

# Thiopental-Fentanyl versus Midazolam-Fentanyl for Emergency Department Procedural Sedation and Analgesia in Patients with Shoulder Dislocation and Distal Radial Fracture-Dislocation: A Randomized Double-Blind Controlled Trial

D. Farsi, Gh. Dokhtvasi, S. Abbasi, S. Shafiee Ardestani, E. Payani

**Abstract**—Background and aim: It has not been well studied whether fentanyl-thiopental (FT) is effective and safe for PSA in orthopedic procedures in Emergency Department (ED). The aim of this trial was to evaluate the effectiveness of intravenous FT versus fentanyl-midazolam (FM) in patients who suffered from shoulder dislocation or distal radial fracture-dislocation.

**Methods:** In this randomized double-blinded study, Seventy-six eligible patients were entered the study and randomly received intravenous FT or FM. The success rate, onset of action and recovery time, pain score, physicians' satisfaction and adverse events were assessed and recorded by treating emergency physicians. The statistical analysis was intention to treat.

**Results:** The success rate after administrating loading dose in FT group was significantly higher than FM group (71.7% vs. 48.9%,  $p=0.04$ ); however, the ultimate unsuccessful rate after 3 doses of drugs in the FT group was higher than the FM group (3 to 1) but it did not reach to significant level ( $p=0.61$ ). Despite near equal onset of action time in two study group ( $P=0.464$ ), the recovery period in patients receiving FT was markedly shorter than FM group ( $P<0.001$ ). The occurrence of adverse effects was low in both groups ( $p=0.31$ ).

**Conclusion:** PSA using FT is effective and appears to be safe for orthopedic procedures in the ED. Therefore, regarding the prompt onset of action, short recovery period of thiopental, it seems that this combination can be considered more for performing PSA in orthopedic procedures in ED.

**Keywords**—Procedural Sedation and Analgesia, Thiopental, Fentanyl, Midazolam, Orthopedic Procedure, Emergency Department, Pain.

## I. INTRODUCTION

PROCEDURAL sedation and analgesia (PSA) is used in the emergency department (ED) to efficiently and humanely perform painful diagnostic and therapeutic procedures. PSA is the administration of sedative or dissociative anesthetics to induce a depressed level of consciousness while maintaining safety of patient so that a medical procedure can be performed

Davood Farsi, M.D., Ghasem Dokhtvasi, MD., and Saeed Abbasi, M.D., are Assistant Professors of Emergency Medicine, Emergency Department, Iran University of Medical Sciences, Iran (e-mail: davoodfa2004@yahoo.com, dr.dokht@yahoo.com, saieedabbasi@yahoo.com)

Soudabeh Shafiee Ardestani, MD., and Elnaz Payani, MD., are General Practitioners, Tehran University of Medical Sciences, Iran (e-mail: s.shafiee.a@gmail.com, elnaz.pyn@gmail.com)

with minimal pain [1]. Orthopedic procedure such as reduction of extremity's fractures is one of the most important, though most painful procedures in ED. Without using PSA, the pain, anxiety, and muscular tension make the reduction more painful and unpleasant for patients. For choosing better drugs for PSA, many factors are important; such as prompt onset of action, adequate analgesia, less proportion of patients experiencing a respiratory adverse event, short duration of action, and low side effects. Furthermore, the drug routinely used must be available and easy to use, and the patients should be able to afford it [2], [3]

In recent years, the combination of Midazolam-Fentanyl (FM) is used not only in orthopedic procedures, but in other medical procedures such as bone marrow biopsy in leukemic patients [4], dentistry procedures [5], endoscopy [6], colonoscopy [7] and cataract surgery [8]. In Orthopedic procedures, this combination is used with lot parity among emergency physicians. [2], [9] However, in a study regarding the best combination, FM was ranked fourth after Propofol-Fentanyl, Axillary block and Ketamine-Midazolam for sedation of patients with forearm fracture reduction. [10]

Although the safety and efficacy of thiopental in rapid sequence intubation has been established, the effectiveness of it in procedural sedation and analgesia in orthopedic procedures has not been well studied. Furthermore, to our knowledge, no published double-blinded clinical trial study has compared thiopental sedative effects with other drugs in the ED. We compared the effectiveness of Midazolam-Fentanyl versus Thiopental-Fentanyl in group of patients with shoulder dislocation and distal radial fracture-dislocation.

## II. MATERIALS & METHODS

### A. Setting and Study Design

We conducted a double-blind randomized clinical trial study which compared two regimens of PSA. The study was performed between December 2011 and September 2012 at two general teaching hospitals (Hazrat Rasoul and Sina) in the Tehran, Iran. Our study population was recruited from all patients admitted to our EDs with shoulder dislocation or distal forearm fracture-dislocation.

The patients were randomly assigned to receive either

Fentanyl-Midazolam (FM) or Fentanyl Thiopental (FT). This study is conducted in concordance with the principles of the Declaration of Helsinki. Approval for the conduct of this study was obtained from the Research Ethics Committee and Institutional Review Board of Tehran University of Medical Sciences (Ethic code: 90/d/10/2343). This trial has also been registered at International Clinical Trials Registry Platform (registration number: IRCT201110307751N2 at <http://www.who.int/ictrp>). All participants or their next of kin were aware of the presence of the study and signed consent was received prior to the procedure.

### *B. Selection of Participants*

All patients were between 15 to 60 years old. Participants were in class I or II according to American Society of Anesthesiologists' (ASA) Physical Status Classification. [11] In addition, subjects with symptomatic cardiovascular diseases, central nervous system disorders, known case of Multiple Myeloma, history of Asthma, chronic bronchitis and porphyria, patients with more than one fracture or dislocation, and patients with psychiatric or neuro-developmental disorders were excluded from our study. Patients were also excluded if they were unable to give informed consent, were pregnant, or had a known allergy to either study medication.

The sample size was calculated 46 in each group by means of relevant formula. The statistical power is set at 0.80 and  $\alpha$ -level equal to 0.01. One hundred patients were selected for our study in order to consider probable loss to follow up cases and prevent loss of power. Two of selected patient had ASA score III or higher and 7 did not sign the consent form. At the end, 91 patients were entered in the study.

### *C. Intervention*

Participants were randomized to receive either FM or FT in a double-blind fashion. Eligible subjects were selected and enrolled the study by emergency physicians (attending or residents). The attendant nurse of the patients was in charge of drugs preparation and the resident and the researcher physician were not aware of the type of the PSA. The responsible nurses were not involved in patient recruitment, sedation procedure and assessment of PSA efficacy. All physicians and nurses in the ED who were in team of research were informed about the study design, protocol, and exclusion criteria.

First eligibility of subjects assessed by emergency physicians and the patients were transferred to critical care room. We had provided 100 tags and put them in secured box which was available for responsible nurses. The tags were kept in secured box in critical care room and the names of the drugs were written equally in slice of paper. This box was available to be opened during the procedure only if clinically necessary at the discretion of the treating emergency physician. After every admission, one of the papers was randomly selected and the nurse recorded selected drugs and prepared study medication. The tags were attached to the checklist of each patient Thus the attendant nurse was aware about the type of drugs but treating physician was completely

blinded to intravenous drugs which were administered to the patients. All syringes were identical and were prepared by the following:

Midazolam: intravenous dose of 0.1 mg/kg as the loading dose and 0.05 mg/kg for subsequent doses. All vials were manufactured in a 5 mg/ml ampoule by Aboureihan Drug Company, Iran. In every procedure, 2 vials of Midazolam were diluted by 8 ml water. The nurse filled a 10 cc syringe by 1 ml of the solution which contains 1mg of Midazolam.

Fentanyl: intravenous dose of 1.5 $\mu$ g/kg as the loading dose and 0.75 $\mu$ g/kg as subsequent doses. All vials were manufactured in a 500  $\mu$ g/ml ampoule by Aboureihan Drug Company, Iran. In every procedure, the nurse filled a 10 cc syringe by 1 ml of the drug which contains 50  $\mu$ g of Fentanyl.

Thiopental: intravenous dose of 2 mg/kg as the loading dose and 1 mg/kg as subsequent doses. All vials were manufactured in a 500 mg/ml ampoule by Rotexmedica Drug Company, Germany. In every procedure, the nurse filled a 10 cc syringe by a diluted solution of the drug with 10 ml water, which every 1 ml contains 50 mg of Thiopental.

The study medications were prepared in identical 10-mL syringes and the drugs were administered by a venous catheter number 18. There were no mixtures of the drugs in any syringes. The thiopental vials were prepared under the direct orders of the manufacturer instructions and were held in the refrigerator for a maximum of 24 hours.

Once a patient was deemed eligible but before he or she received sedation, the treating physician obtained informed consent from the patient. The loading dose was administered intravenously in 10-20 seconds and the procedure was initiated after the sedation was desirable. The goal of PSA was to attain moderate, dissociate, or deep sedation [12]. At the time of the drug administration, the researcher physician had written down the time and a maintenance dose was administered if the sedation was not enough for the procedure after 3 minutes and another maintenance dose after 2 minutes if the sedation was not at the desired level; however, after the total 5 minutes, if the sedation was not complete, we used another type of sedation and were excluded from the study as a un-successful sedation.

All patients were referred into a Critical care room, with full equipment of resuscitation and received continuous pulse oximetry, capnography, and cardiac monitoring. No pre-oxygenation was provided. Blood pressure was performed every 5 minutes with an automated cuff and recorded by the emergency physician. Flumazenil and naloxone (as antidotes) were available in case of any emergency.

### *D. Data Collection and Processing*

Data collection was performed on data sheets. Before the sedation, the treating emergency physician recorded patient study sequence number, demographic data, American Society of Anesthesiology class, and pain severity on a scale from 1 to 10. The medication dose and timing of medication administration, as well as the, were registered by treating physicians. She/he was also recorded the vital signs before, during and after the each procedure until specific discharge

criteria were met. During each procedure until patients met discharge criteria, the treating physician documented the presence or absence of an explicit list of adverse events, including necessity for airway intervention, apnea, hypotension, hypoxia, nausea, vomiting, nystagmus, skin rash, seizure, and etc.

PSA with each of combination was considered efficacious (success rate) if the required procedure was completed and no adjunctive medications were required. Satisfaction ratings were recorded on a 5-point Likert Scale, with one being very unsatisfied and 5 being completely satisfied. Pain level was checked before the procedure, right after the end, 5 min and 10 min after the procedure. The onset of action was defined as the interval from first dose of medication administered until the time to desired sedation level in the patient as mentioned above. Recovery time was calculated as the time from the last dose of medication given until discharge criteria were met (Aldrete score 18) [13]. All times were calculated by a digital chronometer.

Apnea was defined as cessation of breathing for at least 20 seconds with or without oxygen desaturation. Hypotension was defined as a decrease in mean arterial blood pressure of 20% from pre-procedural levels or decreases 30 mmHg in systolic blood pressure. Hypoxia was defined as oxygen saturation below 90% at any time during the PSA protocol and recovery period.

#### E. Data Analysis

All statistical analyses were performed using SPSS 16.0 (SPSS Inc. Chicago, IL, U.S.A.) by a blinded statistician. In our trial, a modified intention-to-treat analysis was performed for comparing the two regimens, with exclusion of patients who did not receive any dose of the study drug. In data analysis we compared success rate and adverse events in patients receiving FT with those of patients receiving FM. Parametric and categorical data were reported as mean  $\pm$  standard deviation and No. (%) respectively. Independent t, Mann-Whitney U, Chi2, and Fisher's exact tests were used to analyze statistically significant differences between the FT and the FM groups. Categorical variables were compared using the Chi2 and Fisher's exact tests. The independent t-test was used to analyze variables with a normal distribution and because pain and satisfaction scores were not normally distributed, we used Mann-Whitney-U test. Any p value  $<0.05$  was considered statistically significant.

#### F. Outcomes

Primary outcome was to compare the effectiveness (success rate) of Fentanyl-Midazolam versus Thiopental-Fentanyl in a randomized double blinded manner. Secondary outcomes included the onset of action, recovery time, and the incidence of adverse events in each study group.

### III. RESULTS

#### A. Baseline Data

Ninety-one patients were enrolled in the study, consisted of 45 (49.5%) in the FM and 46 (50.5%) in the FT group. Sixty-

one (67%) patients suffered from shoulder dislocation and 30 (33%) had a fracture in their distal forearm. The study groups were similar with regard to demographic characteristics and orthopedic procedures performed. The mean of age was  $35.96 \pm 14.19$  years old. Demographic characteristics of the study subjects are presented in Table I.

TABLE I  
CHARACTERISTICS OF THE PARTICIPANTS RECEIVING FENTANYL/THIOPENTAL OR FENTANYL/MIDAZOLAM

Characteristics	Fentanyl/Thiopental	Fentanyl/Midazolam	P value
Male sex (%)	47 (51.64)	44 (48.35)	0.572
Age, y, mean (SD*)	37.5 (12.9)	34.1 (14.9)	0.122
Distal of Radius (%)	16 (53.34)	14 (46.66)	0.690
Shoulder Dislocation (%)	30 (49.2)	31 (50.8)	0.742

\*SD, Standard Deviation

#### B. Success Rate of PSA

Success rate: PSA were successfully performed with administration of loading (first) dose in 33 (71.7%) of FT group versus 22 (48.9%) of FM group. (Table II) Obviously, the difference was statistically significant. (Chi2,  $p=0.044$ ) However, after second and third dose, there was no significant difference in success rate between our two groups (Fisher's Exact,  $p=0.18$  and  $p=0.35$  respectively). The ultimate unsuccessful rate after 3 doses in the FT group was higher than the FM group (3 to 1) but it did not reach to significant level (Fisher's Exact,  $p=0.61$ )

TABLE II  
THE SUCCESS RATE OF PSA IN TWO REGIMENS

	Fentanyl/Thiopental	Fentanyl/Midazolam	P value
Success rate after loading dose (%)	33 (71.73)	22 (48.89)	0.044*
Success rate after second dose (%)	40 (86.95)	42 (93.33)	0.180†
Success rate after third dose (%)	43 (93.47)	44 (97.77)	0.357†
Not successful (%)	3 (6.52)	1 (2.22)	0.617†

\*Chi-Square test, †Fisher's Exact test

#### C. Onset of Action and Recovery Time

The mean onset of action were near equal between both groups (t,  $P=0.464$ ). However the recovery time for patients sedated with FM was longer than FT group which was statistically significant (t-test,  $P<0.001$ )

#### D. Pain Survey

We could not measure the pain in 2 patients because of low social level and language difference. The mean of pain intensity regarding to NRS scale were measured in both groups before initiating the procedure and were  $8.3 \pm 1.9$  in FT group versus  $8.2 \pm 1.5$  in FM group. The difference was not statistically significant (Mann-Whitney-U test,  $P=0.480$ ).

The severity of pain was reassessed at the end of PSA and the pain score reduction was similar between two groups ( $7.25 \pm 2.7$  in TF vs.  $7.24 \pm 2.2$  in FM, Mann-Whitney U,  $p=0.7$ ). Furthermore, after 5 and 15 minutes from the end of PSA, the reduction in pain severity scores did not differed markedly amongst two groups. ( $p>0.05$ ) Details are shown in Table III.

TABLE III  
COMPARING THE ONSET OF ACTION, RECOVERY TIME, PAIN SCORES AND  
PHYSICIANS SATISFACTION BETWEEN STUDY GROUPS

	Fentanyl/Thiopental	Fentanyl/Midazolam	Pvalue
Onset of Action, second, mean (SD)	144.5 ± 100.4	160.1 ± 76.4	0.464*
Time to Aldrete score 18, second, mean (SD)	425.8 ± 367.7	879.0 ± 486.9	<0.001*
Pain score before starting PSA (SD)	8.28 ± 1.9	8.21 ± 1.5	0.480†
Pain score at the end of PSA (SD)	7.25 ± 2.7	7.24 ± 2.2	0.709†
Pain score after 5 minutes of completion PSA (SD)	6.69 ± 2.5	7.15 ± 2.2	0.406†
Pain score after 15 minutes of completion PSA (SD)	6.31 ± 2.5	5.76 ± 2.4	0.351†
Treating physician satisfaction, scale 1 (very dissatisfied) to 5 (very satisfied)	4.8 ± 0.6	4.6 ± 0.7	0.876†

\* Unpaired T test †Mann-Whitney U test

### E. Adverse Effects

We studied potential adverse effects of sedation drug regimens. (Table IV) The prevalence of adverse effects during the sedation and recovery period until discharge were 26.08% and 20% in FT and FM groups respectively. Although the occurrence of adverse effects in FT group was slightly higher than the FM group, it was not significant (Chi2, p=0.31). No other adverse events (chest wall rigidity, seizure, vomiting, and skin rash) were seen.

TABLE IV  
ADVERSE EVENTS DURING AND AFTER PSA IN PATIENTS RECEIVING  
FENTANYL/THIOPENTAL OR FENTANYL/MIDAZOLAM

	Fentanyl/Thiopental	Fentanyl/Midazolam	Pvalue
O2 saturation <90% (%)	6 (13.04)	5 (11.11)	0.789*
Apnea (%)	1 (2.17)	1 (2.22)	0.99†
Vomiting (%)	1 (2.17)	1 (2.22)	0.99†
Hypotension (%)	3 (6.52)	1 (2.22)	0.064†
Nystagmus (%)	1 (2.17)	1 (2.22)	0.441†
Total (%)	12 (26.08)	9 (20)	0.541*

\*Chi square test

†Fisher's Exact Test

### F. Treating Physician Satisfaction

After the end of the procedure, the satisfaction of the treating physician was evaluated via a five-point Likert-type scale. The physician who was responsible for reduction procedure was asked to rate their general satisfaction regarding the depth of sedation and level of muscular tension during the procedure. There were no significant difference between our 2 groups, however, satisfactory levels was a little bit higher in FT group. (4.8 ± 0.6 vs 4.6 ± 0.7, Mann-Whitney U, p=0.87).

## IV. DISCUSSION

The management of analgesia and sedation is a primary concern for the emergency physician [14]. It is necessary for the emergency physician to be familiar in the use of PSA. Painful orthopedic procedures are unavoidable in emergency department. In our study, two thirds of the patients in FT

group reached a desirable sedation level when loading dose was administered and no adjunctive medications required. Our study also revealed that when using FM combination, less than half of the patients put in an appropriate sedative state to perform the procedure. However, ultimate unsuccessful PSA was more seen in FT group.

The onset of action was similar in both groups; however, recovery time was longer in FM group. Regardless to their effect, these results show that patients receiving FM had a longer recovery time and therefore longer stay in the ED in comparison to patients who receive FT. The explanation could be because of pharmacokinetics of drugs. The thiopental is an ultrashort-acting barbiturate and has high lipid solubility, which promotes rapid entry into the brain [15]. The other reason might be because the patients receive higher dosage of midazolam to reach desirable sedation state.

The advantages of barbiturates as induction agents include their high potency, rapid onset, and short duration of action. They reduce cerebral metabolism and oxygen consumption and, secondarily, cerebral blood flow and ICP [16]

Our study showed that pain reduction in FT group was higher than FM group; however, no significant difference was detected. The pain reduction, 5 minutes after the procedure, was higher in FM group, but still, not significant. Our study showed that FT side effects were presented more in FT group but it should be noted that all of adverse events occurred in both groups were mild and managed with minimal interventions. No patients needed tracheal intubation, vasoactive drugs or other aggressive interventions.

The recovery period was longer in FT group, a finding that was anticipated because of previous publications. Reitan et al. conducted a study on 31 healthy patients undergoing minor elective surgery. In their study anesthesia was induced intravenously with either midazolam (0.2 mg/kg) or thiopental (3.5 mg/kg). Induction time with midazolam was significantly longer than with thiopental and time to orientation postoperatively was significantly longer after midazolam [17]. Another study comparing thiopental (2.5 mg/kg) with propofol (1 mg/kg) for induction of anesthesia in the elderly showed that thiopental had significantly faster onset than propofol in elderly surgical patients. The drop in mean arterial pressure was more significant in propofol group [18]

### A. Limitations

We believe our results may confound with some factors. Determination of enough sedation and analgesia was based on relevant criteria but in fact the judgment of treating physicians was playing a great role. Different physicians might have different judgment. The sample size was relatively small. It is possible that some rare associated complication would appear when more cases are studied.

## V. CONCLUSION

Patients presenting to the ED because of orthopedic problems frequently require PSA [19]. Procedural sedation is a fundamental skill expected of a specialist in emergency medicine [14]. Although the safety and efficacy of various

sedation regimens have been extensively studied, published experience about the usage of thiopental for ED PSA is limited [12]. We studied adverse in-hospital events in our participants receiving FT or FM and found that both mixtures are safe for using in ED. The time that patients filled discharge criteria was statistically lower in FT group and it may be clinically significant. Thiopental in combination with fentanyl can be administered to produce profound sedation while permitting rapid recovery. Other potential advantages of Fentanyl-Thiopental over Midazolam-Fentanyl include the more muscle relaxation. Further trials with larger samples comparing thiopental to other common PSA drugs could further document the safety and efficacy of thiopental for ED PSA.

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