Original Article

Comparison of Haloperidol, Promethazine, Trifluoperazine, and Chlorpromazine in Terms of Velocity and Durability of the Sedation among Acute Aggressive Patients: A Randomized Clinical Trial

Seyed Ghafur Mousavi, Shima Mirnezafat, Mohammad Javad Tarrahi[1]

From the Department of Psychiatry, Behavioral Sciences Research Center, Faculty of Medicine, Isfahan University of Medical Sciences, [1]Department of Epidemiology and Biostatistics, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Knowledge and skill about sedation of aggressive patients is necessary for each psychiatrist. The purpose of this study was comparing the velocity and durability of sedation induced by the haloperidol, trifluoperazine, promethazine, and chlorpromazine in aggressive patients. **Materials and Methods:** This randomized clinical trial was done on 76 aggressive patients referred to Psychiatry Emergency Service of Noor Hospital of Isfahan University of Medical Sciences that were randomly divided into four groups of haloperidol, promethazine, chlorpromazine, and trifluoperazine. Patients were evaluated at 30 min intervals for aggressive symptoms, and if they did not respond to intervention after the first 30 min or if they showed aggression again, a same dose of the injected drug was prescribed. The length of sedation time was recorded for each patient. **Results:** Seventy-six patients with the mean age of 31.89 ± 8.73 years were participated and 63.2% of them were male. Response to intervention after the first injection was seen in 40.8% and 59.2% needed the second injection. The mean time needed for obtaining sedation was 17.38 ± 8.23 and 19.66 ± 4.64 min after the first and second injection, respectively. The mean times of sedation induction were not significantly related to age, gender, type of substance used, type of aggression, and type of psychiatric disorder. Considering the type of drugs, there was no significant difference between velocity and durability effect of sedation after the first and second injection. **Conclusion:** Comparing the velocity and durability of sedative effect of the four studied drugs on acute aggressive patients, did not show any significant difference between them.

Keywords: *Aggression, chlorpromazine, haloperidol, promethazine, trifluoperazine*

Introduction

Aggression defined as hostile, injurious, or destructive behavior, often caused by frustration, and it can be verbal or physical.[1] There are several factors related to the incidence of aggression including psychological, pharmacological, economical, and psychosocial factors.[2] About 30% of patients who referred to psychiatric emergency have aggression.[1,3] Aggression and agitation are nonspecific symptoms that can be caused by different medical situations. Psychotic patients and those with bipolar or personality disorder and depressed patients may experience episodes of aggression in their disorder courses.[4]

To prevent injuries of patients and individuals who are around aggressive patients, it is necessary to manage patient's aggression as soon as possible.[5] To achieve this purpose, antipsychotic medications and benzodiazepines were used alone or in combination; the efficacy of these medications in calming down the aggressive patients was approved by several studies.[6,7] The second generation of antipsychotics has shown less sedative effects in comparison to the first generation, higher costs, and often cause weight gain and other metabolic syndrome symptoms and also may be unavailable easily in some countries.[8] There are limited studies that compared the efficacy of different types of the first generation antipsychotics on sedation of the aggressive behaviors, moreover, their findings are controversial.[7,9,10] Some studies reported the effectiveness of the promethazine, an antihistamine medication, on de-escalation of aggressive patients.[11,12]

Most of the previous studies have compared two medications, and there are

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Address for correspondence:
Dr. Shima Mirnezafat, Department of Psychiatry, Behavioral Sciences Research Center, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: mirnezafat1392@yahoo.com

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limited comparison studies of more than three medications. Moreover, although the velocity of sedation has been a concern in previous studies, the duration of the sedative effect has been less studied. Thus, this study aimed to compare the velocity and durability effect of the four drugs which are used usually for sedation of aggression in our country, i.e. haloperidol, trifluoperazine, promethazine, and chlorpromazine, on sedating the aggressive patients who admit to the psychiatry emergency service.

Materials and Methods

This study was an open-label randomized clinical trial (RCT) on 76 aggressive patients who were referred to the Psychiatry Emergency Service of Noor Hospital of Isfahan University of Medical Sciences (IUMS) (Isfahan, Iran), during December 2017–September 2018.

The inclusion criteria were: (1) above 18-year old; (2) no contraindication for prescribing medication which used in this study; (3) verbal or physical aggression in the emergency room at the first visit; and (4) informant consent of the patient's family or attendant for participation in the study.

The exclusion criteria were participant discontinuance, arising any drug side effect which prevent from continuance of the study.

The sample size was estimated according to similar studies which was 76 patients, and hence, we estimated 19 patients for each group. Participants were selected according to simple sampling methods, i.e. evaluated all patients aggressive who referred to psychiatric emergency service, according to the inclusion and exclusion criteria.

The patients were randomly divided into four groups by psychiatry resident using the same simple method. The ampoules of haloperidol, promethazine, chlorpromazine, and trifluoperazine, were labeled as 1–4. To divide the patients into four groups, the random allocating system was used from 1 to 4 according to this method.

The intervention medications were manufactured by pharmacological companies as followed: promethazine (Alborz Darou, Qazvin, Iran), chlorpromazine (Tehran Chemie, Tehran, Iran), haloperidol (Exir, Tehran, Iran), and trifluoperazine (Caspian Tamin, Gilan, Iran). We used haloperidol 5 mg for the first group, 50 mg promethazine for the second group, 50 mg chlorpromazine for the third, and trifluoperazine 1 mg in the fourth group, intramuscularly by an experienced nurse. All patients were followed up during 2 h for sedation induction by psychiatry resident and evaluated 30 min intervals for aggressive symptoms, and if they did not respond to intervention at the first 30 min, or if they showed aggression relapse, the same dose of the injected drug was prescribed again. The effectiveness of intervention was defined as discontinuation of the physical and verbal aggression. Verbal aggression defined as: shouting, threatening or insulting others, and physical aggression defined as: kicking, knocking, beating him/herself or others, or throwing objects. The time last for sedation was recorded by chronometer for each patient by psychiatry resident. During and after each injection, patients were observed for probable side effects, and necessary treatments were done in case of any complication.

Before the intervention, the patients' demographic information and also data of their past psychiatric and substance history were recorded. Considering ethical issues, this study was open-labeled, and researchers were not blinded, for better managing severe aggression and other problems as soon as possible.

For evaluating differences between groups in quantitative variables, it used Chi-square test, and for the qualitative variables, Kruskal–Wallis was used. All statistical analyses were performed using SPSS version 22 (SPSS corp., Chicago, IL, USA). A two-sided α level of 0.05 was used to assess statistical significance. This study was approved by the Regional Bioethics Committee of IUMS and recorded by the Iranian RCT Registration Center (IRCT: IRCT20090726002232N4).

Results

In this study, 100 aggressive patients were assessed for eligibility that 24 of them were declined; 15 patients because of <18-year-old age and 9 patients because of nonconsent to participation; ultimately, 76 patients were participated [Figure 1]. None of the patients showed any side effects due to medications used in this intervention.

The mean time needed for obtaining sedation was 17.38 ± 8.23 min just after the first injection, but this was 19.66 ± 4.64 min after the second injection. Furthermore, the mean time of sedation durability was 100.37 ± 31.25 min just after the first injection (59.2% of patients needed the second injection), but after the second injection, this was right for 52.21% of the patients. These mean times of sedation induction were not significantly related to age, gender, type of substance used, and type of aggression [Table 1].

After the first injection, the shortest time needed for sedation induction was in patients who received chlorpromazine (15.42 ± 10.08 min), and the longest one was in patients who received promethazine (21 ± 4.8 min). Furthermore, in patients who received the second injection, the shortest time was in promethazine group (18.88 ± 5.77 min). Regarding the type of drugs, there were no significant differences between velocity and durability effect of sedation [Table 2].

Discussion

In this study, the velocity for obtaining sedation and its durability after injection was evaluated in each group

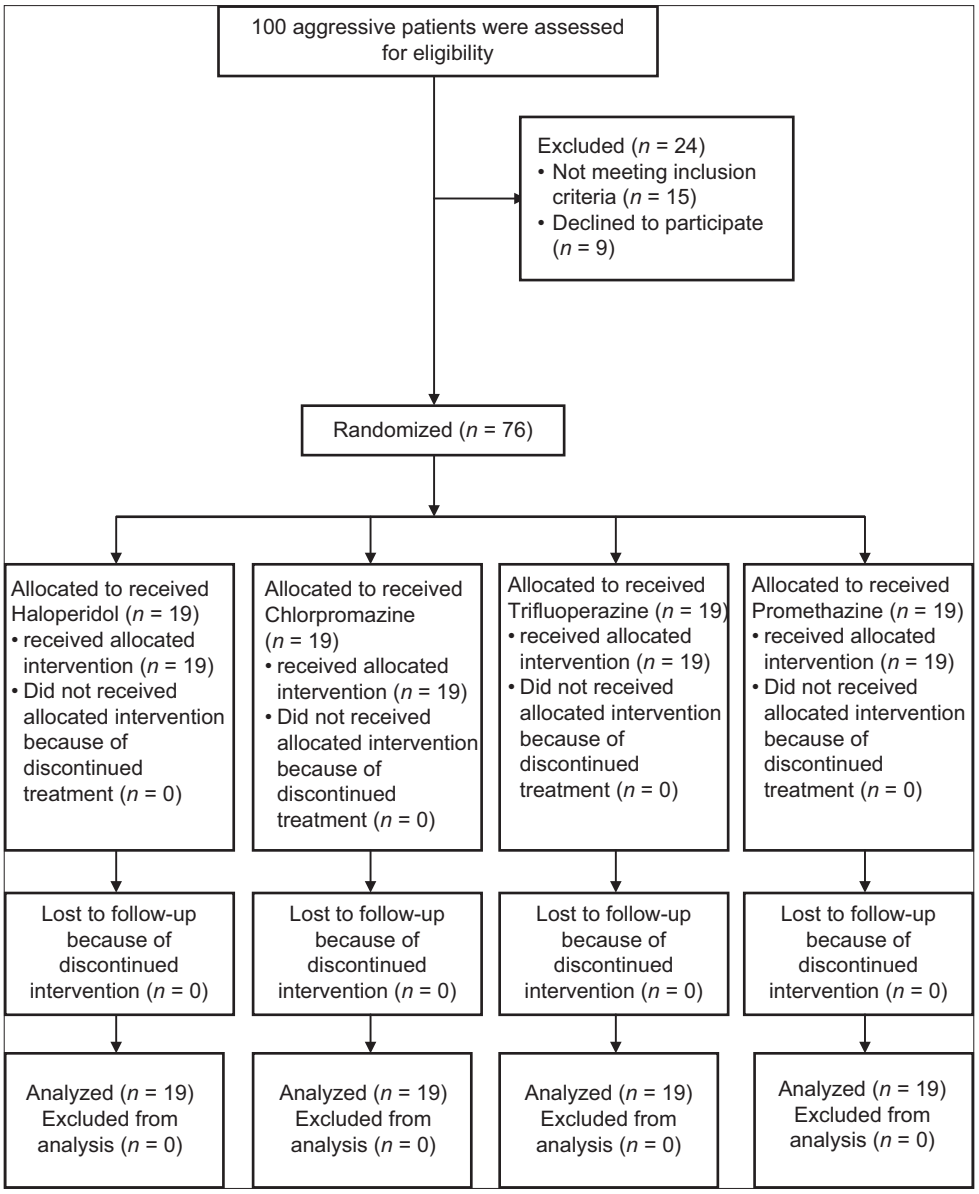

Figure 1: Consort flow diagram

Table 1: Descriptive statistics of the research

Variables	Chlorpromazine	Promethazine	Haloperidol	Trifluoperazine	*P*
Age, mean±SD	31.89±8.73	35.47±11.49	31.68±12.02	35.47±8.069	0.637
Gender, male (%)	63.2	73.7	57.90	36.8	0.779
Married, *n* (%)					
Yes	11 (57.9)	14 (73.7)	7 (36.8)	6 (31.6)	0.035
Substance, *n* (%)					
Ok	11 (57.9)	0	9 (47.4)	11 (57.9)	0.9
Physical aggression, *n* (%)					
Ok	10 (52.6)	0	10 (52.26)	11 (57.9)	0.73
Diagnosis, *n* (%)					
Bipolar	7 (36.8)	10 (52.6)	6 (42.10)	9 (26.3)	0.772
Schizophrenia	6 (31.6)	6 (31.6)	8 (31.6)	5 (47.4)	
Schizoaffective	1 (5. 3)	0	0	0	
Substance	5 (26.3)	3 (15.8)	5 (26.3)	5 (26.3)	

SD: Standard deviation

Table 2: Analytical statistical of the research

Variables	Chlorpromazine	Promethazine	Haloperidol	Trifluoperazine	*P*
Velocity of sedation - first injection, mean±SD	15.42±10.08	21±4.8	17.5±10.60	16.05±7.44	0.147
Velocity of sedation - second injection, mean±SD	20.25±5.11	18.88±5.77	19.16±3.97	20.37±3.73	0.767
durability effect - first injection, mean±SD	105±28.22	92.64±34.55	98.15±33.79	105.71±28.47	0.678
The need for a second injection (%)					
Yes	57.8	52.63	68.42	57.8	0.793
No	42.2	47.37	31.58	42.2	

SD: Standard deviation

of chlorpromazine, trifluoperazine, haloperidol, and promethazine, in aggressive patients. However, the four considered drugs were not significantly different in velocity and durability effect of sedation. Some of the previous studies evaluated the effect of combined promethazine and haloperidol in comparison with haloperidol alone and reported that this combination is highly effective for sedating aggressive patients and causes less needs for further medications and mechanical restriction with lesser side effects.[13] A case series of eight patients who had agitation after receiving electroconvulsive therapy (ECT) had prescribed promethazine 2 h before ECT, and showed that using promethazine can improve patients well-being and decrease agitation.[14] A case report of aggression and psychosis after bone marrow transplantation showed significant remission in psychotic symptoms after promethazine administration.[15] Another study with promethazine and chlorpromazine on agitated patients showed sedative effects on them.[16] Another study compared the efficacy of haloperidol with other low potent antipsychotics and found haloperidol has not any superiority to others antipsychotics in sedating agitated patients.[7] A comparison between the effect of chlorpromazine and haloperidol in aggressive people showed their similar effects, although this study had a small sample size that did not prepare evidence for this outcome.[17] A systematic review on antipsychotic agents reported that chlorpromazine not only had any superiority to other antipsychotics but also it has more side effects.[17] Another study showed that injection of haloperidol is significantly more effective than injection of chlorpromazine in controlling agitation,[18] and in the last-related study, promethazine has the most rapid effect on sedating aggressive patients in comparison to haloperidol, chlorpromazine, and trifluoperazine.[19] Most of the previous studies have evaluated the effects of promethazine in combination with other sedative medications such as antipsychotics, but there are limited studies that evaluated the effect of promethazine monotherapy on aggression or agitation.

Most of the previous studies on managing aggressive patients compared two medications, but there are a few studies that compare more than three medications. Although in some of the previous studies, the velocity of sedation has been a concern, the durability effect of sedation has been less focused that is a gap and it was aimed to work on it. Another priority of this study was evaluation the effects of the second injection, i.e., when the first injection was not effective.

Considering the drugs' side effects, neither of our patients showed any side effects of used medications during the 2 h follow-up. In contrast to our findings, a previous study reported that chlorpromazine is a local irritant medication and which may be associated with some cardiovascular risks such as hypotension, when used intramuscularly.[20] Furthermore, it has reported that promethazine had some side effects such as gastrointestinal disturbances and dry mouth, and haloperidol showed akathisia, dystonic reaction, and neuroleptic malignant syndrome, in some cases.[11,21] These differences between side effects in our study and previous findings may be due to short-term follow-up in our study, i.e. only 2 h after injection, although some manufactory-related factors of drugs may also cause also these differences.

Limitations

Our study had some limitations that must be taken into account in the generalization of the results. The first one is the somehow small sample size, which causes to be cautious in generalizing the findings. The second one is evaluating these drugs in aggressive patients than the different psychiatric disorders, although our different statistical methods decrease the importance of this limitation. The third limitation is the short time of follow-up. This may appear as the most important limitation, although we have mainly aimed to evaluate the velocity and durability effect of different drugs' action, but not other factors. Surely, future studies without these limitations can give us more reliable information.

Conclusion

Comparing the velocity and durability of sedative effect of the four drugs, i.e. chlorpromazine, haloperidol, trifluoperazine, and promethazine, on acute aggressive patients, did not show any significant difference between them. More studies with longer times of the follow-up are necessary for generalization of the findings.

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Conflicts of interest

There are no conflicts of interest.

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