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ORIGINAL RESEARCH

Haloperidol-Midazolam vs.Haloperidol-Ketamine in Controlling the Agitation of Delirious Patients; a Randomized Clinical Trial

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Abstract: **Introduction:** Agitation management in delirious patients is crucial in a crowded emergency department (ED) for both patient and personnel safety. Benzodiazepines, antipsychotics, and newly derived ketamine are among the most commonly used drugs in controlling these cases. This study aimed to compare the effectiveness of haloperidol-midazolam with haloperidol-ketamine combination in this regard. **Methods:** In this double-blind randomized clinical trial, delirious patients with agitation in ED were randomly assigned to a group: group A: haloperidol 2.5 mg IV and midazolam 0.05 mg/kg IV or group B: haloperidol 2.5 mg IV and ketamine 0.5 mg/kg IV. Sedative effects as well as side effects at 0, 5, 10, 15, 30 minutes and 1, 2, 4 hours after the intervention were compared between the 2 groups. **Results:** We enrolled 140 cases with Altered Mental Status Score (AMSS)≥+2 and mean age of 52.819.4 years (78.5% male). Agitation was significantly controlled in both groups ($p<0.05$). In group B, AMSS score was more significantly and rapidly reduced 5 ($p = 0.021$), 10 ($p = 0.009$), and 15 ($p = 0.034$) minutes after drug administration. After intervention, oxygen saturation was significantly decreased in group A 5 ($p = 0.031$) and 10 ($p = 0.019$) minutes after baseline. Time required to the maximum effect was significantly lower in group B versus group A ($p=0.014$). Less patients in group B had major side effects ($p=0.018$) and needed physical restraint ($p=0.001$). **Conclusion:** Haloperidol-ketamine can control agitation in delirium more rapidly than haloperidol-midazolam. This combination had lower adverse events with lower need for physical restraint.

Keywords: Ketamine; Haloperidol; Midazolam; Delirium

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1. Introduction

Delirium designates an acute, transient clouded state of mind with cognitive disruption and confusion (1). Disturbance in consciousness and inattention are the hallmarks of delirium (2, 3). Thus, many such patients are referred to emergency department (ED) for an urgent intervention in controlling agitation (4).

Generally, agitated patients can manifest overtly violent behaviors leading to injuries to themselves, other patients, medical staff, and their surrounding environment (5, 6). This extreme restlessness accounting for 2.6% of ED encounters, is an obstacle to provision of timely and appropriate medical services (7).

The most important initial steps in controlling such patients are: verbal de-escalation techniques, and physical and chemical restraints (8, 9). Administrating parenteral sedatives can decline agitation more rapidly and facilitates more efficient control of agitated cases (10).

Severe agitated/excited delirium if left untreated can cause metabolic derangement, cardiac arrest and death (11).

Benzodiazepines, antipsychotics, and their combination are commonly used in EDs as the main drugs in controlling agitation (12). Both classes have major side effects (13, 14). Midazolam, a short-acting anxiolytic agent, has amnestic, hypnotic, and sedative effects with different routes of administration (intravenous (IV), intranasal (IN) and intramuscular (IM)) and provides desirable sedation in less than 20 minutes. Haloperidol is a first-generation antipsychotic with oral, IV and IM administration routes. It takes almost 30 minutes to

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show its sedative effect (15, 16).

Ketamine, a highly dissociate sedative, provides rapid and safe control of agitated and violent cases in ED with lower rates of adverse events (17-20). It's low dose (1-2 mg/kg) is usually used as a second line agent when the previous tranquilizers fail (21). It has a rapid onset of action of around 2 minutes (IV) and 5 minutes (IM) (22).

Research in this field recommends that further studies should be performed to exactly determine the best drug option when facing agitation in an emergency situation. Many factors are involved in making the best decision; patients' situation, age, initial medical diagnosis, underlying diseases, and available resources. Considering the fact that midazolam can cause respiratory apnea, haloperidol can cause extrapyramidal reactions and ketamine can cause emergence phenomenon (13-17), we used the combination formula to see whether we can reach the best combination with the least adverse events in controlling agitation in delirious cases mostly in elderly age range. Since the data in dealing with agitation in delirious patients in ED is scarce, we designed this study to evaluate the effectiveness of combination drugs of haloperidol-midazolam with haloperidol-ketamine in controlling agitation in delirious patients in ED.

2. Methods

2.1. Study design and setting

The present study, a double-blind randomized clinical trial, was performed on delirious patients with agitation in EDs of Shariati, Sina, and Imam Khomeini Hospitals from January to December 2020. The study protocol was approved by the Ethics committee of Tehran university of medical sciences (Ethics code: IR.TUMS.MEDICINE.REC.1397.532) and registered in Iranian Registry of Clinical Trials with code: IRCT20120130008872N13. Informed written consent was obtained from patients' guardians.

2.2. Participants

Patients older than 18 years with delirium and agitation (Altered Mental Status Score (AMSS)≥+2) (23-25) were enrolled in our study and randomly allocated to either group A: haloperidol 2.5 mg IV and midazolam 0.05 mg/kg IV (max dose 3 mg) or group B: haloperidol 2.5 mg IV and ketamine 0.5 mg/kg IV (max dose 75 mg). Pregnant cases and patients with history of severe head trauma, suspicion of high intracranial pressure, history of epilepsy, shock status and hemodynamic instability, cases with unwillingness to participate in the study and prior tranquilizer administration in out of hospital settings were excluded.

2.3. Data gathering

Basic demographic data, past medical and habitual histories (underlying diseases such as: cardiovascular, cerebrovascular, diabetes mellitus, neurologic diseases, and allergy), vital signs, intervention side effects, time to maximum effect, number of repeated doses required, number of cases needed physical restraint, and AMSS score were assessed during the study. Vital signs and AMSS score were recorded at 0, 5, 10, 15, 30 minutes and 1, 2, 4 hours after the intervention.

AMSS score is an ordinal scale of agitation from 4 (unresponsive) to +4 (combative). Severe agitation is defined as AMSS score of +2 or +3, and profound agitation is defined as AMSS score of +4.

We defined "time required to the maximum effect", as the time needed to reach AMSS score below +2 and also to decrease AMSS by at least 1 unit. The presented side effects in this study included: respiratory apnea, hemodynamic instability (drop in systolic blood pressure (SBP)<90 mmHg), extrapyramidal reactions (occurrence of stiffness, restlessness, and tremor) and emergence phenomenon (occurrence of new agitation, hallucinations, and illusions). An emergency physician examined patients and recorded all these adverse effects.

2.4. Procedure

Method of sampling was block-randomization, based on random numbers table; two blocks of 35 were created from zero to 70 in a random way. Patients were randomly assigned to one of the two blocks based on the order of numbers. Study was double blinded, neither the patient nor the emergency physician was aware of randomization and the prescribed sedation in each group. Drugs' syringes were covered in order to hide the color and volume differences. Triage nurse administered the drug and the emergency physician diagnosed and evaluated the patient and recorded all study variables at a specific time.

If the patient remained agitated (AMSS≥+2) despite drug administration after 15 minutes, repeated dose of the same combination was prescribed in both groups. If a patient did not achieve the optimum goal of sedation after 4 hours, alternative sedatives (such as diazepam, etomidate, ...) would be used to control agitation. All patients were closely and continuously monitored for side effects, apnea, and hemodynamic changes.

2.5. Outcomes

Primary outcomes were comparing AMSS score and vital signs within and between the 2 groups. Secondary outcomes were comparing the side effects, time to maximum effect, and number of repeated doses between the 2 groups. Patients' surveillance and follow-up for side effects and other

secondary outcomes such as physical restraint and repeated dose requirement were continued up to 6 hours.

2.6. Statistical analysis

With an assumed average baseline AMSS score of 3 with SD=1, α=0.05 and β=0.1 (26), we calculated the sample size and 50 patients in each group were required to detect a 1-point difference in AMSS scores between the 2 groups. All data were analyzed using SPSS V.25 software. All the descriptive data are presented as mean ± standard deviation (SD). We conducted a Kolmogorov–Smirnov (KS) test and all data had normal distribution. Analytical statistical tests included two-tailed t-test for continuous variables. Chi-square and Fisher's exact tests were used to compare proportions of the qualitative variables. Repeated measures analysis of variance (ANOVA) was used to determine the difference within each group. The level of significance was 0.05. We performed analyses on an intention-to-treat basis. For presenting the effects, number needed to treat (NNT), number needed to harm (NNH), absolute risk reduction (ARR), and relative risk reduction (RRR) with 95% confidence interval (CI) were calculated and reported.

3. Results

3.1. Baseline characteristics of studied cases

Overall, 140 patients with delirium and agitation were included in this study based on emergency physician diagnosis and study inclusion criteria (flow diagram of the study is shown in figure 1). The mean age was 52.8±19.4 (range : 31-78) years (78.5% male). Baseline characteristics of patients showed no significant differences between the 2 groups (Table 1).

3.2. Outcomes

Comparison of studied outcomes between groups is shown in tables 2 and 3.

3.3. AMSS score

Agitation was significantly controlled within each group (group A (p=0.001) and group B (p=0.012)). In group B, AMSS score was more significantly and rapidly reduced 5 (p = 0.021), 10 (p = 0.009), and 15 (p = 0.034) minutes after drug administration. Two-way repeated measure ANOVA showed this significant difference in AMSS score reduction between the 2 groups during the study (p=0.044). NNT was 10 (95%CI: 3.8 to 17.5), ARR=0.1, and RRR=0.25.

3.4. Vital signs

Pulse rate (PR) significantly improved within each group (group A (p=0.046) and group B (0.019)). In group B, PR reduction was more significant than group A 5 (p=0.049) and 10 (p = 0.050) minutes after drug administration. All these variables declared that agitation was more rapidly controlled in group B.

After intervention, oxygen saturation (SPO2) was significantly lower in group A in comparison to group B 5 (p=0.031) and 10 (p = 0.019) minutes after baseline.

3.5. Time to maximum effect

Time required to the maximum effect was significantly lower in group B versus group A (p=0.014). Incidentally, half of patients (50%) in both groups needed repeated doses to achieve agitation control (p=0.068). None of our cases needed alternative sedatives after 4 hours. Less patients needed physical restraint in group B (p=0.001).

3.6. Side effects

More cases in group B had no side effects in comparison to group A (p=0.018). In group A, 11 patients faced hemodynamic changes, 4 experienced extrapyramidal reactions, and 9 cases had apnea (mostly transient and resolved with oxygen, non-invasive modalities, and airway maneuvers and only 3 cases need intubation). In group B, 5 patients experienced emergence phenomenon and 1 extrapyramidal reaction. NNH of experiencing a side effect was 3.8 (95%CI: 2.5 to 7.8).

4. Discussion

In the present study, we compared the sedative effectiveness of haloperidol-midazolam versus haloperidol-ketamine in controlling agitation in delirium state in ED. We realized that the latter combination decreased AMSS score more rapidly than the first 5, 10, and 15 minutes after drug administration. Time required to maximum effect (lowering AMSS score below +2 and at least by 1 unit) was significantly lower in group B versus group A (p=0.014). Side effects and physical restraint were less common in group B versus group A.

Emergency physicians often encounter acute agitation in different groups of patients, who can harm themselves and cause chaos in ED. A wide array of factors is involved in disorganized and violent behavior including: drug overdose, chemical intoxication, psychiatric disorder, and acute medical illnesses like delirium (5, 6).

Similar studies evaluating agitation control in ED, concluded that time to adequate sedation for ketamine alone is 4.2 to 7.7 minutes (27-29). In our study, time to maximum effect for IV haloperidol-ketamine was 3.190.7 minutes. Many studies confirmed the faster sedative effect of ketamine in ED in agitation control and even suggested the possibility of using ketamine as the first line agent (30).

Heydari et al. in 2018, compared the effects of IM ketamine versus IM haloperidol on acutely agitated patients in ED.

They revealed that mean time to adequate sedation (AMSS score<+1) in ketamine group (7.73±4.71 minutes) was significantly lower than haloperidol group (11.42±7.20 minutes) (p=0.005). 15 minutes after intervention, the sedation score did not differ significantly in the two groups (p=0.167) (29). Our results with IV combination administration were the same.

Cole et al. in 2016, conducted a prospective study on agitation control in the prehospital setting and announced that IM ketamine was significantly superior to IM haloperidol in terms of time to adequate sedation. The median time to adequate sedation was 5 minutes for ketamine and 12 minutes for haloperidol (p<0.0001). In their study, more patients in haloperidol group needed additional sedation with midazolam. While, ketamine was associated with higher intubation rate of 39% versus 4% (p<0.0001) (22). In our study, only 3 cases all in the haloperidol-midazolam group needed intubation.

Li et al. in 2020, determined the effect and safety of 1mg/kg IV and 2 mg/kg IM ketamine in excited delirium. They perceived that ketamine significantly reduced agitation (Richmond Agitation Sedation Scale) (p=0.001). They reported a lower incidence of adverse events (including intubation) in comparison to previous studies. It seemed that most of these effects occurred at higher doses (31). We administered lower doses of ketamine as sedative agent and also considered a maximum dose in order to avoid major side effects. Lin et al. in 2020, compared the efficacy and safety of ketamine (4 mg/kg IM or 1 mg/kg IV) versus haloperidol (5-10 mg IV or IM) plus lorazepam (1-2 mg IV or IM) for initial control of acute agitation. They found that more patients in ketamine group were sedated at 5 and 15 minutes (p=0.001 and <0.001, respectively). The median time to sedation was lower in the former group in comparison to the latter, 15 versus 36 minutes (p<0.001) (32). Their findings were similar to ours. Despite few emergence phenomena in our study, authors in the mentioned study did not report any major side effects even in higher doses of ketamine. They also detected that ketamine was related to tachycardia and hypertension, and a nonsignificant increase in hypoxia. In our study, we did not discover such findings, rather in group B, PR reduction was more significant than group A 5 and 10 minutes after drug administration (p=0.049 and 0.050, respectively) and SPO2 was significantly decreased in group A in comparison to group B 5 and 10 minutes after baseline (p=0.031 and 0.019, respectively).

5. Limitations

Most of our patients were in older age range compared to previous studies. We tried to compensate for most limitations in previous studies like larger sample size and prospective design.

6. Conclusion

Our study discovered that haloperidol-ketamine can control agitation in delirium more rapidly than haloperidol-midazolam. This combination had lower adverse events with lower need for physical restraint.

7. Declarations

7.1. Acknowledgments

None.

7.2. Conflict of interest

The authors had no conflicts of interest.

7.3. Funding Sources

None.

7.4. Authors' contribution

EV, ZN and MS conceived the study, designed the trial, supervised the conduct of the trial and data collection. MA and HA undertook recruitment of participating centers and patients and managed the data, including quality control. ZN and MS provided statistical advice on study design and analyzed the data. EV drafted the manuscript, and all authors contributed substantially to its revision. EV takes responsibility for the paper as a whole. All authors read and approved final version of manuscript.

7.5. Using artificial intelligence chatbots

None.

7.6. Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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Table 1: Comparing the baseline characteristics between the two groups

Variable	Group A (n = 70)	Group B (n = 70)	P value
Age (year)			
Mean ± SD	47.51 ± 22.9	54.06 ± 18.5	0.138
Gender, N (%)			
Male	50 (71.4)	60 (85.7)	0.145
Female	20 (28.6)	10 (14.3)	
Habitual history (drug or alcohol)			
Positive	32 (45.7)	28 (40.0)	0.629
Negative	38 (54.3)	42 (60.0)	
Underlying diseases			
Yes	2 (2.9)	12 (17.1)	0.106
No	68 (97.1)	58 (82.9)	
AMSS score			
Mean ± SD	3.49 ± 0.7	2.89 ± 0.4	0.531

Data are presented as mean ± standard deviation (SD) or frequency (%). AMSS: Altered Mental Status Score.
Group A received Haloperidol-Midazolam and group B received Haloperidol-Ketamine.

Table 2: Comparison of primary outcomes within and between groups A (Haloperidol-Midazolam) and B (Haloperidol-Ketamine)

Variable	Baseline	5 min	10 min	15 min	30 min	60 min	120 min	240 min	P[1]	P[2]
A	3.49±0.7	2.23±1.7	2.01±1.1	1.06±1.0	0.19±0.5	0.53±0.9	0.94±0.8	1.03±0.7	0.001	0.044
B	2.89±0.4	0.31 ±1.2	-0.83±1.2	-0.71±1.3	0.26 ±0.6	0.41 ±0.7	1.06±0.9	0.91 ±0.9	0.012	
P-value[3]	0.531	0.021	0.009	0.034	0.067	0.051	0.050	0.083		
Pulse Rate (Beats/min)										
A	99.66±18.8	97.03±8.9	99.54±12.6	96.09±11.5	98.31±10.1	86.29±11.4	82.89±10.1	83.26±10.6	0.046	0.102
B	98.57±9.5	87.43±7.6	82.17±11.3	83.29±10.1	85.57±9.2	83.22±8.4	85.37±11.1	87.6 ±9.7	0.019	
P-value	0.641	0.049	0.050	0.112	0.065	0.813	0.641	0.093		
Systolic blood pressure (mmHg)										
A	151.77±14.7	147.65±11.8	138.43±17.8	168.86±9.9	148.47±16.7	131.82±8.2	128.09±9.0	131.43±10.6	0.125	0.064
B	134.71±17.1	137.14±9.9	115.14±10.7	126.09±15.5	105.14±10.8	107.14±12.7	117.43±13.8	121.14±12.4	0.719	
P-value	0.634	0.059	0.703	0.126	0.094	0.214	0.078	0.630		
Diastolic blood pressure (mmHg)										
A	77.77±5.7	79.14±10.3	68.53±8.8	80.86±8.7	69.11±7.5	73.92±9.3	76.43±6.5	79.01±5.6	0.159	0.115
B	69.14±3.1	71.86±2.7	69.57±9.2	84.71±7.2	72.71±8.4	68.65±4.6	67.91±5.3	77.34±6.2	0.081	
P-value	0.818	0.235	0.719	0.093	0.110	0.207	0.0830	0.513		
Respiratory (rate /min)										
A	19.02±4.5	17.32±3.1	16.08±1.2	17.64 ±0.2	15.05 ±3.2	11.57 ±0.2	12.29 ±2.5	14.64 ±1.2	0.914	0.072
B	17.43±3.1	16.52±5.2	18.14±6.1	15.96±2.2	18.41±0.9	14.92±2.3	13.07±0.6	17.20±3.9	0.835	
P-value	0.281	0.068	0.119	0.817	0.093	0.411	0.784	0.086		
Oxygen saturation (%)										
A	92.83±9.3	90.12±7.6	89.71±5.5	91.74±9.1	93.08±4.5	90.16±1.7	92.91±4.8	92.64±1.9	0.316	0.052
B	93.41±5.8	95.04±2.6	92.50±8.3	94.14±3.9	96.04±4.7	92.06±1.5	94.52±6.6	93.15±3.3	0.805	
P-value	0.157	0.031	0.019	0.218	0.085	0.230	0.194	0.073		

Data are presented as mean ± standard deviation (SD). AMSS: Altered Mental Status Score. Min: minute.
[1]P-value of intragroup changes during the study based on repeated measures ANOVA.
[2]P-value of intergroup changes during the study based on repeated measures ANOVA.
[3]P-value of intergroup changes at specific time intervals during the study based on T-test.

Table 3: Comparison of secondary outcomes between groups A (Haloperidol-Midazolam) and B (Haloperidol-Ketamine)

Variable	Group A	Group B	P-Value
Time to maximum effect (Minute)			
Mean ± SD	8.82 ± 1.6	3.19 ± 0.7	0.014
Repeated doses			
Once	21 (30.0)	28 (40.0)	0.068
Twice	14 (20.0)	7 (10.0)	
Number of physical restraints			
Number (%)	29 (41.4)	13 (18.5)	0.001
Side effects			
Yes	24 (34.3)	6 (8.6)	0.018
No	46 (65.7)	64 (91.4)	

Data are presented as mean ± standard deviation (SD) or frequency (%).

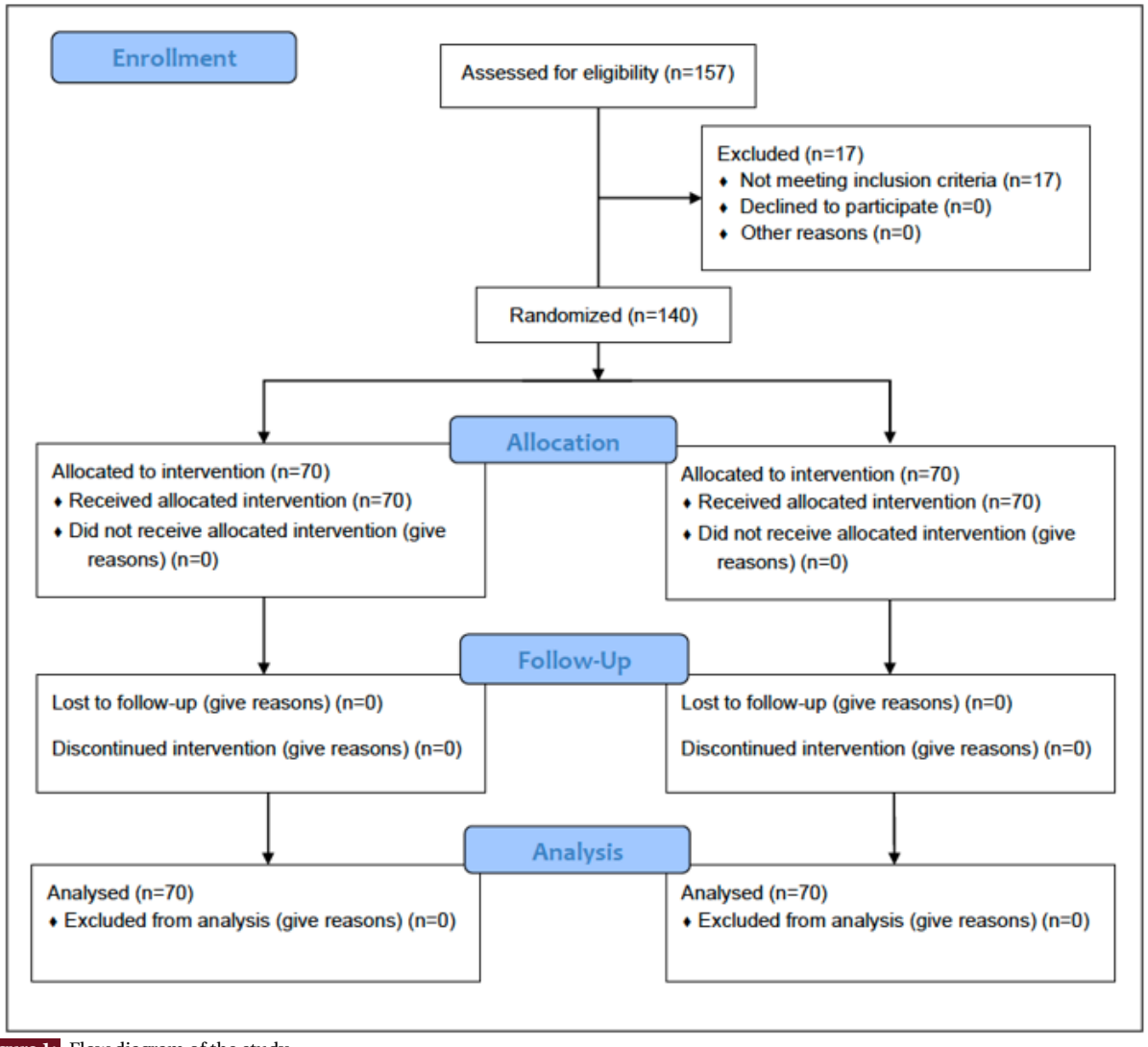

Figure 1: Flow diagram of the study.