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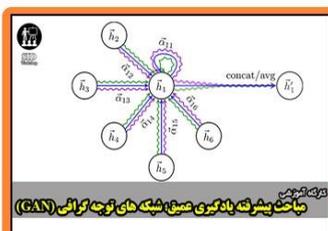


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ORIGINAL RESEARCH

Remifentanil versus Fentanyl/Midazolam in Painless Reduction of Anterior Shoulder Dislocation; a Randomized Clinical Trial

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Abstract: **Introduction:** Performance of painful diagnostic and therapeutic procedures is common in emergency department (ED), and procedural sedation and analgesia (PSA) is a fundamental skill for every emergency physician. This study was aim to compare the efficacy of remifentanil with fentanyl/midazolam in painless reduction of anterior shoulder dislocation. **Methods:** In this randomized, double blind, clinical trial the procedural characteristics, patients satisfaction as well as adverse events were compared between fentanyl/midazolam and remifentanil for PSA of 18–64 years old patients, which were presented to ED following anterior shoulder dislocation. **Results:** 96 cases were randomly allocated to two groups (86.5% male). There were no significant difference between groups regarding baseline characteristics. Remifentanil group had lower duration of procedure (2.5 ± 1.6 versus 4.6 ± 1.8 minutes, $p < 0.001$), higher pain reduction (53.7 ± 13.3 versus 33.5 ± 19.6 , $p < 0.001$), lower failure rate (1 (2.1%) versus 15 (31.3%), $p < 0.001$), higher satisfaction ($p = 0.005$). Adverse events were seen in 12 (25%) patients in midazolam/fentanyl and 8 (16.7%) cases in remifentanil group ($p = 0.122$). **Conclusion:** It seems that use of remifentanil resulted in lower procedural time, lower failure rate, and lower pain during procedure as well as higher patient satisfaction in comparison with midazolam/fentanyl combination in anterior shoulder dislocation.

Keywords: Conscious sedation; midazolam; fentanyl; remifentanil [supplementary concept]; shoulder dislocation

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1. Introduction

Performance of painful diagnostic and therapeutic procedures is common in emergency department (ED), and procedural sedation and analgesia (PSA) is a fundamental and required skill for every emergency physician (1, 2). With the wide range of procedures and high patient population, the ability to individualize PSA and maximize the risk/benefit ratio for each unique situation is essential (3). One of the common painful procedures in ED is reduction of dislocated shoulder joints. The glenohumeral joint is the most commonly dislocated major joint in the body. The an-

nual incidence is 17 per 100,000, and two distinct age peaks are recognized, the first in men 20 to 30 years of age and the second in older women (4). Analgesia and muscle relaxation through procedural sedation are often used to facilitate reduction (5). Fentanyl combined with midazolam is frequently used as a safe PSA agent in ED (3). However, caution must be exercised when using benzodiazepines and opioids together because the risk for hypoxia and apnea is significantly greater than when either is used alone (6, 7). Remifentanil is a relatively new synthetic opioid with a potency comparable to fentanyl but an exceptionally short context-sensitive half-life of only 3–5 minutes (8, 9). However, currently there are insufficient published studies to warrant its routine use. Efficacy of remifentanil in combination with other agents is supported by several clinical trials (10–14), but few studies have described the use of remifentanil alone during performing procedures (15–17). The aim of this ran-

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domized clinical trial was to compare the efficacy of a pure analgesia-based sedation regimen with remifentanyl with a conventional regimen consisting of fentanyl/midazolam for moderate sedation of patients with anterior shoulder dislocation.

2. Materials and Methods

2.1. Study design and settings

This study was a prospective, randomized, single-center, parallel group clinical trial, comparing fentanyl/midazolam to remifentanyl alone for moderate sedation in patients aged 18–64 years with anterior shoulder dislocation, who were presented to the ED of Imam Reza Hospital, Mashhad for closed reduction. This study was approved by the Ethics Committee of our institute (91/570419 November 4, 2012) and registered in Iranian registry of clinical trials under the number IRCT: 2013011312115N1. Informed consent was obtained from all the selected patients after explaining the study.

2.2. Participants

The studied subjects were selected using convenience sampling among the patients presented to the ED of a university-affiliated tertiary care medical center over a 9-month period between February 2013 and October 2013, with anterior shoulder dislocation and requiring closed reduction. Those aged 18–64 years with physical condition I (healthy and normal patients without previous medical history) and II (patients with mild systemic disease with no functional limitation) according to the classification of American Society of Anesthesiologists (ASA) were enrolled. All subjects with history of allergy to benzodiazepines and narcotics; prolonged use of opioids or alcohol; consumption of sedative or analgesic drugs before presenting to ED; sleep obstructive apnea syndrome; maxillofacial malformations with high probability of airway maintenance failure; pregnant; anterior dislocation requiring referral to orthopedic operating room; severe trauma and unstable hemodynamics; advanced heart disease; kidney failure; pneumonia; uncontrolled seizures; and finally patients not willing to participate in the study were excluded.

2.3. Intervention

Using convenience sampling 96 patients were randomized and included in the intention-to-treat analysis, 48 in fentanyl/midazolam group and 48 in remifentanyl group. Allocation assignments were generated by an online random number generator from <http://www.randomizer.org/> and placed in sealed opaque envelopes to be opened in sequential order by research associates. Physicians (trained senior emergency medicine residents) and patients were blinded to

the type of medication. The investigators doing the analysis were not the same as those administering drugs and performing the procedures.

On arrival to the intervention room, where the requirements to protect the airway and prevent aspiration as well as the suitable pulmonary ventilation facilities were predicted, intravenous access, supplementary oxygen via nasal cannula (2 liter/min), routine pulse oximetry and cardiac monitoring were established for all the patients. Remifentanyl hydrochloride (lyophilized powder in sterile vials each containing 1 mg of the compound) was reconstituted diluted with standard diluent. The pharmacy at the institute supplied the fentanyl and midazolam from commercial stock.

The patients in group 1 received remifentanyl (1 $\mu\text{g}/\text{kg}$ body weight bolus intravenous administration at a concentration of 50 $\mu\text{l}/\text{ml}$, and repeated additional titrated to effect doses of 1 $\mu\text{g}/\text{kg}$ administered every minute until the completion of reduction), while those in group 2 received 1.5 $\mu\text{g}/\text{kg}$ fentanyl in combination with 0.1 mg/kg midazolam titrated to effect doses intravenously.

It should be noted that in this study, the aim of giving the drugs was to achieve moderate sedation or conscious sedation (Ramsay Sedation score 3), which implied the following: patients only responded to commands; airway intervention was not necessary; spontaneous ventilation of the patients was adequate; and the patients cardiovascular function was maintained. The amount of drugs to give score 3 sedation, was determined by an attending emergency medicine specialist and the patient was judged to be sedated adequately to begin undergoing reduction by him.

After sedation, reduction of anterior shoulder was performed by employing traction and counter traction method in both groups. Our trained emergency medicine resident rated the pain perceived by the patient before and during the procedure using 100 mm visual analog scale (VAS).

Demographic data were gathered for all patients. The incidence of adverse events was determined by a trained emergency medicine resident and was marked in a checklist that included the following: respiratory adverse events (the need for supplemental oxygen, ventilation with a bag-mask, maneuver practices for maintaining the airway open, insertion of airway, respiratory stimulation, and respiratory depression with $SpO_2 < 92\%$ at any time during intravenous administration of the drug until hospital discharge), and non-respiratory complications (dysphoria, vomiting, headache, myoclonus, nausea, stiffness, rash, cough, bronchospasm, laryngospasm, stridor, apnea, seizures, restlessness, agitation, and aspiration). At the time of discharge, our trained emergency medicine resident recorded patient satisfaction rate using a Likert scale with four options of excellent, good, average, and poor.



2.4. Study end-points

The primary end-points were pain reduction, procedure time, patient satisfaction, and incidence of respiratory adverse events. Secondary end-points included non-respiratory adverse events.

2.5. Definitions

A successful reduction was determined clinically by the presence of a palpable clunk, decrease in pain, and improvement in the range of motion.

Procedure time was defined as time from start of traction to completion of reduction. The timing was measured and recorded using a stopwatch.

2.6. Data Analysis

IBM SPSS statistics 21 was used for statistical analyses. Categorical variables were reported as number and percentage and continuous ones as mean \pm standard deviation. Chi-square and Fisher exact tests were used for comparing categorical variables and t-test for comparing mean between groups. P value < 0.05 was considered statistically significant.

3. Results

48 cases received remifentanyl and 48 received a combination of fentanyl and midazolam (86.5% male). The mean age of remifentanyl patients was 39.7 ± 10.3 years compared to 39.8 ± 9.9 years for fentanyl and midazolam group ($p = 0.952$). In remifentanyl group 41 (85.4%) and in fentanyl and midazolam group 42 (87.5%) cases were male ($p = 0.5$). The subjects in both groups were stable regarding hemodynamic status. The mean pain score at baseline was 70.3 ± 10.8 mm for fentanyl and midazolam and 76.6 ± 11.9 mm for remifentanyl group ($p = 0.008$). Since the minimum clinically significant difference of pain score was considered 30 mm for this study, the baseline difference of pain severity between two groups was not clinically significant. Table 1 compares the 2 groups regarding procedure characteristics and observed complications. Respiratory adverse event was not experienced in any of the groups. Non-respiratory adverse events were seen in 12 (25%) patients in midazolam/fentanyl and 8 (16.7%) cases in remifentanyl group ($p = 0.122$).

4. Discussion

When choosing a strategy for PSA, it is important to consider the type of procedure being performed (painful or not), the length of the procedure, specific procedural requirements (anxiolysis vs. immobility), and whether sedation needs to be prolonged. A risk-benefit analysis should be conducted before performing PSA and the benefits of reducing anxiety

and pain versus the risk of respiratory depression and airway disorders should be measured.

The results of the present study demonstrated a significantly lower duration of procedure and lower failure rate in patients that were sedated using remifentanyl. On the other hand, the mean pain reduction was significantly higher in remifentanyl group. Two groups had the same condition regarding respiratory and non-respiratory adverse events. The level of patient satisfaction was significantly higher in remifentanyl group.

Rai et al. studied remifentanyl versus propofol for awake fiberoptic intubation and reported significantly shorter endoscopy and intubation times for remifentanyl group (15). Dunn et al. demonstrated that propofol and remifentanyl provide excellent sedation and analgesia for the reduction of anterior glenohumeral dislocation (10, 11). In Phillips et al. case series an initial bolus dosage of 0.5–3 mcg/kg intravenous remifentanyl with subsequent 0.25–1 mcg/kg boluses resulted in mean pain severity of 1.1, mean procedure time of 4 minutes and 17% respiratory complications requiring temporary intervention during procedure (16).

The lower mean pain severity during the procedure with remifentanyl (9.4 ± 8.5 mm vs. 26.1 ± 20.2 mm) revealed greater effectiveness and potency of this drug. This finding was similar to Dunn et al., Phillips et al., Swann et al., Sacchetti et al., and Cok OY et al. findings (10, 12, 13, 16, 17).

Some non-respiratory adverse events have been reported using combination of midazolam/fentanyl (18). Application of remifentanyl in combination with midazolam for performing painful procedures in children resulted in high and unacceptable rate of hypoxemia (14). The incidence of respiratory and non-respiratory adverse events was similar in both groups of the present study.

In this study, significantly higher patient satisfaction was reported for patients sedated with remifentanyl, which was compatible with findings of Dunn et al. (10).

In the present study, for eliminating further confounding factors, the same technique of reduction was performed for all patients in both groups. The study revealed that remifentanyl works effectively in PSA of patients with anterior shoulder dislocation without addition of any sedative agents. Since only adults between the ages of 21 and 64 years were studied, our findings cannot be extrapolated to children and the elderly.

5. Conclusion

It seems that use of remifentanyl resulted in lower procedural time, lower failure rate, and lower pain during procedure as well as higher patient satisfaction in comparison with midazolam/fentanyl combination for procedural sedation and analgesia in anterior shoulder dislocation. The 2 groups had the same condition regarding respiratory and non-respiratory



Table 1: Comparison of the 2 studied groups regarding procedure characteristics and observed complications

Variable	Fentanyl + Midazolam	Remifentanil	P value
Mean procedure time (minute)	4.6 ± 1.8	2.5 ± 1.6	< 0.001
Pain severity during procedure [#]	36.8 ± 22.9	22.9 ± 9.9	< 0.001
Mean pain reduction	33.5 ± 19.6	53.7 ± 13.3	< 0.001
Failure rate	15 (31.3)	1 (2.1)	< 0.001
Non-respiratory adverse events			
Vomiting	2 (4.2)	0 (0)	0.247
Nausea	5 (10.4)	1 (2.1)	0.102
Itching	2 (4.2)	5 (10.4)	0.218
Cough	2 (4.2)	1 (2.1)	0.5
Agitation	1 (1.2)	0 (0)	0.5
Dysphoria	4 (8.3)	2 (4.2)	0.339
Total	12 (25)	8 (16.7)	0.122
Patient satisfaction			
Excellent	32 (66.7)	43 (89.6)	< 0.005
Good	16 (33.3)	5 (10.4)	

Values are presented in mean ± standard deviation or number (%), pain severity was measured based on visual analogue scale (millimeter), failure rate: failure in pain reduction ≥ 30 mm.

adverse events.

6. Appendix

6.1. Acknowledgements

The authors appreciate the insightful cooperation of Emergency Department staff.

6.2. Author contribution

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors.

6.3. Funding

None.

6.4. Conflict of interest

None.

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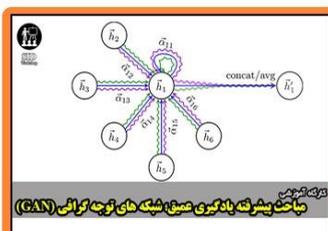


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