedural sedations. For example, a meta-analysis showed that hypoxia is the most important side-effect of using sedation and its prevalence is 40.2 people in every 1000 cases. This side-effect is immediately relieved with prescription of oxygen and is therefore easily managed in emergency departments (6). One of the limitations of the present study is its short follow-up duration. Shoulder reduction is a painful procedure and in many cases, after the half-life of sedative drugs passes, pain restarts and troubles the patient. The half-lives of drugs used vary; therefore, if the patients would be followed for a longer period of time (not just until they were completely conscious) the findings might have been different.

5. Conclusion

Findings of the present study showed that addition of a bolus and single-dose of IV lidocaine to the combination of IV midazolam + fentanyl does not provide additional analgesia and sedation in reduction of anterior shoulder dislocation in patients presenting to the emergency department.

6. Appendix

6.1. Acknowledgements

This article derived from Aida MohammadianâĂŹs residency thesis to gain specialty in the field of emergency medicine. All the staff members of the emergency department of Imam

Hospital are thanked for their cooperation throughout the study period.

6.2. Author contribution

All authors meet the standard criteria of authorship based on the recommendations of the international committee of medical journal editors.

6.3. Funding/Support

None.

6.4. Conflict of interest

The authors declare that there is no conflict of interest in any phase of performing the study.

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