

Original Article

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Propofol-Ketamine vs. Propofol-Fentanyl Combinations in Patients Undergoing Closed Reduction: A Randomized, Double-blind, Clinical Trial

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Abstract

Introduction: Painful surgical procedures require adequate sedation and analgesia. A vast array of medications can be used for Procedural Sedation and Analgesia (PSA) in Emergency Departments (EDs).

Objective: The present study was conducted to compare Propofol-Ketamine (PK) and Propofol-Fentanyl (PF) compounds in patients undergoing closed reduction in EDs.

Methods: This randomized, double-blind, clinical trial was conducted on 110 consecutive patients who required sedation for closed reduction. The patients were randomly divided into two groups of equal sizes. The PK group received an intravenous bolus of 1 mg/kg of propofol plus 0.5 mg/kg of ketamine, and the PF group received an intravenous bolus of 1 mg/kg of propofol plus 1 µg/kg of fentanyl. The analgesic effect and success rate were the primary outcomes under study.

Results: The PK group achieved more effective analgesia at the end of the experiment. The success rate was almost the same in both groups Shivering ($p=0.005$) and a drop in oxygen saturation to below 92% ($p=0.048$) were two side effects that were more prevalent in the FK group. The mean recovery time was significantly shorter in the PK group ($p<0.001$). The patients in the PK group were more satisfied.

Conclusion: In comparison with the PF compound, the use of KP leads to better pain relief and greater patient satisfaction and shorter sedation time in PSA.

Key words: Analgesia; Emergency department; Fentanyl; Ketamine; Pain, procedural; Propofol

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INTRODUCTION

The combination of Ketamine and Propofol (named Ketofol) is currently a choice sedative agent for Procedural Sedation Analgesia (PSA) in Emergency Departments (EDs) (1, 2). The possible superiority of this drug combination is attributed to the supportive effect of ketamine on the cardiovascular system by way of increasing cardiac output and systolic blood pressure and modifying the central venous pressure, which are very helpful in hypotensive and hypovolemic critical states (3). Ketamine is an anesthetic sedative that acts as the antagonist of the NMDA receptors and is widely used for its high efficacy and safety and also for its little side effects for the cardiovascular system. The main side effects of ketamine include nausea, vomiting and psycho-mimetic effects, which appear in about one-third of the patients (4-6). Before the introduction of Ketamine-Propofol (KP) as a new anesthetic combination, the compounds most widely used included propofol and fentanyl. Despite the significant effectiveness of the

combination of propofol and fentanyl (PF), the complications of this compound are considerable (7). First, fentanyl may exacerbate the drop in blood pressure after propofol consumption. Second, the adverse effects of propofol on the cardiovascular system may be intensified by the addition of fentanyl (8, 9). Third, the compound KP may be more suitable and might lead to more pain relief and less post-reduction respiratory suppression in comparison with PF. Nonetheless, there is little evidence on the clinical and hemodynamic benefits of KP in comparison with PF after procedures. The present study was conducted to compare KF and PF compounds in the PSA of patients undergoing closed reduction in EDs.

METHODS

Study design

This randomized, double-blind, clinical trial (RCT) was conducted in the EDs of two teaching hospitals in Tehran, Iran, in 2014. Consent forms containing

detailed information on how to implement the study were presented to the patients and those who declared their consent for participation in the study were included in the project. The RCT protocol was registered at the Iranian Registry of Clinical Trials under the code IRCT2015082522734N2. All the investigators complied with the Helsinki Declaration throughout the study.

Study population

The sample size was calculated using Altman's nomogram. The assumed power was 80% and the standardized difference was obtained through dividing the clinical difference by the standard deviation. In this study, the mean pain scores were compared between the PK and PF groups. The clinical difference for the pain scores was taken as 3 with a standard deviation of 0.5. Considering an 80% power and a standardized difference of 6, the sample size was estimated as 100 overall and 50 per group. Consecutive sampling was applied and all the patients aged 18 to 70 years, presenting to the ED and needing closed reduction were included in the study. The patients who met the following criteria were excluded from the study: Unwillingness to participate in the study, known psychiatric disorders, chronic opiate users, known hypersensitivity to the drugs under assessment, a BMI higher than 30 kg/m², active infection in the upper respiratory tract or any anatomical abnormality in the upper airways.

Intervention and data collection

First, the baseline characteristics were collected through interviews with the patients. Then, before the analgesia procedure, the patients were randomly divided into two groups using the block randomization method. Intravenous propofol (1 mg/kg) was then slowly injected into all the subjects. The first group (the PK group) received 0.5 mg/kg of intravenous ketamine and the second group (the PF group) received 1 µg/kg of intravenous fentanyl. Each syringe was prepared at the pharmacy sections of the hospital EDs in a way that it could contain 25 mg/mL of ketamine or 50 µg/mL of fentanyl. All the syringes had the same appearances and the nurses who injected the drugs were unaware of their content. The patients who required more sedation received 0.5 mg/kg of pure propofol. It happened when patient interfere with the reduction because of inadequate sedation or pain relief. If required, the patients were supported by controlled or assisted airway. Blood pressure, heart rate, saturation and drug side effects were recorded at 0, 15 and 30 min after sedation, respectively.

A case of hypotension was considered when the systolic blood pressure dropped by 20% of its baseline value and was managed by a bolus of fluid and vasopressor. Desaturation and apnea were defined as oxygen saturation <92% at any time during the procedure and the cessation of breathing, respectively. Both conditions were managed by head tilt-chin lift or jaw thrust and bag mask ventilation as needed. Bradycardia was mentioned when the heart rate per minute dropped to below 60 and the patient was managed by 0.5 mg of IV atropine.

Outcome assessment

The primary outcomes to be assessed included the analgesic effect of each combination and the success rate of the procedure. The pain score using the 11-point Numerical Rating Scale (NRS) was determined at baseline and after recovery. The patients orally scored their pain during the reduction on a scale of 0 to 10 (0: no pain, 10: the worst possible pain) after they became fully awake. The procedures were considered successful if a complete reduction was performed in the ED without further reductions required in the operating room.

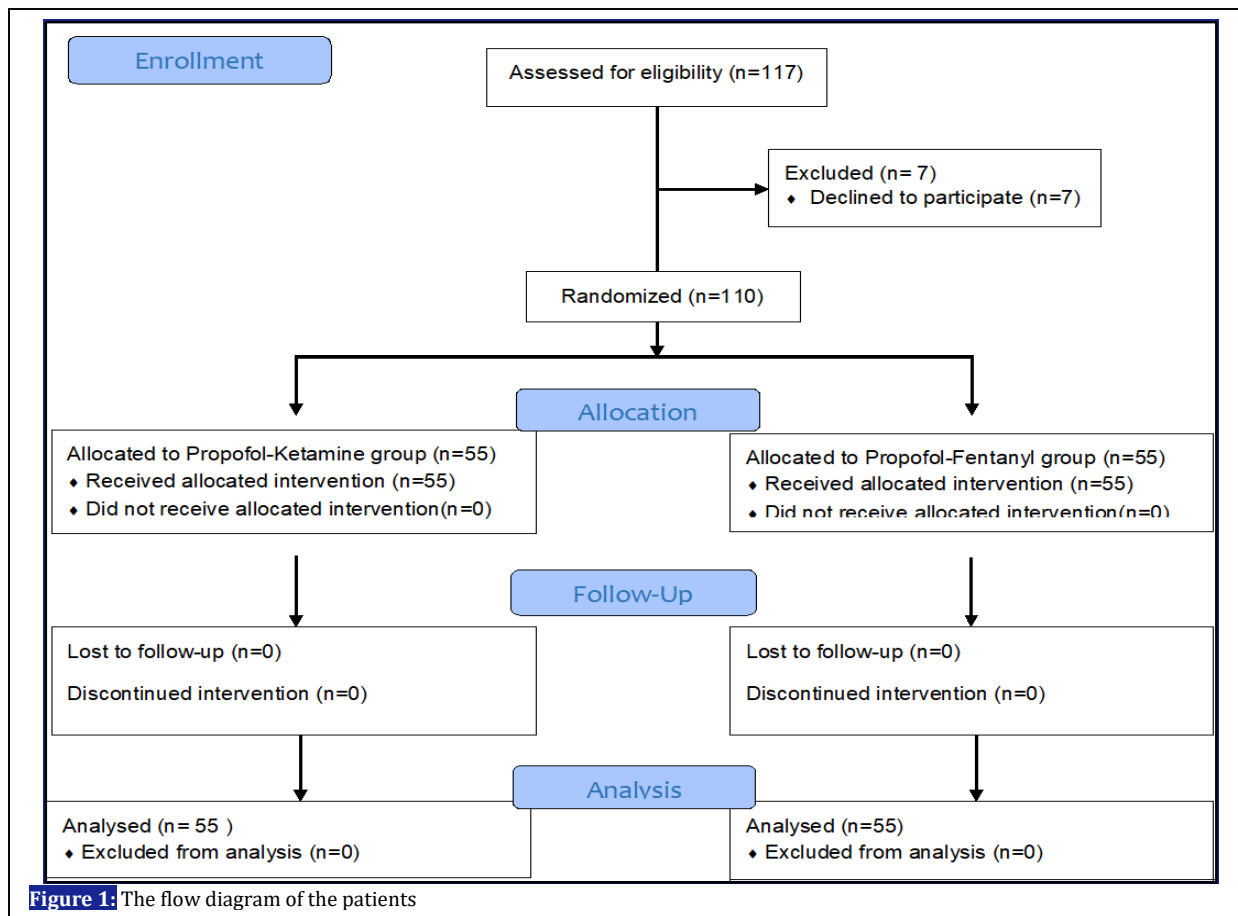
The secondary outcomes to be assessed included adverse health effects, patient satisfaction and recovery time (from the completion of the procedure until return to the baseline mental status). Patient satisfaction was inquired about one-hour post reduction on a 5-point scale of quality, i.e. excellent, very good, good, fair and poor. The 'excellent' and 'very good' responses for each component were regarded as having reached proper analgesic effect.

Statistical analysis

The results were presented as mean ± standard deviation (SD) for the quantitative variables and were summarized using absolute frequencies and percentage for the categorical variables. The categorical variables were compared using the Chi-square test or Fisher's Exact Test when more than 20% of the cells were observed with an expected count of less than five. The quantitative variables were also compared using the student t-test or Mann Whitney's U-test. The statistical analyses were performed in SPSS-18 software. P-values of 0.05 or less were considered statistically significant.

RESULTS

Of the 117 patients selected for this study, seven were excluded due to their unwillingness to continue participation (Figure 1). Finally, 110



patients were assigned into two equal groups of 55 each. The baseline characteristics were similar between the two groups (Table 1). The mean pain score did not differ between the groups before the reduction, but the patients who received PK had

less pain after the reduction (Table 2). Nine patients in the PF group and four in the KP group required a second dose of propofol, but the difference between the groups was not statistically significant in this regard (p=0.23).

Table 1: The background parameters and factors under assessment in the two groups

Patient Characteristics	Fentanyl (n=55)	Ketamine (n=55)	p
Age (year)	37.71 ± 12.21	33.82 ± 11.26	NS [†]
Gender (male: female)	48: 7	45: 10	NS
Weight (kg)	72.24 ± 5.12	76.33 ± 4.78	NS
Mean propofol consumption (mg)	87.82 ± 3.44	84.91 ± 4.11	NS
Need more sedation	9	4	<0.001*
Recovery time (min)	28.07 ± 3.54	19.98 ± 2.47	<0.001*

†: Not Significant, *Statistically Significant

Table 2: A comparison of the adverse effects of the drugs between the PF and PK groups

Complication	Fentanyl	Ketamine	p
	Number (%)	Number (%)	
Shivering	18 (32.7)	6 (10.9)	<0.001*
Nausea	8 (14.5)	15 (27.3)	NS
Desaturation	14 (25.5)	6 (10.9)	NS
Apnea	2 (3.6)	1 (1.8)	NS
Bradycardia	0 (0.0)	0 (0.0)	NS
Hypotension	4 (7.2)	1 (1.8)	NS

*Statistically Significant

Table 3: Comparing the changes in some of the variables between the PF and PK groups

Variable	Ketamine	Fentanyl	p
Heart Rate (/min)			
Before sedation	86.24 ± 5.15	89.27 ± 4.82	NS
15 th minute	78.98 ± 4.88	79.24 ± 4.86	NS
30 th minute	75.89 ± 3.81	76.47 ± 3.89	NS
Systolic Blood Pressure (mmHg)			
Before sedation	126.36 ± 5.82	127.22 ± 5.76	NS
15 th minute	115.56 ± 5.96	115.98 ± 3.85	NS
30 th minute	114.73 ± 3.83	115.51 ± 3.92	NS
Pain severity score (0 to 10)			
Before reduction	7.65 ± 0.14	8.00 ± 0.16	NS
During reduction	1.44 ± 0.71	2.56 ± 0.82	0.011*

*Statistically Significant, PF: Propofol+Fentanyl, PK: Propofol+Ketamin

Also, the mean propofol consumption was more in the PF group than in the PK group (87.8±6.4 mg vs. 84.9±7.1 mg), although the difference was not statistically significant (p=0.71).

Patient satisfaction was inquired about one hour after the reduction. The PK group was more satisfied than the PF group, with the rates being 83.6% vs. 63.6% (p=0.01).

No serious adverse events were observed in the subjects in either of the groups. Table 3 presents the experienced complications. Except for shivering, which was more frequent in the PF group (32.7% vs. 10.9%, p<0.001), no statistically significant differences were observed between the two groups for the other side effects at 0, 15 and 30 minutes. The mean recovery time was significantly shorter in the PK group, 19.9±2.4 min vs. 28±3.5 min (p<0.001).

DISCUSSION

As demonstrated in this study, the addition of ketamine to propofol as KP has multiple benefits for PSA. First, in comparison with the combination of fentanyl and propofol, KP further reduced pain. Also, shivering decreased in O₂ saturation and recovery time was significantly lower and the patients' satisfaction was higher in the PK group. These results emphasize the efficiency of KP in comparison with FP in PSA in EDs.

The combination of ketamine and propofol can reserve the efficacy of these two drugs and can also minimize their adverse effects. Some researchers believe that the reduced side effects of this combination may be attributed to the reduced dosages of the drugs based on the fact that the observed side effects are dose-dependent (10). Furthermore, since the cardiovascular effects of these drugs are opposite, the drugs seem to balance each other out in terms of cardiovascular complications when combined (11). The beneficial effects of ketamine are thus confirmed, especially

with regard to its cardiovascular, respiratory and hemodynamic effects (1).

Several studies have been carried out to compare these two combinations with varying results. To the best of the researchers' knowledge, the present trial is the first study to compare these two combinations for PSA in EDs. Kb et al. compared these combinations in 60 patients undergoing puerperal sterilization in a gynecologic operating room and concluded that, given the stability of vital signs and respiratory suppression, the PK combination had a safer profile compared to the PF combination (12). In a study by Khajavi on 60 patients in need of colonoscopy, sedation with PK led to more satisfaction than PF (13). Khutia compared the two combinations for their respiratory and vital sign complications in 92 pediatric laryngeal mask airway (LMA) application events and found a preference for PF in short surgical procedures compared to PK (14).

In a randomized, double-blind study conducted on patients undergoing endometrial biopsy, the combination of propofol and fentanyl was compared with KP (15). In this study, more apnea events were detected in the PF group than in the PK group (five vs. one), although the difference was not statistically significant. Other complications, such as nausea, vomiting and visual disturbances, were also observed significantly more frequently in the PK group. The onset of awakening was the same between the two groups, but the PF group had a higher satisfaction rate.

In a study by Goh et al., the side effects of three combinations were compared, including propofol with ketamine, propofol with fentanyl or placebo for LMA insertion (16). The comparison of vital signs across the three groups showed a higher systolic blood pressure in the ketamine group, while prolonged apnea was more frequent in the fentanyl group. These researchers finally concluded that the use of KP can minimize

respiratory side effects and also elevate systolic blood pressure, which could be useful for hypotensive patients.

To compare the side effects and recovery time between the propofol-ketamine and propofol-fentanyl combinations, Vallejo et al. performed a randomized, double-blind trial on patients who underwent laparoscopic tubal ligations with general anesthesia (17). No differences were ultimately observed with regard to recovery time, pain scores and emesis between the groups.

This disparity of findings in the studies could be due to the differences in drug dosages and procedural characteristics.

Limitations

The combinations used present other complications as well, such as laryngospasm and aspiration, which were not assessed in the present study. In the present study, recovery time was longer in the PF group than in the PK group, although this difference could be explained by the additional doses of propofol required.

CONCLUSIONS

The use of ketamine-propofol with the standard dosages used in the present study is better than fentanyl-propofol in candidates of PSA in EDs and can lead to better pain relief and shorten the recovery time.

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AUTHORS' CONTRIBUTION

MM, DF and RR: Research idea and design; RR, BM and PH: Registering the study at IUMS Research Center, communicating with the manager of the hospitals and arranging the study's implementation; MM, BM and RR: Data collection (visiting the patients and performing ultrasounds); SA, PH: Quality control; MR and DF: Writing the article (search for data in databases and producing the primary manuscript); MR, DF and SA: Analysis of the findings in SPSS and finalizing the article; DF: Takes responsibility for the paper. All the authors approved the final version to be published and consider themselves accountable for all the aspects of the work in ensuring that the questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

None declared.

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