Comparing the Impact of Atropine Drops and Amitriptyline Tablets in Treatment of Clozapine-Induced Sialorrhea: A Randomized Double-Blind Placebo Controlled Clinical Trial

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Abstract- Clozapine is an atypical antipsychotic employed to treat patients with psychotic disorders. It is associated with sialorrhea as a problematic adverse effect in 30-80% of cases. Various medications such as atropine and amitriptyline have been suggested for its treatment. We aimed to compare the effects of atropine drops and amitriptyline tablets in the treatment of clozapine-induced sialorrhea. The present double-blind, randomized clinical trial aimed to evaluate the effect of atropine drops and amitriptyline tablets in reducing clozapine-induced sialorrhea in patients with psychotic disorders. Forty-six patients were treated for 4 weeks in two groups: group "A"(atropine drops and placebo tablets) and group "B" (amitriptyline tablets and placebo drops). Toronto Nocturnal Hypersalivation Scale (TNHS) and Clinical Global Impression (CGI) rating scale were used for measurement of the severity and frequency of sialorrhea and global symptom severity and treatment response, respectively. Kolmogorov–Smirnov, *Chi*-square and Fisher's exact tests were used for statistical analyses. Demographic information of the two groups had no significant difference ($P>0.05$). There was no patient with adverse effects that interfered with the study. Mean TNHS and Meier scores in groups "A" and "B" were 3.48±0.21 vs.3.24±0.18, and 1.9±0.07 vs.1.86±0.07, respectively, and the difference was not statistically significant ($P=0.35$ vs. $P=0.67$). In patients with clozapine-induced sialorrhea, 1% atropine drops (1.7 mg sublingual drops daily) can be just as effective as amitriptyline tablets (29.08 mg daily, oral) in controlling sialorrhea.

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Keywords: Amitriptyline; Atropine; Clozapine; Sialorrhea

Introduction

Psychotic disorders are a group of psychiatric disorders, in which the patients detached from reality. During psychosis, most patients experience hallucinations and delusions (1). General appearance, behavior, emotions, cognition and other aspects of mental state may be affected too. Schizophrenia, which includes variable highly destructive psychosocial trauma that involves cognition, emotion, perception, and other aspects of the behavior is a major (2). The prevalence of this disorder is about 1% during lifetime and is the most costly psychiatric disorder (3). This disorder usually begins before the age of 25 and remains until the end of life. Schizophrenia can be seen in all social classes (2).

Clozapine acts as dopaminergic, 5HT2-5, histaminergic1, muscarinic M1, M2, M5 receptor antagonist and M5 receptor agonist (4). It has been shown that clozapine is more effective in the treatment of psychotic patients who are resistant to other antipsychotic medications, especially who have suicidal ideas and mood elements and neurological disorders, as well as in the treatment of tardive dyskinesia (5). Despite the usefulness of this medication, its use has been limited because of its adverse effects (5). Clozapine has some

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rare, life-threatening adverse effects, including agranulocytosis, myocarditis, and seizures (6). Other adverse effects which are observed in 17% of patients include sialorrhea, sleepiness, weight gain, and nocturnal incontinence (6). Clozapine-induced sialorrhea is observed in 30-80% of cases (5).

Sialorrhea is stigmatizing and can cause many other adverse effects. Complications of sialorrhea include aerophobia due to high swallowing, parotitis, sleep disturbance, and increased risk of asphyxia during sleep due to aspiration pneumonia (7,8). The mechanism of clozapine-induced sialorrhea is not fully understood, but theories proposed include blocking of α1, α2, and norepinephrine receptors, which leads to increased blood flow to the salivary glands and increased salivation (9). The agonistic theory of muscarinic receptors type 4, and decreased peristaltic motion of the larynx also plays a role in creating sialorrhea (10).

Various options have been suggested for the treatment of clozapine-induced sialorrhea, including non-pharmacological strategies such as sugar–free gum and traditional medicines (7), which are usually not effective as the first line of treatment (11). Various medication therapies have been used, including amitriptyline, glycopironium, benztropine, botulinum toxin (11), clonidine (12), amisulpride (13), ipratropium bromide (14), pirenzepine (11), trihexyphenidyl (6), and atropine (15). However, the wide use of these medications has been limited due to multiple adverse effects (16). Currently, none of the mentioned medications are approved by the America Food and Drug Administration (FDA), and their safety and efficacy have been limited to case reports in different patients with different diagnoses and different doses of clozapine (11).

Atropine which is an anticholinergic medication that inhibits muscarinic receptors on the salivary glands, and reduces saliva production is one of the most suggested medications in the treatment of clozapine-induced sialorrhea (6,9,17). Every drop of 1% atropine sulfate solution contains 500 micrograms of atropine (17). Amitriptyline is a third amine tricyclic anti-depression that inhibits reuptake of norepinephrine and serotonin. In addition, this medication is the antagonist of muscarinic and histaminergic receptors.

Given the controversy on the effect of these two medications in the treatment of clozapine-induced sialorrhea, this study aimed to compare the efficacy of atropine drops and amitriptyline tablets for clozapine-induced sialorrhea.

Materials and Methods

This double-blind, randomized placebo controlled clinical trial (registration number: IRCT201701136691N3) was conducted on patients with psychotic disorders, admitted to Zare Hospital in Sari-Iran, who were treated with clozapine and were complicated with clozapine-induced sialorrhea. Patients aged 18 to 65 years with a diagnosis of schizophrenia, schizoaffective, and other psychotic disorders, based on DSM-IV-TR enrolled in the study. Other inclusion criteria included sialorrhea with a minimum score of 2based on TNHS scale, who gave consent to participate and cooperate in the study. Exclusion criteria included allergy to amitriptyline and/or atropine, other diseases that can cause sialorrhea, such as Parkinson's disease and cerebral palsy, untreated constipation, bladder obstruction, urinary retention; concomitant use of medications such as tricyclic antidepressants, atrovent and oxybutynin; breastfeeding and pregnancy; and history of myasthenia gravis disease, cardiac arrhythmia, glaucoma, pyloric obstruction, paralytic ileus, prostate hypertrophy, renal failure, severe dysautonomia, and mental retardation.

Base on the previous studies, and using the following sample size formula, the sample size was calculated:

$$n_1 = n_2 = \frac{\left(Z_{1-\alpha_2} + Z_{1-\beta}\right)^2 \left(d_1{}^2 + d_2{}^2\right)}{\delta^2} = 23$$

$\alpha = 0.05$, $\beta = 0.2$, $d1 = 1.95$, $d2 = 2.92$

Accordingly, regarding the inclusion and exclusion criteria, 46 hospitalized patients participated in the study were randomly divided into two groups: in group "A" 23 individuals received atropine drops and placebo tablets and group "B" 23 patients received amitriptyline tablets and placebo drops. The diagnosis was confirmed by faculty members and a psychiatric assistant by clinical interview based on DSM-IV-TR.

Medications were given to the patients by a clinical pharmacist according to their random ID code. All patients' demographic information was recorded by a psychiatry assistant, and the amount of sialorrhea was monitored every day in the first week and then once a week for four weeks using the relevant scales. Thus, in a period of 4 weeks, one group received one 25mg tablet of amitriptyline at night (13) with placebo (one drop three times a day) and the other group was given sublingual drops of atropine three times a day (0.56 mg) with a placebo tablet (every night). All amitriptyline tablets were produced by Iran Farah Company, and atropine

drops were produced by Sina Daru Company both with the same manufacturer serial number. The placebo pills and drops were similar to amitriptyline and atropine in terms of shape, color, and taste, produced by Sari School of Pharmacy.

Patients and the psychiatric assistant who assessed the patient were unaware of the type of medication/placebo prescribed. Patients were monitored every day. In the case of massive sialorrhea, tablets increased to 4 pills per night (18) and the number of drops increased to two drops, three times a day (13). Changes in dose and relevant results were recorded. All scales were measured after inclusion of patients into the study every day in the first week and then in weeks 2, 3, and 4. Adverse effects of medications were also evaluated weekly. All patients had the same food diet.

Evaluation of sialorrhea

Toronto Nocturnal Hypersalivation Scale (TNHS) and Clinical Global Impression (CGI) rating scale, as well as adverse effects checklist, were used for measurement of the severity and frequency of sialorrhea and global symptom severity, treatment response and adverse effects respectively TNHS scale is based on the integration of the two measures of Drooling Severity Scale (DSS) and Nocturnal Hypersalivation Rating Scale (NHRS) (14,19) that measures the severity and frequency of sialorrhea, scored from 0 to 4 points, reported and recorded based on the severity of sialorrhea as wetting extent of pillows or clothing, and based on the number of nights with sialorrhea.

Another criterion used was Meier criteria that includes 0–9 points, scored based on wet lips, and dress and based on the frequency of sialorrhea. The adverse effects were recorded on a weekly basis. In both groups, based on CGI, adverse effects were recorded as mild, moderate and severe.

Ethical considerations

This study was approved by the Research Council of the Psychiatry Center for Research and Behavioral Sciences and Ethics Committee of the Research and Technology Dept (codes as) of Mazandaran University of Medical Sciences. After complete description of the protocol to participants, the patients and their legal guardians signed the written informed consent. Other principles of the Declaration of Helsinki (21) have been fully met.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) software version 21 was used for data analysis. The normal distribution of data was first tested by the Kolmogorov-Smirnov test. Quantitative variables were described by the mean±standard deviation (SD) and qualitative variables by frequency. Chi-square test was used to compare qualitative variables and, if necessary, Fisher's exact test and *t*-test were used for comparison of quantitative variables between the groups. In this study, *P* less than 0.05 was considered as the level of significance.

Results

In this study, out of 52 psychotic patients who received clozapine, 46 eligible patients were selected, and each patient was randomized to a group of 23 patients, including group “A” (atropine drops and placebo tablets) and group “B” (amitriptyline tablets and placebo drops) (Figure 1).

There was no statistically significant difference in gender, age range, marital status and educational level of patients between the groups ($P>0.05$) (Table 1).

Only 3 patients in group “B” and 4 patients in group “A” received biperiden or trihexyphenidyl. Fisher's exact test with $P=1$ showed that the two groups were not significantly different regarding the use of these medications.

During the study, no significant adverse effects such as cardiac complications, severe constipation, urinary retention, and complications that interfere with the continuation of the study were observed in any of the groups. Two female patients were excluded from group “A,” because of an inappropriate response to treatment and severity of symptoms at the end of the third week, who were treated with ECT.

Paired comparison of groups “A” and “B,” based on Meier tool using Generalized Estimating Equation resulted in $P=0.35$, and based on this scale, there was no significant difference between groups (Table 2). Mean calculated scores earned in the groups “A” and “B” were 3.24 ± 0.21 and 3.24±0.18, respectively (Table 3 and Figure 2).

Paired comparison of groups “A” and “B” by Mann–Whitney test based on TNHS scale for evaluation of the effect of medicines was performed by Generalized Estimating Equation test. Autoregression correlation structure and according to test results with respect to $P=0.67$, no significant difference was observed between the two groups (Table 4). Overall mean scores were 1.89±0.74 and 1.87±0.73in group “A” and “B” respectively (Table 5, Figure 3).

In this study, the overall mean obtained for sublingual atropine drops was 1.7 mg daily and for amitriptyline tablet was 29.08 mg per day. In both groups, sialorrhea decreased significantly, based on both scales. No important adverse effect was observed at the studied doses.

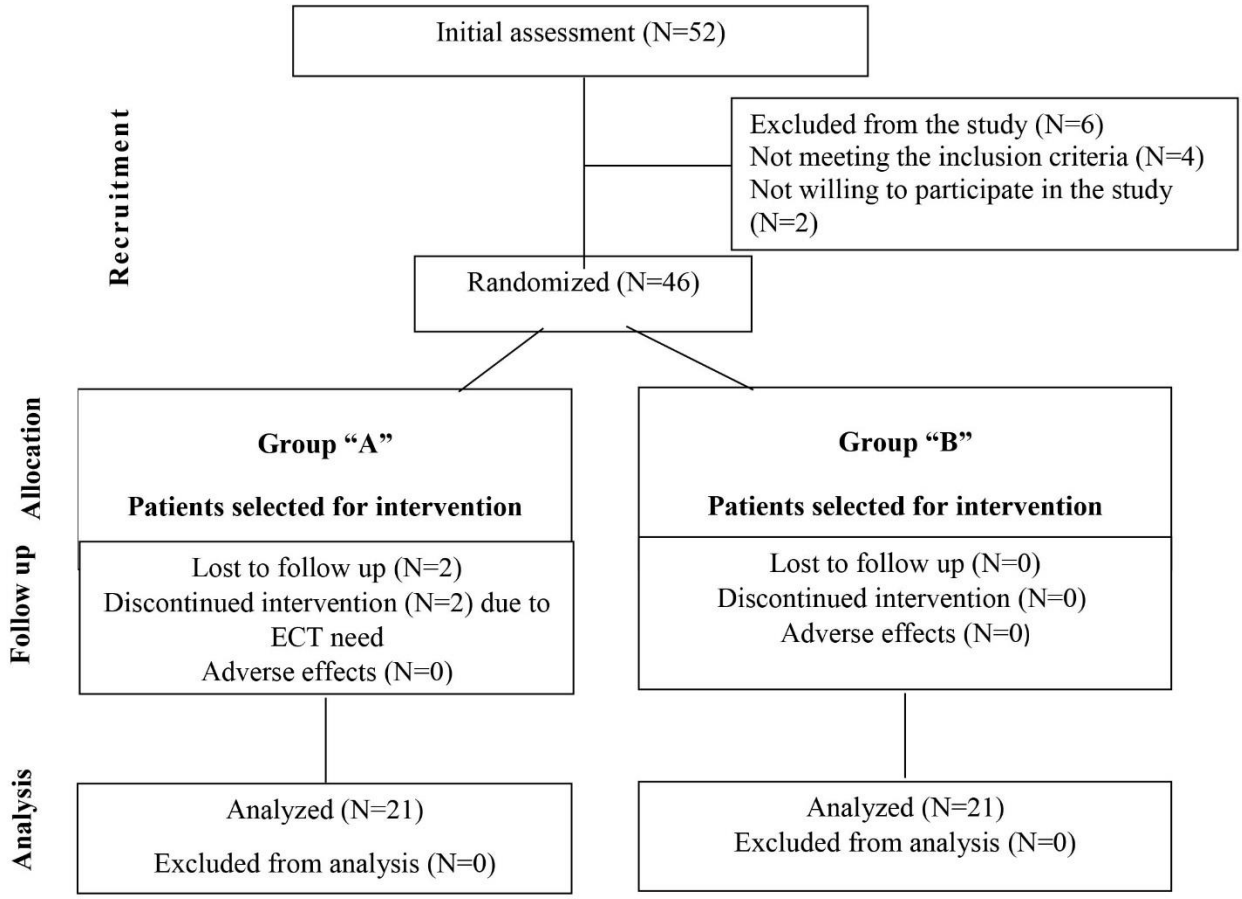

Figure 1. Flowchart of patients' allocation into two groups receiving oral amitriptyline tablets–placebo drops or Atropine drops–placebo tablet

Table 1. Demographic characteristics of patients

Investigated factor		Group A	Group B	*P*
Sex	Female	11	11	1
	Male	12	12	
The frequency of age groups (Year)	<25	0	1	0.93
	25–40	14	14	
	40–50	9	7	
	>50	0	1	
Age range		28–48	22–54	
Age (Mean ± SD) (years)		38.26 ± 5.33	38.43 ± 7.1	
Marital status	Single	8	6	0.56
	Married	11	10	
	Divorced	4	7	
Educational level	Under high school diploma	11	15	0.37
	High school diploma	11	6	
	Associate and higher	1	2	

Group A: patients received atropine drops and placebo tablets
Group B: patients received amitriptyline tablets and placebo drops

Table 2. Mean scores of Meier scale for each of the groups on days 1, 7, 14, and 28

Group		Mean	Std Error	95% Wald Confidence Interval	
				Lower	Upper
A*	Day1	4.09	.085	3.92	4.26
	Day7	3.83	.210	3.44	4.26
	Day14	3.83	.299	3.28	4.46
	Day21	3.13	.315	2.57	3.81
	Day28	2.75	.266	2.28	3.32
B**	Day1	4.17	.079	4.02	4.33
	Day7	3.83	.210	3.44	4.26
	Day14	3.61	.219	3.20	4.07
	Day 21	2.61	.252	2.16	3.15
	Day28	2.35	.265	1.88	2.93

*Atropine drops + placebo tablets, **Amitriptyline tablets + placebo drops

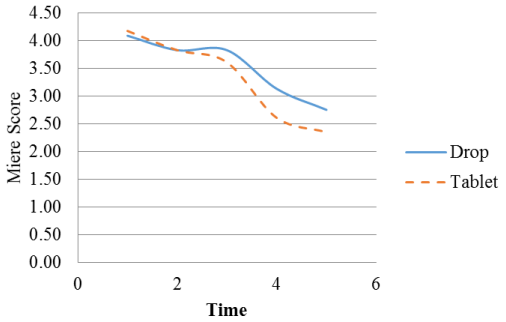

Figure 2. Comparison of Meier scores for atropine drops+ placebo tablets (A) and amitriptyline tablets + placebo drops (B) groups

Table 3. Mean total scores earned on Meier scale for two groups

Group	Mean	Std Error	95% Wald Confidence Interval	
			Lower	Upper
A*	3.48	0.210	3.09	3.92
B**	3.24	0.176	2.91	3.61

*Atropine drops + placebo tablets, **Amitriptyline tablets + placebo drops

Table 4. Mean scores based on TNHS scale for each of the groups on the first 7 days, and days 14, 21, and 28

		Mean	Std Error	95% Wald Confidence Interval	
				Lower	Upper
Group A	Day1	2.00	0.000	2.00	2.00
	Day 2	1.87	.070	1.74	2.01
	Day 3	1.74	.110	1.54	1.97
	Day 4	1.83	.133	1.58	2.11
	Day 5	2.09	.085	1.93	2.26
	Day 6	2.09	.085	1.93	2.26
	Day 7	2.09	.085	1.93	2.26
	Day14	2.04	.097	1.86	2.24
	Day21	1.75	.143	1.49	2.05
	Day28	1.51	.138	1.26	1.80
Group B	Day 1	2.00	.000	2.00	2.00
	Day 2	2.00	.000	2.00	2.00
	Day 3	1.96	.043	1.87	2.04
	Day 4	2.09	.105	1.89	2.30
	Day 5	2.04	.115	1.83	2.28
			Day 6	2.04	2.24
	Day 7	2.04	.115	1.83	2.28
	Day14	2.04	.115	1.83	2.28
	Day21	1.33	.138	1.09	1.63
	Day28	1.34	.144	1.09	1.66

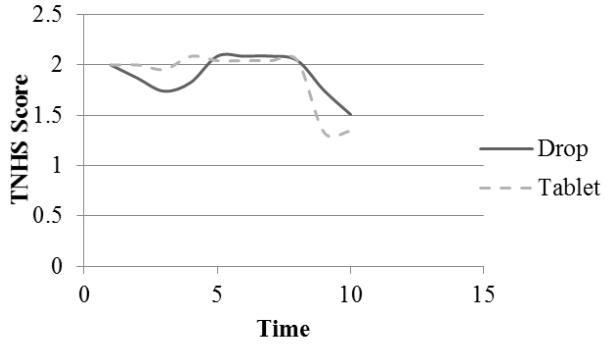

Figure 3. Comparison of TNHS scores of atropine drops+ placebo tablets (A) and amitriptyline tablets + placebo drops (B) groups

Table 5. Mean total scores earned on TNHS scale for amitriptyline tablets and atropine drops groups

Groups	Mean	Std Error	95% Wald Confidence Interval	
			Lower	Upper
A	1.89	.074	1.75	2.04
B	1.87	.073	1.73	2.01

*Atropine drops + placebo tablets
**Amitriptyline tablets + placebo drops

Discussion

To date, most studies on clozapine-induced sialorrhea are case reports, investigating various medications, such as amitriptyline, clonidine, amisulpride, and trihexyphenidyl tablets, ipratropium bromide spray, and atropine drop (16). In these studies, atropine drops and amitriptyline tablets were effective in reducing the amount of sialorrhea, but a trial on a higher number of patients was not conducted.

Of course, none of the medications used to treat sialorrhea are FDA approved, and their safety and efficacy are limited to case reports in different patients with different diagnoses and different doses of clozapine (11).

Given the importance of clozapine in the treatment of patients with psychosis and given that sialorrhea is a common and distressing adverse effect of clozapine, in this randomized, double-blind placebo controlled clinical trial on 46 patients, we compared the effects of amitriptyline tablets and atropine drops on clozapine-induced sialorrhea. According to the results obtained in this study, both medications were effective to the same extent on controlling sialorrhea.

Using TNHS and Meier tools, there was no statistically significant difference between the two groups receiving mean 1.7 mg atropine or 29.0 mg amitriptyline (P=0.35, and P=0.67).

The proposed theories about the etiology of sialorrhea include blocking NE α1, α2 receptors, which leads to increased salivary flow and increased secretion of salivary glands (9). Another theory suggests that agonistic M4 muscarinic receptors play a role in sialorrhea (10). Atropine is an anticholinergic medication that inhibits muscarinic receptors on salivary glands and reduces saliva production, and amitriptyline is a third amine tricyclic anti-depression (TCA) that inhibits the reuptake of norepinephrine and serotonin. In addition, amitriptyline is an antagonist of muscarinic, and histamine receptors. The common mechanism between these two medications is the antagonism of muscarinic receptors. Given that the effects of amitriptyline were not different from atropine and the mechanism of sialorrhea is not clear, it is recommended to use medications without effect on muscarinic receptors to compare with atropine. This may also help to find the mechanism of sialorrhea. However, clinically, to select any of these medications, adverse effects of these two medications should be considered. For example, the manic or hypomanic mood may be induced by amitriptyline in patients with bipolar and schizoaffective disorders. Also, weight gain and sleepiness caused by amitriptyline should be considered in patients prone to obesity and sleepiness induced by clozapine. On the other hand, if the patient lacks bipolar elements and complains of insomnia or nightmares, amitriptyline is preferable to atropine. Also, in patients with depressed mood (depression in patients with

schizophrenia, or depressed patients with a psychotic disorder), amitriptyline reduces depression, as well as sialorrhea. In the present study, no significant adverse effect (such as cardiac complications, severe constipation, and urinary retention) was observed, which could lead to the exclusion of patients from the study in any of the groups. This suggests the tolerability of both medications in patients with sialorrhea. Since most of the previous studies were case studies, the higher number of patients, as well as the randomized, double-blind placebo controlled study of patients with amitriptyline tablets and atropine drops are among the strengths of this study. Another strong point of this study is assessing patients with multiple scales on the frequency and severity of sialorrhea and adverse effects of the medications.

In patients with clozapine–induced sialorrhea, 1.7 mg atropine drops and 29.08 mg of amitriptyline tablets are equally tolerable and effective in controlling sialorrhea.

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