

The effect of adding sodium bicarbonate drip infusion to its bolus administration in patients with tricyclic antidepressant poisoning: a randomized clinical trial

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ABSTRACT

Introduction: Tricyclic antidepressants (TCAs) are widely used in psychiatric and medical conditions and are a major cause of drug overdoses and fatal poisonings in many countries. Sodium bicarbonate administration is widely recommended as the first line treatment in TCAs intoxication but the best method of its administration has not been yet established; therefore, we decided to compare the efficacy of drip infusion versus bolus administration of sodium bicarbonate in the treatment of TCAs poisoning.

Method: In this randomized clinical trial, 80 patients who had TCAs poisoning and, had been admitted to ICU were selected and divided into two groups. Both groups received 2 meq/kg of sodium bicarbonate in one bolus dose then group 1 received drip infusion of 2 liters of sodium bicarbonate (1.4% solution) additionally for the first 24 hours until the resolution of ECG and ABGs abnormalities. Patients' outcomes in the two groups were compared.

Results: More patients, after 8 hours, attained conscious in the drip infusion group. ($p = 0.012$) and also this group reached significantly more normal ECG findings at 16 and 24 hours. ($p = 0.013$ and 0.005) There was no significant difference in ABGs outcomes between the two methods of administration.

Conclusion: Although our results support the beneficial effects of adding bolus sodium bicarbonate on consciousness and electrocardiographic abnormalities in TCAs poisoning patients, to identify more effective ways of sodium bicarbonate administration, further trials are warranted.

Keywords: Tricyclic Antidepressants, Poisoning, Sodium Bicarbonate, Drip Infusion, Electrocardiogram Pattern, Consciousness

INTRODUCTION

Tricyclic antidepressants (TCAs) are widely used in psychiatric and medical conditions such as major depression, anxiety, panic, phobia, obsessive-compulsive disorder, chronic pain syndrome, nocturnal enuresis, peripheral neuropathies, migraine headache, and eating

disorders (1). Despite the advent of newer and safer antidepressants the popularity of tricyclic antidepressants in the treatment of major depression has not decreased (2). U.S. poison center reported over 12,000 exposures to tricyclic antidepressants (TCAs) in 2004 (3). Three fourth of all exposures occur in patients older than 19

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and 60% of cases are intentional (1). A survey in 1996 in United Kingdom showed that between 8 and 12% of drug overdoses were due to TCAs ingestion and TCAs may be involved in up to 33% of all fatal poisonings (4). Self-poisoning from tricyclic antidepressives is a leading cause of death among children and adults; furthermore, toxicity has been reported even with very small doses in children (5). In addition, toxicity of TCAs is one of the common causes of ICU admissions (9).

The main pharmacological properties causing the toxic effects of TCAs include: inhibition of norepinephrine reuptake at nerve terminals, direct adrenergic block, a membrane stabilizing or quinidine-like effect on the myocardium, and anti cholinergic action (2). The most frequent side effects of tricyclic antidepressant overdose consist of agitation, sinus tachycardia, QRS prolongation, terminal R-wave deviation, hypotension, respiratory depression, convulsions and coma (6-8). It is suggested that toxic effects of TCA exacerbates in the presence of other medications that have similar pharmacological actions(1).

Immediate interventions are necessary for symptomatic patients with TCAs poisoning. Administration of sodium bicarbonate, gastric decontamination techniques, and meticulous supportive care are some of efficacious treatments, especially in the first 24-48 hours of admission (7). Sodium bicarbonate infusion is widely recommended for the treatment of cardiac conduction disorders accompanied with TCAs overdose (10). Ventricular dysrhythmia and QRS complex widening greater than 100 m sec are the indications for serum alkalinization in TCAs toxicity (1). Vrijlandt and his colleagues reviewed observational studies and case reports that supported the use of sodium carbonate in TCAs poisoning. They found that all studies noted a rapid improvement in hypotension and cardiac arrhythmias following administration of sodium bicarbonate (11). Experimental studies reported that

both serum alkalinization and sodium loading are effective in achieving normal cardiovascular condition. Some investigators suggested that sodium bicarbonate seems to exerts its beneficial effects through sodium loading, whilst other studies proposed that its effect are due to pH changes (12).

The best method of sodium bicarbonate administration has not been yet established; therefore, we decided to compare the efficacy of drip infusion versus bolus administration of sodium bicarbonate in the treatment of TCAs poisoning.

MATERIAL AND METHODS

The present investigation was a randomized clinical trial and participants were recruited from the ICU of Loghman Hakim Hospital Poisoning Center (LHHPC). LHHPC is a unique referral center of poisoning in the capital city of Iran. Each year about 20000 patients are admitted in this center. The study period was from Feb to Dec 2007. To be eligible patients had to meet the following inclusion criteria: 1) TCAs poisoning 2) abnormality in Electrocardiography (ECG) 3) abnormality in blood PH. Patients with a history of cardiac disease, active renal disease, abnormal ECG, high serum level of sodium (Na) and a history of concomitant drug consumption such as antipsychotics, salicylates, and cardiac drugs were excluded. 80 patients who had TCAs poisoning and, had been admitted to ICU without any therapeutic management in emergency room were selected and they were divided into two groups, each composed of 40 patients. Both groups received 2 meq/kg of sodium bicarbonate in one bolus dose then group 1 received drip infusion of 2 liters of sodium bicarbonate (1.4% solution) additionally for the first 24 hours until the resolution of ECG changes and attainment of normal ABGs. Currently, there is no standard guideline concerning administration of sodium bicarbonate; thus, the amount of drug used was mostly influenced by our clinical

experience. All the patients were observed under supportive care for 24 hours post admission. In order to prevent fluid overload, regular lung auscultation was carried out, they were visited by trained physicians every 8 hours and ECG and arterial blood gas (ABGs) were performed for all of them regularly. The ECG parameters, that we considered in our study included: ECG rhythm, QRS duration, and T wave changes. The ABGs changes consisted of alkalosis, acidosis, and normal condition. Questioners were filled out by physicians and included demographic (sex, age, history of previous chronic diseases), clinical (consciousness status, blood pressure, respiratory rate and pulse rate) and paraclinical data (ECG, ABGs).

Statistical analysis:

The data were analyzed by appropriate statistical tests, such as Chi-squared and t-test using SPSS software version 16. A p-value of less than 0.05 was considered statistically significant.

The study protocol with code number 9 was approved by the ethical committee of the Shahid Beheshti University, M.C.

RESULTS

There were 45 (56.3 %) females ranging in age from 13 to 50 years (mean, 34.22 years) and 35 males ranging in age from 17 to 60 years (mean, 36.71 years). Mean age among patients who received drip infusion of sodium bicarbonate was 30.1 years (Std.Deviation=11.0)

, whereas mean age among bolus administration of sodium bicarbonate-treated group was 28.7 years (Std.Deviation=9.5). At the time of entry 23 (27.5%) cases presented with a systolic BP of ≤ 90 mm Hg, 58 patients (67.5 %) were normotensive, and 4 (5.0%) had high blood pressures (≥ 150 mm Hg). Statistically, there was no significant difference in sex, age, and blood pressure between the two groups.

Table 1 portrays the vital signs data of the study population which were detected at the admission time. Comparison of patients' outcomes including: mental status, ECG, and ABGs findings according to the method of treatment are given in Tables (2-4).

More patients were conscious in drip infusion group after 8 hours ($P = 0.012$), but on the contrary there were no differences in consciousness status of the two groups after 16 hours.

There were statistically significant differences between the ECG findings among the two groups during 16 ($p = 0.013$) and 24 hours ($p = 0.005$) after admission and the majority of patients with drip infusion of sodium bicarbonate treatment attained normal ECG findings in the first day. Comparison of patients' ABGs outcomes between the two methods of treatment displayed no significant differences. It should be noted that, the frequency of patients with alkalosis increased during the first 24 hours, in both groups.

Table 1: Vital signs of TCAs poisoning patients

Parameter	Drip infusion		Bolus administration		Statistics
	Mean	SD	Mean	SD	P value
Body temperature (C°)	37.1	0.4	37.1	0.4	0.687
Respiratory rate(n/min)	14.3	5.8	11.9	7.8	0.197
Pulse rate(n/min)	92.8	13.7	92.3	19.5	0.062
Systolic blood pressure (mmHg)	107.5	21.1	106.0	20.1	0.559
Diastolic blood pressure (mmHg)	70.1	13.5	68.2	15.2	0.563

Table 2: Comparison of mental status outcomes of the two administration methods

Mental status \ Time	During first 8 hours		During first 16 hours		During first 24 hours	
	Group1*(n)	Group2**(n)	Group1(n)	Group2(n)	Group1(n)	Group2(n)
Conscious	15	4	14	10	21	16
Lethargic	6	10	11	10	9	14
Coma	18	26	14	20	9	10
P-value	0.012		0.415		0.406	

* Bolus administration + drip infusion of sodium bicarbonate

** Bolus administration of sodium bicarbonate alone

Table 3: Comparison of ECG outcomes of the two administration methods

ECG \ Time	During first 8 hours		During first 16 hours		During first 24 hours	
	Group1*(n)	Group2**(n)	Group1(n)	Group2(n)	Group1(n)	Group2(n)
Normal	17	15	25	16	37	27
Sinus tachycardia	21	21	11	24	3	13
Ventricular tachycardia	-	1	2	-	-	-
Wide QRS complex (>100 msec)	1	1	-	-	-	-
T wave inversion	-	1	2	-	-	-
Peaked T wave	1	1	-	-	-	-
P-value	0.832		0.013		0.005	

* Bolus administration + drip infusion of sodium bicarbonate

** Bolus administration of sodium bicarbonate alone

Table 4: Comparison of patient ABGs outcomes of the two administration methods

ABG \ Time	During first 8 hours		During first 16 hours		During first 24 hours	
	Group1*(n)	Group2**(n)	Group1(n)	Group2(n)	Group1(n)	Group2(n)
Normal	16	19	26	27	30	27
Alkalosis	4	2	5	4	6	9
Acidosis	20	19	9	9	3	4
P-value	0.804		0.988		0.491	

* Bolus administration + drip infusion of sodium bicarbonate

** Bolus administration of sodium bicarbonate alone

DISCUSSION

Sodium bicarbonate has been considered as the first line treatment in TCAs intoxication but despite its importance, randomized prospective trials in humans on the best method of administration of sodium bicarbonate in TCAs poisoning are lacking. We only came across one study about recommended indications and methods of serum alkalinization that was performed in the United States Poison Centers (PC). Based on the mentioned investigation, 71% of authors recommended a bolus dose of sodium bicarbonate followed by an infusion and 14 medical directors (24%) recommended a sodium bicarbonate bolus alone. However, patients' outcomes had not been compared considering methods of sodium bicarbonate administration (13).

According to the previous reports, lethargy, seizures, and coma are the most common central nervous system complications in TCAs overdose (14, 15). Likewise Roy et al reported seizure in 10 (12.2%) of 82 patients admitted in ICU due to TCAs poisoning (16). On the contrary in our study, no seizure was detected among the patients. Although, Boehlert and his colleagues reported seizures were associated with QRS greater than 100 msec, seizure did not occurred even among our patients who had prolonged QRS (15).

We found that, during the first 8 hours after admission, consciousness levels were significantly different between two groups of patients. According to the results more than one -third of drip infusion sodium bicarbonate-treated group gained conscious during the first 8 hours after admission while only one-tenth of the bolus infusion sodium bicarbonate-treated group became alert in the same period of time. During the next 16 hours we observed no significant differences between mental statues of the two groups. The probable role of method of treatment in patients' consciousness status might need further investigations. Some claim that Sodium bicarbonate decreases sodium channel inhibition caused by TCAs intoxication and

it leads to decreased frequency of ventricular arrhythmias, prevents QRS prolongation, and also corrects hypotension. (17, 18) ; while others suggest that alkalinization by sodium bicarbonate decreases heart rate, shortens QRS interval, and corrects ventricular arrhythmias. (19). According to our findings while during the first 8 hour ECG changes did not differ, at 16 and 24 hours more patients who received drip infusion of sodium bicarbonate achieved normalized electrocardiographic findings.

The resolution pattern of QRS abnormalities has been remained poorly defined. According to Shannon's survey on 22 TCAs poisoned patients, there were no significant differences in the duration of QRS widening between the ten patients received sodium bicarbonate and the ones who did not receive such treatment. They suggested that Sodium bicarbonate may not reduce the total duration of QRS disturbances (20). On the other hand, in the study by Bou-Abboud et al, administration of sodium bicarbonate led to resolution of the ECG abnormalities in patients after a short time (21). Further investigations are needed to find more about the factors which determine the duration of QRS widening.

Improvement in pH parameter in ABGs reports was not statistically different between the two groups. Alkalosis due to administration of sodium bicarbonate, increased similarly during the first 24 hours, in both groups.

CONCLUSION

Although our results support the beneficial effects of adding bolus sodium bicarbonate on consciousness and electrocardiographic abnormalities in TCAs poisoning patients, to identify more effective ways of sodium bicarbonate administration, further trials are warranted.

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