

Oral Clonazepam versus Lorazepam in the Treatment of Methamphetamine-Poisoned Children: A Pilot Clinical Trial

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Abstract

Background: To evaluate the efficacy of oral clonazepam versus oral lorazepam following initial parenteral benzodiazepine administration to control methamphetamine-induced agitation in children.

Methods: In a single-center clinical trial, intravenous diazepam (0.2 mg/Kg) was initially administered to all methamphetamine-poisoned pediatric patients to control their agitation, followed by a single dose of oral clonazepam (0.05 mg/Kg; n=15) or oral lorazepam (0.05 mg/Kg; n=15) to prevent relapse of toxicity.

Results: The median age [IQR] (range) was 15 [10, 36] (6-144) months. The source of poisoning was methamphetamine exposure from oral ingestion in 23 (76.7%) and passive inhalation in 7 (23.3%) patients. The most common symptoms/signs were agitation (29; 96.7%), mydriatic pupils (26; 86.7%), and tachycardia (20; 66.6%). Two in each group (13.3%) needed re-administration of intravenous diazepam due to persistent agitation. There was no report of benzodiazepine complications in either group.

Conclusions: Although both benzodiazepines were effective, considering the similar administered doses of oral clonazepam and lorazepam as well as the higher potency of clonazepam, it seems that lorazepam is a better suited oral benzodiazepine for the maintenance treatment of methamphetamine-induced agitation in children and can be used with minimal complications.

Trial registration: IRCT20180610040036N2, April 18th, 2020. Retrospectively registered

Background

In recent years, Iran has seen a rise in the prevalence of stimulant abuse, including from methamphetamine, methylphenidate, and ecstasy [1-3]. The hidden nature of stimulant abuse among family members has also resulted in a dramatic increase in the frequency of accidental stimulant toxicity in children. Even though accidental opioid poisonings remain more common in Iranian children [1], this change in adult drug use patterns presents a challenge for clinical practice, since no appropriate antidote exists for stimulant poisoning [4]. The most common signs and symptoms of stimulant toxicity in children are irritability, agitation, hyperactivity, ataxia, seizure, inconsolable or constant body movements, roving eye movements, cortical blindness, hyperthermia, tachycardia, hypertension, vomiting, respiratory distress, and rhabdomyolysis [4].

Benzodiazepines (BZOs) are the first-line medications in the treatment of toxicity from stimulants, including methamphetamine. Management of agitation is the cornerstone in the treatment of methamphetamine poisoning, which can prevent further complications including hyperthermia, hypertension, hallucination, delirium, and rhabdomyolysis.

BZO treatment can control methamphetamine-induced agitation and prevent seizures simultaneously. The binding of BZOs to the GABA receptor increases chloride permeability causing an influx of chloride ions intracellularly and result in anti-anxiety, anti-convulsive, and sedative effects [5]. They are generally intravenously administered until the patient becomes symptom-free and calm.

However, in pediatric patients, access to and maintenance of the intravenous (IV) line is a major concern, especially in younger children and in busy wards. A child may not cooperate with the treating team, and the IV line may be lost during the treatment process due to the child's movements. IV administration of BZOs in children needs to be slow and requires respiratory monitoring, as rapid administration of BZOs may induce respiratory depression and apnea [6-9]. This risk is not common with oral BZOs [6].

Early administration of oral BZOs has been advocated in adult patients with methamphetamine poisoning [10]. However, the role of oral BZOs in the treatment stimulant-poisoned children after initial emergency department (ED) management is unclear, as literature on this subject is sparse. In clinical practice, we have observed that initial IV administration of BZOs does not sedate the child or that it can lead to a recurrence of stimulant toxicity. We hypothesize that the combination of two BZOs may have greater efficacy and safety, in which IV administration acts like a loading dose for oral treatment.

The aim of the current study was thus to evaluate the efficacy of oral BZOs in the treatment of methamphetamine poisoning in children referred to the only pediatric poisoning center in Tehran (Iran) after they were initially managed by administration of IV diazepam. For this purpose, we assigned the patients to two groups of oral clonazepam and oral lorazepam and compared the two treatments in their efficacy in terms of reducing agitation and other manifestations of stimulant toxicity.

Methods

Thirty methamphetamine-poisoned children who had been referred to Loghman-Hakim Poison Center in Tehran (Iran) between January 2017 and January 2018 were enrolled in this prospective pilot clinical trial adhering to CONSORT guidelines (Iranian Registry of Clinical Trials ID: IRCT20180610040036N2).

Patients were eligible for inclusion in the study if they were below the age of 12 and met diagnostic criteria for methamphetamine poisoning.

Diagnosis of methamphetamine poisoning was based on summation of three criteria: the history given by the child's parents, a positive urine methamphetamine, and clinical presentation. Patients with mixed poisoning (i.e. methamphetamine and other substance) or those whose urine was negative for methamphetamine were excluded from the study. Normal vital signs were determined based on pre-defined measures for each patient's respective age group [12].

BZO treatment: All thirty patients were initially administered IV diazepam (0.2 mg/Kg) and then consecutively (on a weekly basis) assigned to either the oral clonazepam or the oral lorazepam group (1:1 allocation ratio, 15 patients each, 0.05 mg/Kg [routine dose of oral BZO in children]). After the initial IV diazepam

treatment, oral BZOs were only given once to prevent return of stimulant toxicity by one of three of co-authors on shift. They were given half an hour after the patient was calm and could be switched to oral regimen. If the child was not enough sedated after 45 min, then we considered next dose of IV BZO.

Data collection: Records were kept on the patients' demographic characteristics, urine drug screen results, route of methamphetamine exposure (inhalation versus ingestion), time elapsed between methamphetamine use and hospital presentation, vital signs and signs/symptoms on presentation, type and total dose of the oral BZO administered (clonazepam versus lorazepam), need for re-administration of the IV BZOs after initial management of the patient, time elapsed between BZO administration and resolution of the signs and symptoms, duration of hospital stay, and side effects of treatment (respiratory depression, deep sedation, and paradoxical agitation).

Patient monitoring: Patients were continuously monitored for pulse rate, respiratory rate, blood pressure and cardiac rhythm. However, since they were irritable and using pressure cuffs for blood pressure check could agitate them, blood pressure was only checked every six hours. During the post-treatment observation period, the nurses would call the attending physician if they detected agitation or any changes in the patient's vital signs or cardiac rhythm. Patients' monitoring continued till discharge.

Data analysis: The data were analyzed using IBM Statistical Package for Social Sciences (SPSS) version 21. For qualitative variables, percentage of frequency was reported. Mann-Whitney U-test and chi-square test were used to evaluate the association between continuous and categorical variables. The Friedman's two-way ANOVA was used to test for differences between lorazepam and clonazepam to see timeline difference for respiratory rate, heart rate, temperature and blood pressure. A *P* value of less than 0.05 was considered to be statistically significant.

Results

A total of 30 patients were enrolled, with 15 patients evaluated in each group. Nineteen (63.4%) were male. Their age ranged from 6 to 144 months (median 15; IQR [10, 36]).

Twenty-three patients (76.7%) had ingested methamphetamine, either in the form of crystal powder (16 patients; 53.3%) or as water from a methamphetamine pipe (7 patients; 23.3%). Seven (23.3%) had been passively exposed to methamphetamine smoked by their parents (i.e. fathers, based on patient history).

Most exposures had happened at night (25 cases; 83.3%), including all passive smoking cases (7 cases; 23.3%), 14 cases (46.7%) of crystal powder ingestion, and 4 cases (13.3%) of pipe water ingestion.

The median elapsed time [IQR] between exposure and development of methamphetamine toxicity was one hour [1, 2] (30 minutes to 24 hours), and the median [IQR] time between exposure and hospital presentation was five hours [3, 6] (one hour to 72 hours; Table 1), according to parental report. Urine methamphetamine was positive in all cases.

Table 1: Demographics, on-arrival presentation, and treatment response by group

Variable	Total (n=30)	Lorazepam (n=15)	Clonazepam (n=15)	P (MWU test)
Median [IQR] (range)				
Age (months)	15 [10, 36] (6, 144)	15 [10, 37] (6, 144)	17 [11, 33] (6, 84)	0.637
Weight (kg)	11 [10, 14] (6.5, 40)	11.5 [9.5, 15] (8, 40)	10.7 [10, 13.7] (6.5, 25)	0.697
Time elapsed between exposure and presentation (h)	3 [5, 6] (1, 72)	5 [4, 9] (2, 72)	3 [5, 6] (1, 14)	0.377
Time elapsed between exposure and developments of symptoms (h)	1 [1, 2] (0.5, 24)	1 [1, 2.2] (0.5, 24)	1 [1, 2] (0.5, 2)	0.275
Presentation on arrival				
Temperature (C)	37 [36.5, 37] (36, 37.7)	36.9 [36.5, 37] (36, 37.3)	37 [36.7, 37.1] (36.5, 37.5)	0.142
Systolic BP (mmHg)	90 [90, 100] (80, 110)	92 [90, 100] (80, 110)	90 [90, 100] (80, 110)	0.400
Diastolic BP (mmHg)	50 [50, 60] (40, 80)	60 [50, 70] (50, 80)	50 [50, 60] (40, 70)	0.160
Heart rate (per minute)	127 [110, 140] (90, 160)	130 [110, 150] (92, 160)	120 [102, 140] (90, 150)	0.498
Respiratory rate (per minute)	30 [27, 35] (16, 60)	31 [26, 35] (22, 60)	30 [28, 34] (16, 60)	0.667
Aspartate aminotransferase (U/L)	218 [148, 360] (88, 1584)	225 [148, 461] (117, 698)	211 [126, 324] (88, 1584)	0.697
Treatment response				

Duration of symptoms (h)	4 [3, 5] (2, 20)	3 [2, 4] (2, 13)	5 [3, 7] (2, 20)	0.166
Hospitalization period (h)	24 [24, 48] (24, 72)	24 [24, 48] (24, 48)	24 [24, 42] (24, 72)	0.525

The most common signs and symptoms of toxicity were agitation (29 patients; 96.7%) followed by mydriatic pupils (26; 86.7%), tachycardia (20; 66.7%), insomnia (18; 60%), stereotypical movements (hand shaking, waving, or wringing, head banging, self-hitting, and self-biting; 12; 40%), tachypnea (8; 26.7%), vomiting (7; 23.3%), and talkativeness (5; 16.6%). Other important signs and symptoms were delusion, tremor, and sweating (each in two patients; 6.7%), and hallucinations and seizure (each in one patient; 3.3%). One case (3.3%) had hyperthermia (axillary temperature >37.5 °C) on presentation. Hypotension was present in one patient (3.3%) and hypertension in another (3.3%). Three patients (9.9%) had low diastolic blood pressures (DBP). Rhabdomyolysis (CPK > 1000 U/L) was reported in one patient (3.3%).

Treatment response:

After initial administration of 0.2 mg/Kg IV diazepam in all patients, four patients (2 in each group) needed re-administration of IV diazepam (at 45 minutes, 50 minutes, 60 minutes, and 75 minutes after the first diazepam dose) due to persistent agitation after the first dose.

Oral BZOs were administered only once immediately after the patients became calm and could be switched to oral regimen (mean 1 hour; range, 0.5 to 3 h). 15 patients received oral clonazepam (0.05 mg/Kg) and another 15 received oral lorazepam (0.05 mg/Kg). The mean administered dose of oral BZO was 1.1 mg in both groups.

Statistical analysis showed that on-arrival vital signs were similar between the two groups after treatment (table 1; all *P*s were higher than 0.05).

Almost 73% (22 cases) of patients responded to treatment within five hours of administration of the oral BZOs. All patients remain conscious during observation period and no adverse effects were seen following oral BZOs administration. In three cases (10%), symptoms persisted for 12 hours or more (i.e. up to 20 hours). Although the median duration of symptoms was less in those treated with lorazepam (3 versus 5 hours), the difference was not significant (*p*=0.166). Table 2 shows vital signs including respiratory rate during hospitalization period in a 6-hours basis after IV diazepam and initiation of oral BZOs.

The median [IQR] (range) hospitalization period was 24 hours [24, 48] (24, 72) hours, with 10 patients (33.3%) remaining hospitalized for 24-72 hrs. The duration of hospital stay (*p*=0.525) did not differ significantly between the groups. Figures 1-4 show pairwise multiple comparison of vital signs for each oral BZO in 6-hour time intervals.

Table 2: Vital sign time interval of patients after being calmed in ED and initiation of oral benzodiazepines (n=30)

Variable	BZO	Time post initiation of oral benzodiazepine (hour)				
		0	6	12	18	24
Heart rate [†]	Lorazepam	130 [110, 150] (90, 160)	112 [110, 128] (100, 140)	110 [102, 112] (90, 120)	102 [100, 112] (88, 130)	100 [99, 110] (80, 126)
	Clonazepam	120 [100, 140] (92, 144)	115 [106, 122] (100, 148)	107 [100, 110] (80, 127)	110 [97, 119] (88, 123)	108 [98, 120] (88, 120)
Temperature [†]	Lorazepam	37 [36.6, 37] (36, 37.1)	37 [36.9, 37] (36.7, 37.8)	36.8 [36.5, 37] (36.2, 37.5)	36.8 [36.5, 37] (36.2, 37.5)	36.5 [36.5, 36.8] (36.2, 37)
	Clonazepam	37 [36.6, 37] (36, 37.2)	37 [36.9, 37] (36.5, 37)	36.8 [36.5, 37] (36, 37.2)	37 [36.5, 37] (36.5, 37.2)	36.5 [36.5, 36.9] (36.5, 37)
Respiratory rate [†]	Lorazepam	30 [26, 35] (20, 60)	25 [22, 27] (20, 55)	25 [22, 25] (18, 50)	23 [22, 26] (20, 26)	22 [22, 24] (21, 25)
	Clonazepam	30 [24, 33] (16, 60)	29 [20, 32] (20, 40)	25 [21, 29] (18, 35)	25 [21, 29] (18, 30)	24 [19, 25] (18, 30)
Systolic blood pressure [†]	Lorazepam	92 [90, 100] (80, 100)	92 [90, 90] (80, 100)	90 [80, 97] (80, 100)	90 [75, 100] (70, 100)	90 [77, 92] (70, 100)
	Clonazepam	90 [90, 100] (80, 110)	90 [90, 100] (80, 110)	85 [80, 90] (80, 100)	85 [80, 85] (70, 90)	75 [70, 75] (70, 100)

*Using Friedman's two-way ANOVA, [†]Median [IQR] (min, max)

Discussion

In our study, treatment with oral clonazepam and oral lorazepam had the same efficacy in the resolution of the signs and symptoms of methamphetamine toxicity in children. Further pairwise analyses showed that both BZOs had no significant impact on systolic blood pressure over the time, and both were effective in decreasing respiratory rate, thus constituting what appears to be appropriate control of agitation. Lorazepam was superior to clonazepam in decreasing patients' heart rate and temperature. Limited access to parenteral lorazepam (as a good substitute for parenteral BZOs such as diazepam and midazolam) in Iran had had made us look for safer oral alternatives, and our results show that most of our pediatric patients were sedated adequately with the combination treatment of only 0.2-mg/Kg IV diazepam as loading dose followed by oral BZO administration (clonazepam or lorazepam at 0.05 mg/Kg). This combination treatment was well tolerated, as none of the patients in our sample experienced any complications. Oral lorazepam and clonazepam were both administered at an average dose of 1.1 mg. Considering the BZO equivalency table [11], less duration of symptoms in those treated with lorazepam (not

significant in our limited samples), since the dose was the same for both clonazepam and lorazepam and we found equal efficacy with both agents, with no reported adverse effects, this suggests that lower doses of BZOs such as 0.05 mg/kg lorazepam equivalents may be appropriate.

To the best of our knowledge, this pilot study is the first to investigate the efficacy of oral BZOs in pediatric methamphetamine poisoning.

Literature on the management of stimulant-poisoned children has been limited to reports of IV BZO treatment to date. For instance, Van Rijwijk (10-mg diazepam), Duffy MR (5-mg diazepam and 2-mg IV lorazepam), Campbell (Diazepam and IV lorazepam), Cooper (IV diazepam), and Bedford Russel (2.5 mg/kg IV diazepam) have previously evaluated the effectiveness of IV BZOs for the treatment of ecstasy-poisoned children [12-16]. Kung and colleagues reported on a 5-year-old MDMA-poisoned patient with hypertension, tachycardia, hyperthermia, and mydriasis. An initial IV dose of 2.5 mg of diazepam was administered followed by other divided doses in 20-minute intervals which recovered the patient. The patient was discharged home after four days of ICU admission completely symptom-free [17]. Strommen and colleagues reported a 17-month-old infant with methamphetamine poisoning who referred with acute irritability, muscle twitching, and severe perspiration whose agitation was controlled within 30 to 40 minutes after administration of parenteral BZOs [18]. Matteucci et al. retrospectively evaluated 47 pediatric cases (age 0-6 years) of methamphetamine poisoning who had been referred to poisoning control centers in the USA between 2004-07, with agitation as most common symptom. Parenteral BZO had been administered to more than half of them, and the mean time to resolution of their signs and symptoms was 22 hours. No death was reported [19]. Ruha and Yarema reported 18 children poisoned with methamphetamine who were admitted to a critical care unit between 1997 and 2004. They were all treated with BZOs, and haloperidol was also administered to 12. They all improved with no important side effect [20].

As depicted in table 1, the median [IQR] treatment response and duration of symptoms was 4 [3, 5] hours for all patients with a hospitalization closer to 24-48 hours. The long hospitalization compared to short duration of toxicity was due to observation period, expected probable adverse effects (i.e. over sedation) and some cases of persisted agitation. Next follow-up showed that although patients were mostly calm, their vital signs were different over time comparing temperature and heart rate. Our findings thus support our hypothesis that treatment with oral clonazepam or lorazepam following only an initial IV diazepam loading dose is efficacious and may reduce the burden for healthcare workers, for whom establishing access to and maintenance of the IV line is a major concern in pediatric patients.

Compared to the aforementioned pediatric studies, we managed to enroll a substantial sample of 30 patients. Replication of our findings would lend further support to the concept of the combination treatment of IV and oral BZO as a practical, novel and cost-efficient intervention. However, further studies to evaluate different BZOs in the setting of acute methamphetamine poisoning in children are also warranted. These may include a comparison of the non-IV administration of different BZOs, e.g. by the intranasal (diazepam, midazolam), buccal and intramuscular (both midazolam) routes, which have already been tested in the management of epileptic seizures in children and shown similar efficacy as IV diazepam for this indication [21].

The generalizability of our findings is limited by the fact that all patients were recruited at a single center in Tehran, and the external validity may be questionable. Moreover, patients were not randomly assigned to their treatment condition, and we cannot rule out the possibility of clinician bias. Future research could compare the treatment regimens more systematically in a blinded RCT. Lack of administration equivalent doses of clonazepam and lorazepam was also a possible limitation. We followed textbook recommendation for recommended dose (mg/kg) of lorazepam and clonazepam, in which they were the same.

Another limitation is lack of agitation score in different times study which should be mentioned in future studies.

Conclusion

This study demonstrates that oral lorazepam and clonazepam are effective and safe adjunct medications to IV diazepam in the treatment of methamphetamine poisoning and its agitation syndrome in children. Oral BZOs are effective to control methamphetamine induced agitation in children with no major side effect.

List Of Abbreviations

BZO= Benzodiazepine, CPK = Creatine Phosphokinase; DBP = Diastolic Blood Pressure; ED = Emergency Department; GABA = Gamma Aminobutyric Acid; IV = Intravenous; IQR = Inter Quartile Range; MDMA = Methylene Dioxy-Methamphetamine; RCT = Randomized Clinical Trial; SBP = Systolic Blood Pressure; SPSS= Statistical Package for Social Sciences

Declarations

Ethics approval and consent to participate: This study approved by Shahid Beheshti University of Medical Sciences ethics committee (IR.SBMU.RETECH.REC.1394.122). Written informed consent was obtained from the parents of all individual participants included in the study.

Consent to publish: Available.

Availability of data and materials: The data is all presented in the text. Full trial protocol can be accessed on <https://www.irct.ir/search/result?query=IRCT20180610040036N2>

Competing interests: None.

Funding: None

Authors' Contributions: FF and HHM are the guarantors of integrity of the entire study. FF, RR and HHM gave the study concepts and designed the study. RR and NG, did the literature research. HHM and LG performed the data analysis. LG and HHM performed the statistical analysis. NZ and RM prepared the manuscript draft and RM edited the final manuscript. All authors have read and approved the manuscript.

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Figures

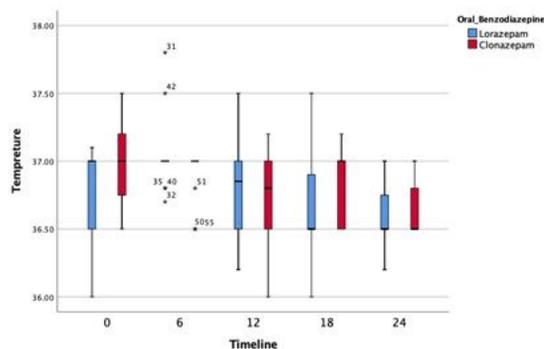


Figure 1

Temperature time interval (hour) following ingestion of bezodiazepines post IV Diazepam (n=30)

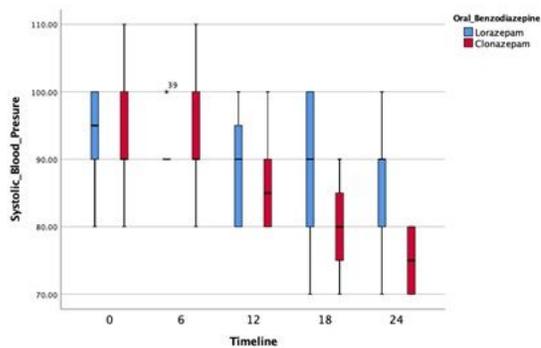


Figure 2

Systolic blood pressure time interval (hour) following ingestion of bezodiazepines post intravenous diazepam (n=30)

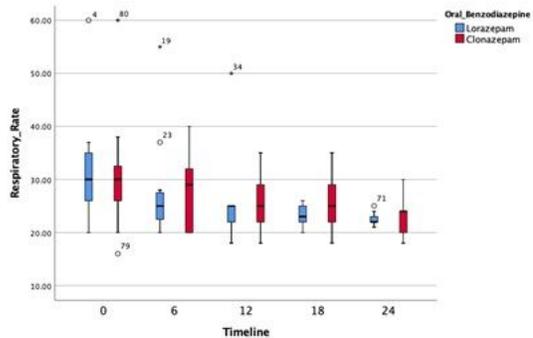


Figure 3

Respiratory rate time interval (hour) following ingestion of bezodiazepines post intravenous diazepam (n=30)

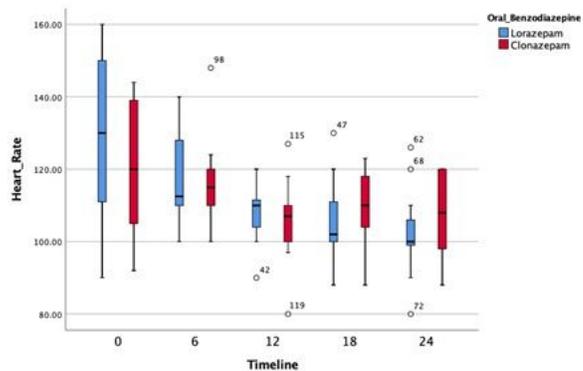


Figure 4

Heart rate time interval (hour) following ingestion of bezodiazepines post IV Diazepam (n=30)

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