Original Article

Efficacy of intramuscular haloperidol versus haloperidol plus promethazine in controlling aggressive behavior of psychiatric patients admitted to emergency rooms

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Abstract

Introduction: The aim of this study was to compare the therapeutic and adverse effects of haloperidol to the combination of haloperidol and promethazine (antipsychotic + antihistamine) for controlling patients with aggressive or violent behavior referred to psychiatric emergency rooms.
Methods: Using a double-blind randomized controlled trial, 100 eligible psychiatric patients admitted to emergency room of Taleghani hospital, Tehran, Iran, randomly received intramuscular haloperidol or haloperidol plus promethazine. The patients were observed at 20, 40, 60, 120 minute intervals and then at 6, 12 and 24 hourly intervals to determine if they were tranquil or asleep, need for further injection, serious adverse effects, acute dystonia, akathisia, need for other medications, and need for admission to hospital based on clinical judgment.
Results: The mean age of patients was 36.25 years and 69% were male. Patients receiving promethazine plus haloperidol were more tranquil after 2, 6 and 12 hours and sustained sleep after hours 2 and 6. Adding promethazine to haloperidol decreased the need for repeated involvement of the psychiatrist on duty, using additional medications and hospital admission. Patients taking the combination of haloperidol and promethazine did not experience more adverse effects than those taking only haloperidol.
Conclusion: The combination of haloperidol plus promethazine can be safely used in emergency rooms for controlling patient with agitation and aggressive behavior resulting in a sustained tranquilization or asleep and lower need for further intervention.
Declaration of Interest: None.

Keywords: Haloperidol, Promethazine, Antipsychotics, Sedation, Aggression, Violence.

Introduction

Aggressive and violent behavior is a common reason for referral to psychiatric emergency rooms and occurs in 1-3% of psychiatric patients (1,2). Such behavior could result from psychotic states especially auditory hallucinations and paranoid delusions, impulsivity, intoxication, cognitive impairment or a combination of these conditions. Aggressive behavior is possibly the most challenging part of management of these patients considering their vulnerability for agitation and violent reactions. It could be verbal or non-verbal and influenced by patients' anger, personality characteristics and emotional stressors such as forced hospitalization. However, the way those patients react and express their emotions have been overestimated and amended (3). The most common medications for management of agitation and aggressive behavior in the emergency settings around the world are antipsychotics,

benzodiazepines or a combination of both (4,5). The newer antipsychotics are the long acting agents like flupenthixol acetate and intramuscular olanzapin and ziprasidone (6, 7, 8). Evidences indicate that irritability, impulsivity, hyperactivity and agitation respond well to short-term treatment with dopamine antagonists. Among these, the least sedating and the more efficient (like haloperidol) are preferred on sedative agents.

The combination of haloperidol and promethazine is a very common method for to quickly calm aggressive patients (9). Promethazine, a drug derived from phenothiazine, blocks histamine receptors, which increases sedation and may prevent dystonic adverse effect of the injected haloperidol (10). Previous studies have compared haloperidol plus promethazine to lorazepam (11), haloperidol plus midazolame (12) and haloperidol alone (13), haloperidol to flunitrazepam (14) as well as olanzapine (15) and have reported benefits and disadvantages for each regimen. The effect may differ because of variation of the primary reason of agitation (16). The effectiveness of rapid tranquillization with haloperidol has also been compared to other antipsychotics such as olanzapine and aripiprazole but the results are not conclusive (17- 19).

To the best of our knowledge there has been no study in Iran aimed at comparing the effect of haloperidol to the combination of haloperidol and promethazine in psychiatric emergency room setting. Hence, this trial was designed to close the gap in clinical knowledge in the Iranian population.

Methods

The clinical study protocol was approved by the ethic committee of Ardabil University of Medical Sciences and was carried out according to the provisions of the Declaration of Helsinki. Informed written consent was obtained from the caregiver of the patients. The study sample included all of the patients aged 18-50 years old with aggressive or violent behavior admitted to the emergency room of Taleghani hospital, Tehran, Iran from October 2011 to June 2012. Patients who failed to follow up (because of early discharge from the hospital or death) were excluded from the study.

Consecutive patients were divided to two groups based on randomly assigned numbers to receive intramuscular haloperidol or haloperidol plus promethazine based on double blind randomized clinical trial. The initial dose of haloperidol was 5 mg in both groups, which was increased up to a total of 20 mg (in divided doses) when there was no response. Promethazine was started at 25 mg and could be increased to a total dose of 100 mg if needed.

The psychiatrist on duty who was blind to the medication used for tranquilization, followed-up and observed patients at 20, 40, 60, 120 minute intervals and then at 6, 12 and 24 hourly intervals in terms of being tranquil or asleep, need for further injection, serious adverse effects such as acute dystonia, akathisia and delirium need for other medications and need for admission to hospital. The observations were recorded in a predefined case report form. Patients were considered to be tranquil when they were calm and without aggressive or dangerous behavior. The severity of symptoms was based on clinical judgment of the psychiatrist.

Statistical significance was calculated with the chi-squared test for comparing proportions of patients tranquillized, asleep, requiring multiple visits of the psychiatrist, and requiring additional sedation, as appropriate. Data are expressed as the mean±SD and number (percentage). Statistical significance was defined as $p<0.05$.

Results

From the total of 128 patients admitted to the emergency room, follow-up data was available for 100 patients, including 50 patients receiving haloperidol alone, and 50 receiving haloperidol plus promethazine (figure 1). Characteristics of these patients are shown in table 1. Most of the patients were male (66%, 33/50) and the most common reason for referral was an acute mania or mixed episode.

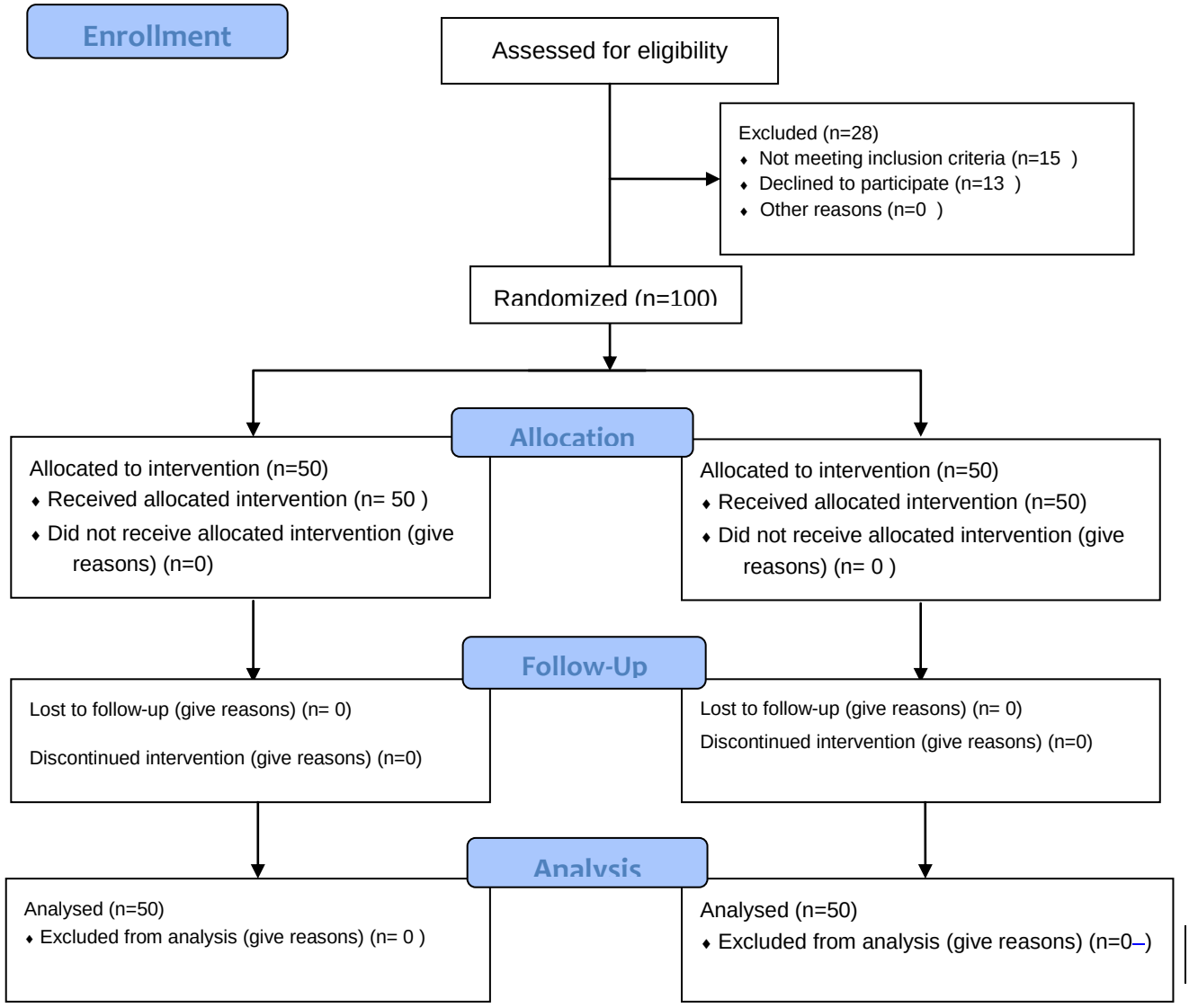

Figure 1 - CONSORT Flow Diagram

Table 1. Baseline clinical and demographic characteristics of patients with aggressive behavior in emergency room.

	Haloperidol	Haloperidol plus promethazine
Male n (%)	33 (66)	36 (72)
Female n (%)	17 (34)	14 (28)
Mean age (SD)	35.98(14.00)	36.52(11.44)
Previous admission		
Yes n (%)	28 (48)	30 (52)
No n (%)	23 (55)	19 (45)
Clinical diagnosis for aggression		
Psychotic disorders	13	9
Substance misuse	0	4
Substance withdrawal disorder	3	9
Personality disorders	2	2
Bipolar mood disorder	24	18
Other*	8	8
Severity of aggression		
Moderate	31	21
Severe	16	21
Very severe	3	8

Main outcomes for this trial are described in table 2. As shown, there was no significant difference between the two groups in terms of tranquility in minutes 20, 40, 60 or after 24 hours, but patients receiving haloperidol plus promethazine were more tranquil at minutes 120 as well as hours 6 and 12.

Though equal numbers of patients from each group were asleep within one hour, the combination of haloperidol plus promethazine was superior to haloperidol alone in maintaining sleep at hours 2, 6 and 12 hours.

Adding promethazine to haloperidol was not accompanied by an increase in adverse effects or further episodes of aggressive behavior or violence and an equal number of patients from both groups needed more injections to be tranquilized (table2). However, the antipsychotic - antihistamine combination significantly reduced the need for repeated involvement of the psychiatrist on duty, using additional medications and hospital admission.

Table 2. Main outcomes related to tranquility and asleep

Tranquil		Haloperidol n(%)	Haloperidol plus promethazine n(%)	$\chi 2$
	20 min	36 (33.0)	2 (33.0)	1.60
	40 min	14 (42.0)	43 (42.0)	0.29
	60 min	36 (28.0)	40 (38.0)	0.87
	120 min	26 (32.5)	39 (32.5)	7.42 **
	6 hr	17 (26.2)	36 (26.8)	13.84 **
	12 hr	9 (16.0)	23 (16.0)	9.007 **
	24 hr	7 (9.0)	11 (9.0)	1.08
Asleep				
	20 min	29 (29.0)	29 (29.0)	0.00
	40 min	29 (31.0)	33 (31.3)	0.67
	60 min	31 (32.5)	34 (32.5)	0.39
	120 min	25 (30.0)	35 (30.0)	4.16 *
	6 hr	17 (23.0)	29 (23.0)	5.76 **
	12 hr	3 (3.5)	4 (3.5)	0.15
	24 hr	0	1 (0.5)	1.01
Need for second injection		19 (17.0)	15 (17.0)	0.71
Further Aggression within 24 hours		23 (19.5)	16 (19.5)	2.06
Psychiatrist recalled		18 (13.5)	9 (13.5)	4.11 *
Adverse effects		5 (6.5)	8 (6.5)	0.76
Additional medication within 24 hours		31 (26.5)	22 (26.5)	3.25 *
Admission more than 2 weeks		23(17.5)	12 (17.5)	5.31 *

Conclusion

This study compared the effect of haloperidol to the combination of haloperidol and promethazine in controlling aggressive behavior in emergency rooms. Results of the current study revealed that patients who received combination of haloperidol and promethazine were more tranquil in hours 2, 6 and 12 after injection. Although few studies have achieved a better result comparatively in the first 20 minutes (13), results presented in this study are compatible with studies by Alexander et al. (11), Baldacara et al. (12) and Raveendran et al. (17) who also found a lengthy and superior effect for this combination. These studies attribute the superior performance to sedative effects of promethazine and its antimuscaranic properties as well as better safety profile in preventing serious adverse effects related to the extrapyramidal system. These results suggest that agitated patients may benefit from this combination to achieve a long-standing effect, particularly in chaotic emergency room situations where on set and duration of medication efficacy is important for operational productivity.

The same pattern was found for maintaining the sleep in patients receiving haloperidol and promethazine. The same number of patients was asleep from both groups during the first 60 minutes as well as last hours of follow up, but sleep was better maintained in hours 2 and 6

after injection in patients receiving the combination. These results are compatible with previous studies (11-12, 16). Sedation by haloperidol is probably explained by blockage of dopamine transport in the brain. Haloperidol is structurally similar to transporter of gamma amino butyric acid (GABA) and interacts with GABA receptors in higher doses (20). Adding an antihistamine to haloperidol could reinforce this effect and induce more sedation than with haloperidol alone (9,10).

We did not find higher instances of adverse effects for the combination. However, unlike some studies (13) the group receiving haloperidol alone did not have higher adverse effects (like dystonia). These results are not conclusive as they could be influenced by several factors such as age and medications taken by the patients. For example, side effects like dystonia are not usually expected in a patient who is already taking an antipsychotic and probably an anticholinergic as prophylactic agent for such adverse effect.

Similar to previous studies, these results showed that the combination of haloperidol and promethazine decreased the need for repeated calling of the psychiatrist on duty, administration of additional medications such as chlorpromazine or lorazepam, and the need for hospitalization after hour 12, which is the normal course of action for patients not responding to the medication (11-15). These outcomes could in part be as a result of sustained sleep and being tranquil.

Main outcomes including being asleep and tranquil, were measured as nominal variables and by clinical judgment according to criteria defined in the patient case report form. The reason for referral was not the same in all patients and could influence the efficacy of medication. Furthermore, studies are suggested to include patients with the same primary reason for aggressive behavior and standard scales. In conclusion, the combination of haloperidol plus promethazine can be safely used in emergency rooms for controlling patient with agitation and aggressive behavior resulting a sustained tranquilization or sleep and reduced need for further intervention.

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Conflict of Interest Statement

Authors declare that there is no conflict of interest.

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