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Parenteral Haloperidol-Promethazine versus Haloperidol-Diazepam for Rapid Tranquillization of Acutely Agitated Psychiatric Patients at Mirembe Mental Hospital, Dodoma: A Randomized Control Trial

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ABSTRACT:

Objective: *To compare the effectiveness between parenteral haloperidol-promethazine versus haloperidol-diazepam in achieving rapid tranquillization of acutely agitated psychiatric patients at emergency settings.*

Methods: *A single blinded permutated block randomization of two treatments was assigned to 86 acutely agitated psychotic patients at Mirembe mental health hospital. Positive and Negative Syndrome Scale Excited Component (PANSS-EC) was used to evaluate severity of agitation at baseline and at 15, 30, 60 and 120 minutes; Ramsay Sedation Scale (RSS) was used to at follow up to assess degree of sedation. Addition of tranquil medication and side effect profile was assessed at 24 and 72 hours.*

Results: *Both treatment groups show effectiveness in reducing agitation symptoms. Haloperidol-diazepam group show rapid reduction of agitation at 15-30 min (P=0.0002; P=0.0017); while differences in mean scores were not significant at 60 and 120 minutes. Haloperidol-diazepam group had significant sedation effect to patients 3.92 (SD=1.38) compared to haloperidol plus promethazine group 2.85 (SD=1.26). At 24 hours and 72 hours, haloperidol-diazepam group had more added injection compared to haloperidol-promethazine group. There were more patients who were either drowsy or stuporous and few unresponsive at 15, 30 and 60 minutes in haloperidol-diazepam group compared to haloperidol-promethazine group which had more patients either alert or drowsy and few stupors.*

Conclusion: *Both combination agents are effective in reducing agitation. However, haloperidol-diazepam had more rapid onset of action with more sedating effect compared to haloperidol-promethazine which had slightly slower onset, prolonged effect and less sedating effect. Guidelines recommend use of medications with rapid action, prolonged effect and less sedating and adverse effects. In this case haloperidol-promethazine appears to be superior compared to haloperidol-diazepam.*

Keywords: Haloperidol; Promethazine; Sedation; Ramsay Sedation Scale (RSS); Tranquillization.

INTRODUCTION

Acutely agitated or aggressive patients are common visits in emergency hospital settings with 10% of cases accounting to common psychiatric disorders like acute psychosis, schizophrenia, bipolar mania and substance/ alcohol use disorder (Garriga, et al.).

Although management guidelines recommend use of verbal de-escalation as first line approach in calming agitated or aggressive patients. This approach however is often hard to practice especially in a busy and crowded emergency area thus a possibility for escalation of behavior and subsequent imminent danger is likely. Thus, many practitioners have shown preference in the use of tranquillizers to calm the patient prior in depth assessment (Garriga, et al.). Choice of medication for tranquility also varies among practitioners across the globe due to variety of reasons including drug

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availability, calm or sedation effect, adverse side effects as well as cost especially among psychiatrist from Africa (Huf, et al.).

While atypical antipsychotics like ziprasidone and olanzapine have recently replaced the long used typical antipsychotics and benzodiazepine due to their side effect profile notably acute dystonia and akathisia (Wilson, et al.). In the middle and low income countries typical antipsychotics and benzodiazepines are still widely used to achieve tranquil in agitated or aggressive patients. Haloperidol-promethazine have been studied against olanzapine and found to have near similar effect in calming the patient with less side effects (Raveendran, et al.).

Thus this randomized clinical trial is designed to assess the effect of parenteral haloperidol-promethazine versus haloperidol-diazepam, the two recommended drug combination in Tanzania for management of acutely agitated or aggressive patients in psychiatric settings (Health and level).

MATERIALS AND METHODS

STUDY DESIGN: Single blinded randomized control trial to compare the effect of parenteral haloperidol-promethazine and haloperidol-diazepam was conducted at a Mirembe mental health hospital from May to July 2022. Good clinical practice and principles of the Helsinki declaration were observed. Study protocol was approved by university of Dodoma ethical committee and permission to conduct study was granted by research and training department of Mirembe mental health hospital.

PARTICIPANTS: 174 number of patients aged 18-60 years old received at outpatient department for psychiatric evaluation with symptoms of agitation or aggression were recruited and assessed for eligibility. Those with diagnosis of psychotic and bipolar disorders with agitation score of ≥ 20 according to Positive and Negative Syndrome Scale Excited Component (PANSS-EC) were included; while patients with symptoms of agitation due to substance use disorders, agitated depression, anxiety, borderline personality disorder, medical cause of agitation such as delirium due to medication or co-morbid physical condition and dementia were excluded; along with patients received past 6 pm, those who express no interest to participate in a study or those who received any medications prior reception particularly psychotropic medications. Consent to participate was sought from escorting partner and was a prerequisite to participation in the study prior assessment.

RANDOMIZATION AND ALLOCATION OF INTERVENTION: Interventions were allocated in a randomized permuted blocks of four using Microsoft excel. Treatments were haloperidol-promethazine and haloperidol-diazepam and repeated until all samples were reached. Minimum recommended dose as per national treatment guideline were assigned in each intervention and included IM haloperidol 5 mg, IM promethazine 25 mg and IV diazepam 10 mg. All interventions were wrapped in a single color coded box with serial numbers.

Both researcher and participants were blinded from the intervention; however, researcher was made aware of the intervention after opening of the intervention kit. This is necessary because the interventions are given in an emergency situation and thus close monitoring of patient requires assessor to have knowledge of the intervention given.

STUDY PROCEDURE: Before treatment administration, patients with symptoms of agitation or aggression were introduced to the study, consent received and screened for underlying cause of agitation or aggression. Those with diagnosis different from that under study were excluded from the study. A register of both excluded and included patients in the study was kept with their provisional diagnosis, next of kin contact and hospital registration number.

Two clinicians designated for research with knowledge of psychiatry and who received training on how to conduct assessment of agitated patients as per protocol instruments were involved in the assessment of all patients with symptoms of agitation or aggression. Due to scarcity of staff and a busy emergency area, it was not possible to use two or multiple raters; thus this study employed a single rater who was trained on how to administer instruments, however where controversy as observed an additional rater was involved who in most cases was a second researcher or principle investigator.

All randomized patients who consented were given either of the intervention by a nurse stationed at out-patient emergency injection room and observed for two hours by a clinician before sent to the respective wards. Follow up was done at 15, 30, 60 and 120 minutes for assessment of agitation or sedation effect and at 24 and 72 hours for addition of parenteral tranquillizers and side effect profile. Vital signs were obtained at baseline and every follow up period.

Patients information was filled in a computerized hospital data base, research questionnaire and transfer form to be submitted to the wards indicating brief history of the patient, diagnosis and medications given at OPD.

ASSESSMENT INSTRUMENTS: PANSS-EC was used to assess severity of agitation or aggression at baseline and a score of 20 or more was needed to be reached before

administration of either of the intervention. RSS was used to assess degree of sedation at follow up. Other instruments used were CAM, GPCOG, CAGE and MINI for diagnostic purposes.

STATISTICAL ANALYSIS: All data were populated and analyzed using Statistical Package for Social Science (SPSS) by the principle investigator. An intention to treat analysis was employed where all randomized participants were included in the analysis based on the group they were originally assigned regardless of the type of treatment they received.

Normality test of variable were done using Shapiro-Wilk and Kolmogorov Smirnov test. Group comparison of baseline demographic and clinical characteristics was analyzed using unpaired independent t-test for continuous variables and *Chi-square* test for categorical variables. Mean PANSS-EC scores at time 30, 60 and 120 minutes was subtracted to the baseline PANSS-EC for each treatment to obtain overall effect of medication. Multiple linear regression analysis was done to determine baseline factors associated with reduction of PANSS-EC scores.

RESULTS

DEMOGRAPHIC CHARACTERISTICS OF STUDY PARTICIPANTS: Out of 174 acutely patients screened, 86 met the inclusion criteria for the study and were randomized to receive either of the researched treatments. Forty-three were randomly assigned to receive parenteral medication from haloperidol plus promethazine arm and the other 43 were assigned to receive parenteral medication from haloperidol plus diazepam arm. Eighty-eight patients did not meet the inclusion criteria and underwent normal hospital procedure after screening; these were those with either agitated behavior due to another disorder other than psychotic disorder or bipolar disorder (Figure 1).

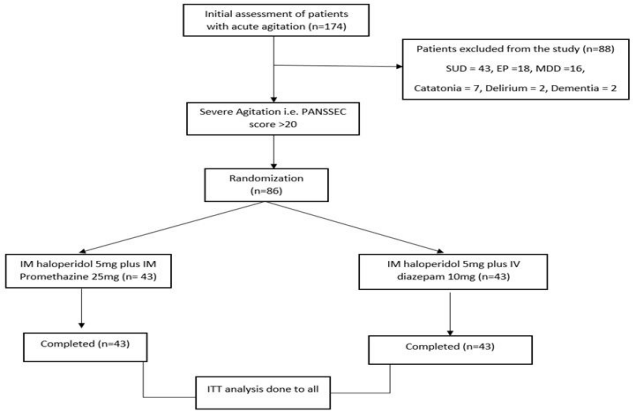

Figure 1. Flow chart of enrollment and randomization.

Table 1 provides demographic and clinical characteristics of the study population and shows that male patients accounted for the majority of study participants 54.7% compared to female patients 45.3%. Average mean age for all studied population was 34.28 (SD=11.996) and 34.81 (SD=12.28) for haloperidol-promethazine group compared to 33.74 (SD=11.86) for haloperidol-diazepam group. On account of education level attained by study participants; majority of participants had primary education 62.8%, followed by secondary education 16.3% and lack of formal education 12.8%. Study population was also assessed for their occupational status and found 44.2% of the study participants did not have any employment, 23.3% were peasants, 18.6% had informal jobs while 10.5% were petty traders and 3.5% were students. 65.1% of study participants had psychotic disorder and 34.9% had bipolar I disorder and baseline mean score for agitation was 29.37 (SD=4.36) based on PANSS-EC.

Table 1.
Demographic andcClinical characteristics of the population.

Variable	Haloperidol plus promethazine	Haloperidol plus diazepam	t/x[1]	P-value
Mean Age, SD	34.81 (12.28)	33.74 (11.86)	.652**	.682
Sex, male/female N	23/20	24/19	.047*	.829
Education level (%)				
Tertiary/graduate	4 (4.7)	2 (2.3)	4,225	.376
Advanced secondary	1 (1.2)	0	4.225	.376

Secondary	8 (9.3)	6 (7)	4.225	.376
Primary	27 (31.4)	27 (31.4)	4.225	.376
No formal education	3 (3.5)	8 (9.3)	4.225	.376
Occupation (%)				
Informal employment	7 (8.1)	9 (10.5)	10.045	.40
Petty trader	7 (8.1)	2 (2.3)	10.045	.40
Student	1 (1.2)	2 (2.3)	10.045	.40
Peasant	5 (5.8)	15 (17.4)	10.045	.40
No employment	23 (26.7)	15 (17.4)	10.045	.40
Diagnosis (%)				
Psychotic disorder	28 (32.6)	28 (32.6)	.000	1.000
Bipolar I disorder	15 (17.4)	16 (17.4)	.000	1.000
PANSS-EC at baseline, mean (SD)	28.86 (4.55)	29.88 (4.14)	0.179**	0.279

REPETITION OF INJECTION TRANQUILLIZER: Table 2 presents additional injection among psychiatric patients used haloperidol plus promethazine compared to those received haloperidol plus diazepam. It was observed that the proportional of additional injection at 24 hrs. among patients who received haloperidol plus diazepam were 30.23% while those who received haloperidol plus promethazine were 20.93%. At 72 hrs, 11.63% of patients received haloperidol plus diazepam had additional injection where those who received haloperidol plus promethazine only 4.65% of them had additional injection. Overall large proportion of additional injectable tranquillizer was observed among patients received haloperidol diazepam group compared to those received haloperidol plus promethazine group.

Table 2.

Additional injectable at different interval.

Additional injection	Total, N (%)	Haloperidol plus promethazine, N (%)	Haloperidol plus diazepam, N (%)	P-value
Within 120 minutes	11 (12.79)	6 (13.95)	5 (11.62)	0.714
At 24 hours	22 (25.58)	9 (20.93)	13 (30.23)	0.353
At 72 hours	7 (8.13)	2 (4.65)	5 (11.63)	0.236

TREATMENT OUTCOMES FOR EACH TREATMENT GROUP: Table 3 shows mean scores of PANSS-EC and RSS for agitation and sedation at different time interval analyzed using independent t test. Mean scores for both treatment groups have shown decreased in mean score values for PANSS-EC. This indicates that both medications showed improvement in symptoms of agitation from baseline scores as time increases to 15, 30 and 60 minutes; however, at 120 which had much steeper decline in scores 6.84 (SD=4.28). minutes there was a slight increase in mean of PANSS-EC score for both treatment groups. Haloperidol-promethazine group had lower baseline mean score 28.86 (SD=4.55) than haloperidol-diazepam group 29.88 (SD=4.14) and showed minimal decline in mean score at 15 minutes 11.09 (SD=7.33) compared to haloperidol plus diazepam group.

Table 3.

Changes mean scores in agitation and sedation.

Variable	Haloperidol plus promethazine			Haloperidol plus diazepam				
	Mean	Std. deviation	Std. error mean	Mean	Std. deviation	Std. error mean	t	p-value

PANSS-EC*								
At baseline	28.86	4.554	0.695	29.88	4.142	0.632	0.179	0.279
At 15 minutes	11.09	7.328	1.118	6.84	4.281	0.653	3.288	0.002
At 30 minutes	7.93	6.006	0.927	5.84	2.734	0.417	2.074	0.004
At 60 minutes	6.41	3.647	0.570	5.81	2.500	0.381	0.884	0.379
At 120 minutes	7.73	6.340	0.990	7.09	6.229	0.950	0.466	0.643
RSS**								
At 15 minutes	2.12	1.199	0.183	3.98	1.551	0.236	-6.224	<.000
At 30 minutes	3.09	1.324	0.202	4.28	1.278	0.195	-4.226	<.000
At 60 minutes	3.45	1.194	0.184	3.95	1.290	0.197	-1.858	0.067
At 120 minutes	2.74	1.326	0.205	3.47	1.403	0.214	-2.455	0.016

*Positive and negative symptom scale; **Ramsay sedation scale

Steeper decline is also seen in mean scores of haloperidol plus promethazine group at 30 minutes 7.93 (SD=6.01) compared to haloperidol plus diazepam group which decreased only slightly 5.84 (SD=2.73). Both treatment groups showed minimal decrease in mean scores at 60 minutes and at 120 minutes both groups had shown slight increase in mean score values (Figure 2).

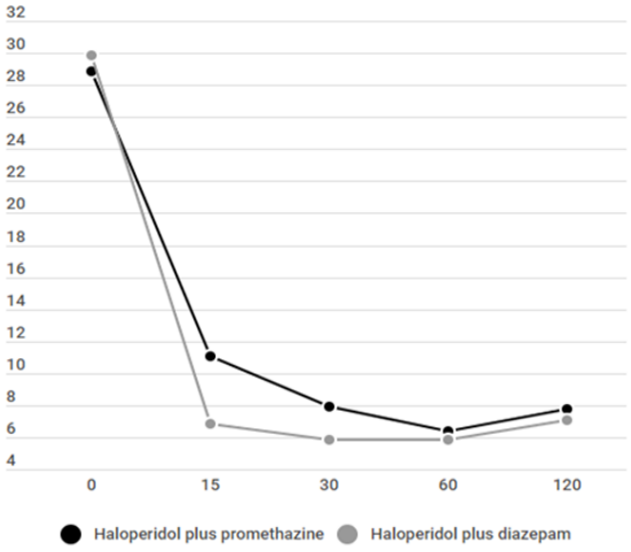

Figure 2. PANSS-EC scores measured at different times.

Patients were also measured for their level of sedation using RSS following administration of treatment at time 15, 30, 60 and 120 minutes. Table 3 shows mean scores of sedation and have shown haloperidol plus promethazine group had lower sedation effect compared to haloperidol diazepam group at 15, 30, 60 and 120 minutes as shown Figure 3.

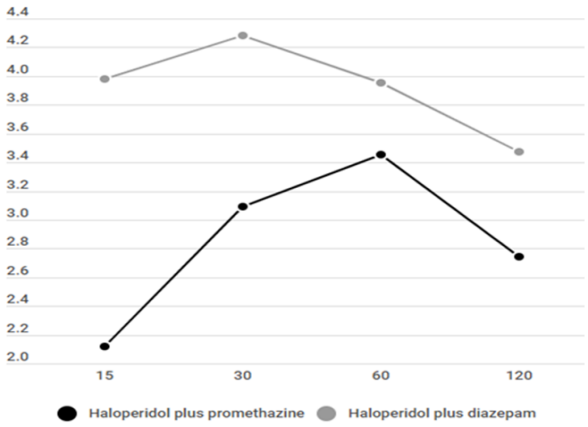

Figure 3. Modified RSS scores measured at different time interval.

TREATMENT EFFECTIVENESS: The Table 4 below displays the independent t test for the PANSSECS core. Comparing the mean of the reduced score between patients treated by haloperidol plus promethazine and those treated by haloperidol plus diazepam. The result showed that, there was significant mean difference at 15 minutes (diff=5.28, p=0.0002) and 30 minutes (diff=2.99, p=0.0171) whereby at 15 minutes haloperidol plus diazepam had high reduced score (mean=23.06) as compared to haloperidol-promethazine (mean=17.77) the same as in 30 minutes, haloperidol-diazepam seem to have high reduced score (mean=24.05) as compared to haloperidol-promethazine (mean=21.05). At 60 minutes and 120 minutes the difference was not significant however haloperidol plus diazepam still had high reduced score.

Table 4.
Treatment effectiveness.

Variable	Mean	Mean diff	t	p-value
Difference in mean PANSS-EC score at 15 minutes				
Haloperidol plus promethazine	-17.77	5.28	3.9	0.0002
Haloperidol plus Diazepam	-23.06			
Difference in mean PANSS-EC score at 30 minutes				
Haloperidol plus promethazine	-21.05	2.99	2.43	0.0171
Haloperidol plus diazepam	-24.05			
Difference in mean PANSS-EC score at 60 minutes				
Haloperidol plus promethazine	-22.44	1.63	1.53	0.1298
Haloperidol plus diazepam	-24.07			
Difference in mean PANSS-EC score at 120 minutes				
Haloperidol plus promethazine	-21.12	1.67	1.02	0.3099
Haloperidol plus diazepam	-22.79			
PANSS-EC=Positive and negative syndrome scale excited component; t=Independent t test				

Level of responsiveness was also assessed and categorized into four levels alert or wakefulness which corresponded to state of being aware, immediately responds, maybe over talkative, may not be fully oriented; drowsy corresponded to reduced consciousness or awareness but aroused on touch/noise or made alert for a short while; stupor corresponded to reduced consciousness and can be awakened only by vigorous stimuli, mutism or immobility; unresponsiveness which corresponded to deeply unconscious cannot be aroused by stimulation. These parameters were compared across groups and found that haloperidol plus promethazine group had more people who were alert or drowsy than haloperidol plus diazepam group that had more people who were drowsy and stupor

and some who were unresponsive at 15, 30 and 60 minutes. However at 120 minutes both groups showed approximately similar results (Figure 4).

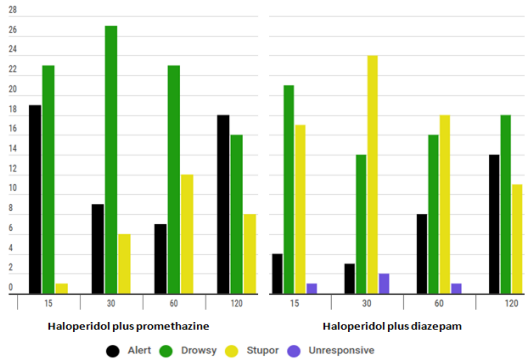

Figure 4. Level of responsiveness.

DISCUSSION

This study evaluated the effects of two parenteral medications *i.e.* intramuscular haloperidol 5 mg-promethazine 25 mg versus intramuscular haloperidol 5 mg-intravenous diazepam 10 mg in inducing tranquillization among severely agitated patient received at Mirembe mental hospital in Dodoma. 86 patients with clinical diagnosis of either psychotic disorder or bipolar I disorder were observed. It is very probable that this is the first published study to compare effectiveness of haloperidol plus promethazine versus haloperidol plus diazepam for management of acutely agitated psychotic patients. Reasons supporting this observation is probably due to the fact that intramuscular diazepam cause erratic absorption and pain at injection site; while intravenous diazepam although has rapid onset of action (1-3 minutes), the short duration of action of approximately 1 hour caused by its high lipid solubility potential cause redistribution of drug from vascular space into fatty tissues, suggesting need for repetition of dose or administration of high dose to achieve sustained tranquil; this is undesired because of potential for development of cardiorespiratory depression (Zareifopoulos, et al.).

Results from our study have shown both studied combinations had significant improvement in reduction of agitation scores at different time intervals from baseline levels which were not statistically different for the two groups (p=.279). We observed that at 15 minutes after administration of treatment, significant reduction in mean scores was seen in the group that received haloperidol-diazepam combination (p=0.002, p=0.004 respectively), these findings are expected due to rapid onset of action of diazepam compared to promethazine especially at 15 minutes, but at 30 minutes promethazine had already started to work and more patients had their minutes promethazine had already started to work and more patients had their agitation controlled (Panayiotakopoulos, et al). While at 60 and 120 minutes both treatment groups show minimal reduction in agitation mean scores and the difference was not statistically significant.

The trend reduction in agitation scores observed in our study resembles findings from other studies that compared haloperidol-plus promethazine against combination of haloperidol with other benzodiazepine class. For example, a study by Baldacara, et al. and a TREC study that compared intramuscular haloperidol plus promethazine *vs* intramuscular haloperidol plus midazolam and intramuscul ar haloperidol plus promethazine *vs.* intramuscular midazol am alone, respectively; have shown, a group with midazolam combination or alone had rapid onset of action from baseline to the first one hour when compared to promethazine group (p=<0.001) due to fast onset of action of midazolam approximately 2 minutes. However, findings of Alexander, et al. that compared i.m. haloperidol plus promethazine *vs.* i.m. lorazepam gave inconsistent results, where patients who received haloperidol plus promethazine were observed to be quickly tranquillized and sedated compared to those who received lorazepam, these findings were possibly due to compounding calming and partially sedating effect contributed by haloperidol for the combination group (Alexander, et al.).

Our study also observed linear association between sex and PANSS-EC scores; it was observed that at 120 minutes female sex had significant reduction of PANSS-EC scores (p=0.0331) compared to male sex, suggesting an influence of treatments on female sex. This association can be explained by differences in pharmacokinetics and pharmacodynamics of drugs seen between men and women; diazepam has high affinity for adipose tissues and thus would be more distributed in female than male because of lower ratio of lean body mass to adipose tissues; this may lead to prolonged half-life, sustained serum concentration and delayed elimination rate. Generally, women require low doses of drugs because of their lower body weight, slower gastrointestinal motility, less intestinal enzymatic activity and slower glomerular filtration rate (Whitley, et al.).

We observed sedation profile between the two studied combination agents and found that patients in haloperidol-diazepam group were more sedated compared to those in

haloperidol plus promethazine group. This is probably due to the fact that benzodiazepine selectively enhances the activity of GABA inhibitory neurotransmitter by binding to gamma subunit of GABA A receptor; since these neurotransmitters and their respective receptors are abundant in the central nervous system, effect of benzodiazepines is profound on CNS (Zareifopoulos, et al.).

Consensus guidelines advocates for non-coercive and restrictive measures at all times and whenever possible a need for tranquillization is foreseen; use of medications with less sedation effect rather than over sedating, fast onset of action with sufficient duration of action and low risk for side effects is recommended forms ideal medication for management of acute agitation (Garriga, et al.). In our study, based on average mean score of RSS, haloperidol plus promethazine group appear to have less sedation effect, prolonged tranquillization but slower onset of action compared to haloperidol plus diazepam group which had more patients sedated.

This study also observed that extrapyramidal side effects occurred equally in both treatment groups; while level of arousal when assessed it showed that haloperidol plus diazepam group had more proportions of patients being drowsy or stuporous and some were unresponsive between 15 and 60 minutes compared to the haloperidol plus promethazine group which had more patients being alert or drowsy and few were stupor in the same time. Previous studies and review papers have reported potential for side effects from use of haloperidol either alone or in its combination with benzodiazepine or promethazine; the high affinity of haloperidol to Dopamine 2 Receptor (D2R) and partial affinity of promethazine to D2R was shown to be associated with extrapyramidal side effects, while the anticholinergic effect of promethazine had a counter effect to development of haloperidol. On the other hand GABA effect of diazepam had sedation effects, while its paradoxical agitation appears to be countered by the effect of haloperidol; antihistamine effect of promethazine has an effect on sedation outcomes (de Almeida, et al.).

Our study has also shown majority of our study participants had normal values for blood pressure, pulse rate and respiratory rate when proportions were compared to those with reduced or high levels; while the sedating effects of medications used tend to have effect on cardiorespiratory functioning, literature have also provided that the effect or reduction in most cases is minimal to majority and worst outcomes are seen to minority groups or when in combination with other drugs with sedating effect or taken in higher doses (JS & A, Southard).

Our study also observed that haloperidol plus diazepam group had more added injectable tranquillizers than haloperidol plus promethazine group at 24 and 72 hours. These findings are similarly explained by the pharmacokinetic profile of the treatments in two combination groups where diazepam reach peak plasma concentration levels and is redistributed to fat tissues, thus rendering levels in the blood to be low for continued inhibitory effect of CNS.

Thus, our findings when compared to recommendations of consensus guidelines show that haloperidol-promethazine has more clinically favorable outcomes compared to haloperidol-diazepam for management of acutely agitated psychotic patients because both treatment in the combination of haloperidol-promethazine are intramuscularly administered thus less invasive or coercive, sedation effect observed was less with no patient ending into non-responsive state, onset of action although not as rapid as haloperidol-diazepam, effect was prolonged in haloperidol-promethazine and less injections were needed. Extrapyramidal effects were observed equally in both treatment groups. Use of haloperidol-diazepam in an emergency setting requires caution.

CONCLUSION

Both studied combination agents were effective in reducing agitation. Haloperidol plus diazepam had faster onset of action and more sedation while haloperidol plus promethazine had moderate onset of action and less sedation. Consensus guidelines for management of agitated psychiatric patients recommend that ideal medication for tranquillization is that which has fast action, prolonged effect, less sedation and adverse effects, thus haloperidol-promethazine has better clinical advantages that haloperidol-diazepam. However, the choice to use either of the two combinations is dependent

LIMITATIONS

This study suffers a number of limitations that affects generalizability of its results. These included; first, busy OPD facility with fewer rooms for clinician consultation resulting in a congestion of clients at waiting bay and increased pressure to both providers and patients, it is likely that this limitation led to more escalation of agitation to patients or prevented clinicians to perform verbal de-escalation. This limitation was minimized by making sure clinicians involved in a study and OPD nurses are vigilant about triaging and attending acutely agitated patients in order to reduce any potential for outbreak of safety. Second, because of inadequate number of staff in the hospital it was not possible to use inter rater system during scoring of PANSS-EC and RSS and thus we relied on the judgement of a single clinician who was trained on how to administer the tools; however, frequent meetings were convened with PI after data collection to share experiences and challenges. Third, sample size for our study was small hence power of the study was also small thus may not be sufficient generalizability; we tried to minimize this by adding an attrition rate of 30% in order to give our study more power. Therefore, our study was able to provide results that gave a clinical outcome of sampled population under studied combination drug.

on circumstances in the emergency setting and severity of agitation.

RECOMMENDATIONS

Management of acute agitation and aggression in psychiatry and emergency settings cannot be overemphasized due to potential for high risk of outbreak of safety. Therefore recommend more RCT studies be conducted to inform suitable practices in our settings.

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