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The Effect of Adjunctive Midazolam on Fentanyl Analgesia and Anxiolysis in Acute Limb Trauma: A Randomized Controlled Trial

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Abstract

Background: *We compared combined midazolam–fentanyl versus fentanyl alone for anxiety and pain relief in adult limb trauma patients.*
Methods: *In this double-blind randomized trial at Imam Hossein Hospital (Shahroud, Iran) during 2021, 78 adults (18–80 years) with direct limb trauma (GCS=15, SBP>90 mmHg) were randomly assigned to receive IV fentanyl (1 µg/kg) plus either 1 mL saline or midazolam (1 mg if <50 kg, 2 mg if 50–75 kg, 3 mg if >75 kg). Pain was assessed by Visual Analog Scale (VAS) at baseline, 30 min, and 60 min; anxiety by Depression Anxiety Stress Scales (DASS) before and 60 min post injection. Vital signs and adverse events were monitored; a rescue dose was given if VAS did not decrease by ≥2 points at 30 min. Repeated measures ANOVA, paired and unpaired t-tests, and chi-square tests were applied with α=0.05.*
Results: *Both groups had significant reductions in pain over time (P-value=0.001) and anxiety (P-value=0.001). Between-group differences were nonsignificant for pain at 30 min (P-value=0.697) and 60 min (P-value=0.124) and for anxiety (P-value=0.802). No episodes of hypotension or respiratory depression occurred.*
Conclusion: *Co-administration of midazolam augments fentanyl's anxiolytic effect and provides equivalent analgesia without additional cardiorespiratory compromise.*

Keywords: Trauma, Pain, Anxiety, Midazolam, Fentanyl.
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Introduction

In Iran, trauma is the second leading cause of mortality and the primary reason for years of life lost[1]. Globally, it accounts for approximately 12% of deaths[2] and imposes significant economic and social burdens[3-5], including temporary or permanent disabilities[2, 6]. Pain affects 70% of patients in emergency and critical care settings, hindering cooperation and timely assessment[7-11]. Fentanyl, an opioid with rapid onset and short duration, is widely used for acute traumatic pain relief[12]. Midazolam, a short-acting benzodiazepine, offers quick anxiolysis, mild side effects, and cost-effectiveness[13-15]. Because anxiety can amplify pain perception, we investigated whether adding midazolam to fentanyl improves analgesia and reduces anxiety compared to fentanyl alone in adult trauma patients[16-18].

Materials and Methods

This double-blind parallel clinical trial (IRCT20201226049832N1; ethics IR.SHMU.REC.1400.010) was conducted on 78 trauma patients aged 18–80 years presenting to Imam Hossein Hospital's emergency department in 2021. Inclusion criteria were direct limb trauma, informed consent, stable hemodynamics (SBP>90 mmHg), and full consciousness (GCS=15). Exclusion criteria included pregnancy, mental retardation, psychoactive drug use, addiction, hypotension (SBP<90 mmHg), hypoxemia (SpO_2<92%), and respiratory depression (RR<10 breaths/min), death, discharge, or transfer. Simple randomization with numbered sealed envelopes determined group allocation. The control group received IV fentanyl (1 µg/kg) plus 1 mL saline; the intervention group received the same fentanyl dose plus age- and weight-adjusted midazolam (1–3 mg). Syringes were identical to maintain blinding; only the prescribing physician knew group assignments.

Pain intensity was measured via a 10-cm Visual Analog Scale (0=no pain, 10=worst pain) at baseline, 30 min, and 60 min post injection[19-21]. Anxiety was assessed via the 5-item Depression Anxiety Stress Scales (0–10 total) before and 60 min after injection[22]. Vital signs (BP, HR, RR, SpO_2) were continuously monitored; if VAS reduction was <2 points at 30 min, a second dose was administered per group protocol.

Data were expressed as mean±SD or n (%). Normality was confirmed by Kolmogorov–Smirnov test. Between-group comparisons used independent t-tests or chi-square tests; within-group changes used paired t-tests. Repeated measures ANOVA assessed VAS over time, controlling for injection frequency. Significance was set at P-value<0.05.

Results

Seventy-eight patients completed the study (39 per group). Demographics and baseline vital signs were similar between groups (Table 1). Anxiety scores decreased significantly in both groups at 60 min (intervention 2.33±1.55 to 0.76±0.82; control 1.92±1.57 to 0.81±0.90; both P-value=0.001), with no intergroup difference at 60 min (P-value=0.802) (Table 2). Pain scores fell progressively from baseline to 60 min in both arms (P-value=0.001 within groups) but without significant differences between groups at 30 min (P-value=0.697) or 60 min (P-value=0.124) (Table 3). Repeated measures ANOVA confirmed a significant time effect (F=173.79; P-value=0.001) but no treatment effect (F=0.08; P-value=0.919) (Table 4). No episodes of hypotension or respiratory depression were observed.

Table 1. Patients' baseline characteristics

Variable	Intervention (n=39)	Control (n=39)	P-value
Age, years	42.5±12.9	37.3±12.5	0.070
Male, n (%)	32 (82)	25 (64)	0.234
BMI, kg/m2	24.6±3.9	24.5±5.4	0.889
SBP, mmHg	133.7±19.1	135.1±13.6	0.713
RR, breaths/min	13.2±1.4	13.9±1.8	0.078

Table 2. Anxiety scores (DASS)

Group	Before Injection	60 min After Injection	P-value
Intervention	2.33±1.55	0.76±0.82	0.001
Control	1.92±1.57	0.81±0.90	0.001

Table 3. Pain scores (VAS)

Group	Baseline	30 min After Injection	60 min After Injection	P-value (within)
Intervention	6.86±1.39	4.85±1.87	2.89±1.39	0.001
Control	6.51±1.46	4.68±1.87	2.44±1.09	0.001

Table 4. Repeated measures ANOVA for pain

Source	F	P-value
Time	173.79	0.001
Time × Injection Frequency	27.30	0.001
Time × Treatment Group	0.08	0.919

Discussion

Our findings indicate that the addition of midazolam to fentanyl provided analgesia equivalent to fentanyl alone in limb trauma patients over a 60-minute period, without evidence of added hypotension or respiratory depression. Pain scores decreased gradually in both groups; a pattern consistent with prior studies of benzodiazepine–opioid combinations[23]. Regarding anxiolysis, while a greater numerical reduction in anxiety scores was observed in the midazolam group, it is important to acknowledge that this difference did not reach statistical significance at the 60-minute assessment (P-value=0.802). This suggests that, although a trend toward improved anxiolysis with midazolam was noted, our study cannot conclusively claim a superior effect within this timeframe. The pronounced stress of traumatic injury remains a critical therapeutic target[24], and while fentanyl alone delivered robust analgesia[25], the combined regimen—offering potential dual benefits of sedation and pain relief—was not associated with compromised safety. Emergency specialists may consider patient-specific factors, including anxiety levels, when tailoring regimens, though further investigation is warranted to clarify the anxiolytic profile of such combinations[24-26].

Conclusion: Co-administration of midazolam with fentanyl provided effective analgesia comparable to fentanyl alone in adult limb trauma patients and was not associated with increased cardiorespiratory adverse effects. While a trend toward greater anxiety reduction was observed with the combination, this difference was not statistically significant at 60 minutes. Therefore, this approach can be considered a safe option that may contribute to patient comfort and cooperation during emergency procedures, though its definitive anxiolytic advantage requires further study.

Limitations: Baseline anxiety scores in our study population were relatively low (mean scores of 2.33 and 1.92). This may have introduced a “floor effect,” limiting the measurable range for anxiety reduction and potentially making it more difficult to detect a statistically significant difference in anxiolysis between the intervention and control groups.

Ethical Considerations

Approved by Shahroud University of Medical Sciences Ethics Committee (IR.SHMU.REC.1400.010; IRCT20201226049832N1); written informed consent obtained.

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Conflict of Interest

None declared.

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