ORIGINAL ARTICLE

The Correlation between the Length of Stay with APACHE and PSS Scores in Baclofen Toxicity

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Abstract

Background: This is a descriptive cross-sectional study to investigate the severity of acute baclofen poisoning and length of hospital stay (LOS).
Methods: The documents of cases with baclofen poisoning diagnosis; Baclofen alone intoxication (BAI) and multidrug intoxication (MDI) (March 2015-2019) were evaluated. Clinical and paraclinical findings, LOS, APACHE, and Poison Severity Scores (PSS) were extracted.
Results: From 46 collected cases, 10 cases were BAI and all of them were women. The adult cases, who attempted suicide were younger (26.09±9.62 years) than those accidentally poisoned (58.29±22.06 years) (PV=0.008). Two BAI (20%) and one MDI (2.7%) were apnotic. None of BAI had hypotension, hypertension, bradycardia, or tachycardia. Past medical history of depression had no statistically significant effect on the clinical manifestation. There were correlations between adult diastolic and mean arterial blood pressures with baclofen ingested dose and renal function test results. MDI and BAI had similar ingested baclofen doses (152.63±67.0 and 130±90.3 mg). All BAI had GCS<10. The mean of the calculated APACHE score was higher in BAI (15.43±3.2) than in MDI (8.8±7.8) groups (PV<0.05). APACHE score positively correlated with the LOS of BAI (R^2=0.830, b=0.287 CI=0.175-0.420; PV=0.001). APACHE score did not correlate with the estimated baclofen ingested dose. There was a positive linear correlation between PSS and APACHE score of BAI patients, (R^2=0.499, PV=0.033, B=5.00±1.89, PV=0.033, CI=0.52-9.479). However, there was no correlation between PSS of BAI cases and LOS (PV=0.24).
Conclusion: APACHE score had a positive correlation with the LOS.

Keywords: Poisoning, Baclofen, Muscle Relaxants, APACHE, Treatment Outcome

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INTRODUCTION

Baclofen is an agonist of β gamma-aminobutyric acid receptors that readily penetrates the blood-brain barrier, resulting in relaxation and strong depression of the central nervous system. Baclofen is currently available as an oral formulation and solution for intrathecal injection [1]. Baclofen is also used to relax skeletal muscle spasms and spasticity, especially in patients with multiple sclerosis [2]. Other uses of baclofen include chronic hiccups [3], autism spectrum disorder [4], chronic post-traumatic stress disorder (PTSD) [5], sleep attacks [6], trigeminal neuralgia [7], and back pain [5].

Rahimi et al reported 135 cases of baclofen intoxication. Most of them had central nervous system symptoms especially loss of conciseness. They found a significant statistical relationship between the dose of baclofen and consciousness level [8].

APACHE score and other severity scores were evaluated for the prediction outcome of poisoned patients. GCS, APACHE, predicted mortality rate (PMR), Modified Early Warning Score (MEWS), and Poison Severity Score (PSS) could appropriately predict the outcome (mortality and need the ICU admission) of the organophosphorus-poisoned patients [9-11]. However, some scholars reported the opposite opinion [12]. APACHE score had also an appropriate predictive value of the outcome of paraquat poisoning [13, 14]. Silakhori et al [15] also reported that APACHE II had no correlation with LOS of poisoned patients in ICU, though, APACHE IV, Sequential Organ Failure Assessment (SOFA), and Simplified Acute Physiologic Score (SAPS) II had a significant correlation with the LOS in ICU.

Since baclofen is currently used in the treatment of vast diseases, intoxication and abuse are possible. Baclofen poisoning should be considered in the conditions of muscle weakness and flaccid paralysis [16] that can be life-threatening. Concerning the increased incidence of baclofen intoxication [17], it is important to find the risk and

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prognostic factors. This descriptive cross-sectional study was conducted to investigate the severity of acute baclofen poisoning and the correlation between the poisoning with clinic-epidemiological properties

METHODS

We retrospectively evaluated the documents of reported cases with baclofen poisoning diagnosis (single drug or multidrug poisoning), who were referred and admitted to the clinical toxicology department of Imam Reza Hospital Mashhad-Iran (CTD-IRH-MUMS) from March 2015 to March 2019, as a descriptive-cross-sectional study. Documents were selected according to ICD-10 codes that were performed by the hospital information system based on the confirmed diagnosis of patients by physicians at discharge. All documents with incomplete data (more than 50% of variables) were excluded.

A checklist was used to collect the data. Information about all patients such as epidemiological data, clinical findings, paraclinical results, methods and type of treatment, length of stay in hospital (LOS), and the outcome were extracted, coded, and registered. APACHE score of patients was calculated according to recorded data from patients' documents [18]. The Poison Severity Score (PSS) of Baclofen-alone intoxication (BAI) cases was graded using a standardized scheme. The scores were as follows: none (grade 0), minor (grade 1), moderate (grade 2), severe (grade 3), and fatal (grade 4) poisoning. The most severe clinical features taken for PSS [19].

Privacy and confidentiality of the patients' information were observed. The research was approved by MUMS ethical committee with the ethical code number: IR.MUMS.MEDICAL.REC.1398.737.

Quantitative variables were expressed using central and dispersion indices. Comparison of continuous quantitative variables in different groups of patients such as gender and marital status was analyzed by t-test or analysis of variance (ANOVA) if they had relevant conditions and non-parametric tests if needed. The relationship between qualitative variables was evaluated by the chi-square test. Statistical threshold p <0.05 was considered to indicate a significant difference.

RESULTS

Epidemiological Findings:

From March 2015 to March 2019, 46 Baclofen poisoning patients were admitted to CTD-IRH-MUMS. The mean age of the subjects was 28.85 ± 18.19 years (Median=24, range 3-79 years) and most of them were females (35 patients, 76.00%). There was no significant difference between the mean of age of men (25.81 ±12.85, median= 28.00, range =4.0-42.00 years) and women (29.80 ± 19.63, median= 23.00, range= 3.00-79.00 years). A history of drug abuse was observed in 6 patients (13.00%).

About three-quarters of the patients (34 cases, 73.9%) ingested baclofen tablets for self-poisoning or suicidal attempts. The other causes of poisoning include accidental poisoning (7 cases, 15.2%), adverse drug reaction (2 cases, 4.3%), medical error (1 case, 2.2%), and unknown cause (2 cases, 4.3%). The adult cases, who attempted suicide were younger (26.09±9.62 years) than others (58.29±22.06 years) (PV=0.008, nonparametric test).

About two-third of the patients (31, 67.40%) had no previous history of a specific disease. Meanwhile, 8 patients (17.40%) including 6 women (75% of cases) and 2 men (25% of cases) had depression. Seven cases have suffered from one of the following issues, at least: spinal cord injury, hypertension, neck pain, low back pain, paralysis and chronic kidney failure (CKD), diabetes and depression, and hypertension plus diabetes and chronic kidney failure.

Most of the patients (36 cases, 78.30%) had multidrug poisoning, and only 10 cases were intoxicated by baclofen alone (BAI) (Supplement 1). Five of the cases (10.9%) were less than 14 years old and 3 of them were intoxicated by multidrug.

All of the BAI patients were female and 70% of them had suicidal attempts (table 1) and none of them were addicts. Two of them had a history of depression.

Table 1. Comparison between the means of the primary vital signs of baclofen-intoxicated patients with multiple drugs or baclofen alone (BAI), who were referred to CTD-IRH-MUMS during 2015 – 2019. Baclofen dosage and primary GCS in all patients were included in the calculation of averages. For other variables, only the values of cases > 14 (adult)years old have been used. BP=blood pressure

Variable	Unite	Multidrug				BAI				PV
		N	Mean ±SD	Median	Rang	N	Mean± SD	Median	Rang	
Baclofen dose	mg	19	152.63±67.0	200	25-250	8	130±90.3	100	30-250	NS
Primary GCS		35	11.5±3.6	14	4-15	10	6.6±1.6	6	4-10	<0.001
Primary adult systolic BP	mmHg	32	118.7±27.4	110	80-231	8	116.9±9.6	120	100-130	NS
Primary adult Diastolic BP	mmHg	32	72.5±12.6	70	40-105	8	74±10.6	75	60-87	NS
Primary adult Mean BP	mmHg	32	87.9±16.6	84.2	56.7-147	8	88.3± 8.9	90	73.3-98.3	NS
Primary adult heart rate	Beat/min	33	80.64±14.1	80	43-110	8	77.6±8.7	80	60-86	NS
Primary adult respiratory rate	Cycle /min	31	16.32±3.8	16	0-24	8	14.1±6.2	17.5	0-18	NS
Primary adult temperature	˚C	31	36.9±0.3	37.0	35.5-37.1	8	37.0±0.2	37	36.8-37.5	NS
Primary adult Blood sugar	mg/dl	20	127.10±73.2	96	68-350	6	111.8±58.9	91.2	80-230	NS
Adult hospitalization time	day	31	2.1±1.3	2	0.25-6	8	1.8±1.0	2	0.42-3.0	NS
APACHE score of adults		26	8.8±7.8	7	0-36	7	15.43±3.2	14	11-25	<0.05

BAI and multidrug-intoxicated patients had similar ages (26.5±23.1 and 29.5±16.9 years, respectively).

Clinical Manifestations and Paraclinical Findings:

The results showed that the chief complaint of half of the patients (23 cases, 50.00%) was drug poisoning and loss of consciousness was the second (19 cases, 41.3%). Only 3 (6.5%) adult patients were hypotensive (mean arterial blood pressure< 65 mm Hg or systolic blood pressure < 90 mmHg) and all of them were multidrug and the ingested dose of one of them was known (200 mg) (table 1). Only one woman, who ingested 100 mg of baclofen and some other unknown drugs had bradycardia (HR= 43 beat /mean). Tachycardia was recorded in four adult patients (HR=100-110) with multi-drug toxicity (none of them was BAI), two men and two women.

Three women were bradypenia-apnotic (RR< 5) when they were admitted to the hospital. One of them was a 3-year-old child, who ingested an unknown dose of baclofen alone 10 hours ago. Another one was a woman, who ingested 250 mg of baclofen alone 12 hours ago for a suicidal attempt, and the third one was a multidrug-poisoned woman.

Past medical history of depression had no statistically significant effect on signs and symptoms of all patients (multidrug + BAI) such as APACHE score, age, baclofen ingested dose, primary systolic, diastolic and mean blood pressure, primary heart rate, primary temperature, and LOS (P>0.05).

We did not register any BAI patients with hypotension, and there was no predictive factor to estimate the systolic blood pressure of BAI patients. But, there were correlations between diastolic and mean arterial blood pressures with baclofen ingested dose, urea, and creatinine serum levels (table 2). Seizure was not recorded in our cases before or during hospitalization. None of the BAI patients had miosis. There was no remarkable abnormal laboratory test result. The lab test results of patients were summarized in (supplement 2).

Glasgow Coma Scale (GCS)

The average of the initial GCS measured of the patients was 10.72±3.89 (median 12, range 4-15), which was significantly lower in BAI patients than in multidrug (P<0.001) (table 1). All of the BAI patients had GCS of less than 15 which took an average of 11.5±7.5 hours (median =4, range =4-27 hours) to return to normal GCS.

The length of unconsciousness of the patient was not related to any of the various clinical variables such as baclofen ingested dose, primary GCS, first-time blood pressures, and heart rate. It also was not dependent on laboratory results of patients, such as urea, creatinine, PCo2 values, etc. In BAI patients, we could not find any correlation between the time to return to normal GCS (15) and the baclofen ingested dose, lag time between ingestion and admission, and other factors (p<0.5).

Ingested Dose:

The mean dose of ingested baclofen was 145.93±73.64 mg (25 to 250 mg), which was known only in 27 patients and others did not report the amount of ingested baclofen. No significant difference was found in the means of baclofen dose of patients with different sex, addiction status, various chief complain and different causes of intoxication (P > 0.05) (supplement 3). Also, the difference between the means of baclofen ingested dose of two groups (multidrug and BAI) was not statistically significant (table 1).

APACHE and PSS

The mean of the calculated APACHE score was higher in BAI patients than in multidrug (table 3) (PV<0.05). APACHE score had a positive correlation with the Length of stay (LOS) of all patients (multidrug and BAI) (table 3 and figure1). None of the lab test results was correlated to APACHE score in BAI patients. However, blood urea level (R2=0.193, PV=0.009; Beta=0.439, CI=0.041 to 0.385, PV=0.016) and blood creatinine level (R2=0.393, PV<0.001; Beta=5.627 CI=2.868 to 8.397, PV<0.001) were correlated to APACHE score in multidrug intoxicated patients.

There was no correlation between APACHE score and the estimated baclofen ingested dose. The patients, who attempted suicide with multidrug had lower APACHE score than others (7.4±5.5 and 14.6±10.3, respectively) (supplement 4). There was a positive linear correlation between PSS and APACHE score of BAI patients, (R2=0.499, PV=0.033, B=5.00±1.89, PV=0.033, CI=0.52-9.479). However, there was no significant correlation between PSS of BAI patients and Length of stay (LOS) (PV=0.24).

Treatment and Outcome:

All patients received supportive treatment. There was no report of death and 56.5%, 28.3%, and 15.2% of the patients were discharged in completely well condition, partially well condition, and by personal discharge, respectively. There was

Table 2. The linear regression between diastolic and systolic blood pressure with baclofen dosages and kidney function tests in baclofen alone intoxicated (BAI) patients referred to CTD-IRH-MUMS during the 2015 – 2019 year

Dependent variable	Independent variables	R square	PV of model	Beta ±SD	95% CI of Beta	P Value of beta
Diastolic Blood pressure	Baclofen dose	0.946	0.021	-0.117±0.032	-0.219 to -0.15	0.036
	Urea			-2.458±0.662	-4.566 to -0.351	0.034
	Creatinine			145.379±31.675	44.575 to 246.183	0.019
Mean Blood pressure	Baclofen dose	0.915	0.041	-0.096 ±0.034	-0.203 to 0.11	0.065
	Urea			-2.114±0.691	-4.314 to 0.085	0.691
	Creatinine			114.385±33.06	9.173 to 219.597	0.041

Table 3. Determining the correlation of APACHE score to age and clinical variables of Multidrug (MDI) and baclofen alone (BAI) intoxicated patients referred to CTD-IRH-MUMS during 2015 – 2019 year due to baclofen poisoning

Variable	MDI/BAI	R Square	P value of Correlations	Beta	95% Confidence Interval for Beta		PV of Beta
					Upper Bound	Lower Bound	
Age	MDI	0.144	0.012	0.417	0.27	0.363	0.24
	BAI	0.029	0.331	0.170	-0.105	0.155	0.662
Baclofen dosage	MDI	0.007	0.180	-0.265	-0.064	0.025	0.359
	BAI	0.128	0.216	0.012	-0.025	0.050	0.865
LOS	MDI	0.122	0.019	0.357	0.004	0.130	0.042
	BAI	0.830	0.001	0.287	0.175	0.420	0.001
primary GCS	MDI	0.708	<0.001	-1.847	-2.289	-1.381	<0.001
	BAI	0.309	0.060	-1.180	-2.758	0.398	0.120
Adult SBP	MDI	0.177	0.009	0.117	0.022	0.213	0.018
	BAI	0.00	0.484	-0.19	-0.371	0.359	0.968
Adult DBP	MDI	0.049	0.072	0.295	-0.061	0.395	0.144
	BAI	0.257	0.143	-0.131	-0.414	0.152	0.287
Adult MABP	MDI	0.125	0.021	0.170	0.006	0.333	0.043
	BAI	0.281	0.197	-0.129	-0.482	0.227	0.394
Adult HR	MDI	0.002	0.418	0.863	-0.260	0.212	0.863
	BAI	0.696	0.298	0.539	-0.494	0.312	0.539
Adult RR	MDI	0.00	0.165	0.330	-1.181	0.414	0.330
	BAI	0.077	0.274	0.584	-0.648	0.388	0.584

DBP= primary diastolic blood pressure; HR= primary Heart rate; LOS=Length of stay in hospital; MABP= primary mean arterial blood pressure; RR= primary respiratory rate; SBP= primary Systolic blood pressure,

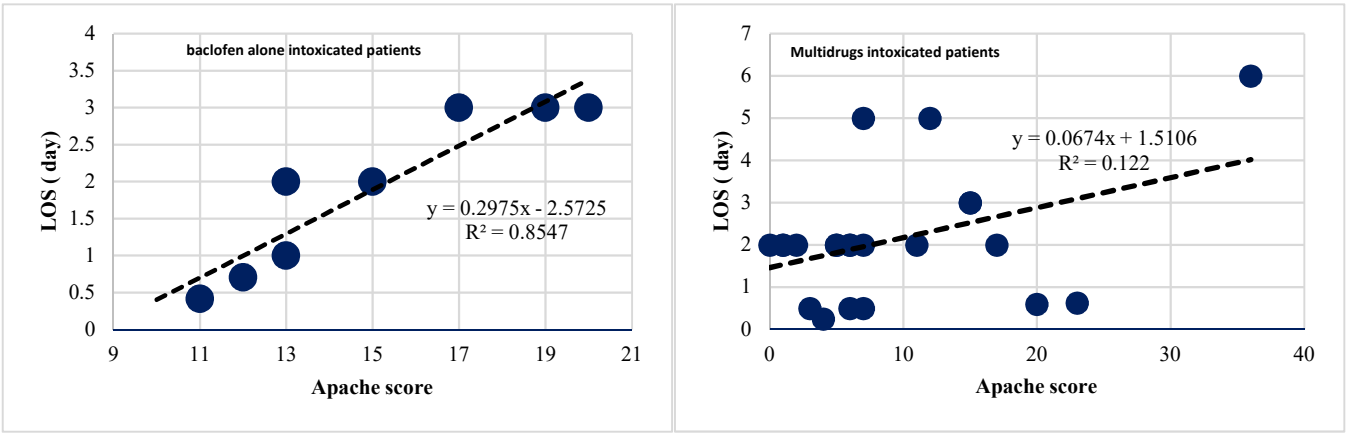

Figure 1. The Correlation between APACHE score and Length of stay (LOS) in Multidrug and baclofen alone intoxicated patients in patients referred to CTD-IRH-MUMS during 2015 – 2019 year due to baclofen poisoning.

no difference between BAI and multiple drug intoxication in type of the patients' discharge. Six of the patients were complicated by pneumonia, neuropathic paralysis, and gait disturbance from whom four were BAI and two were multidrug intoxicated.

DISCUSSION

This retrospective study presents a course of cases of self-intoxication or accidentally poisoning with off-label or prescribed baclofen admitted in CTD-IRH-MUMS from March 2015 to March 2019. In the current research, we found that the APACHE score had a positive correlation with the Length of stay (LOS) of baclofen intoxicated patients. Moreover, there was a positive linear correlation between PSS and APACHE score of BAI patients. None of the laboratory test results or ingested baclofen dose correlated with PSS or APACHE scores. The kidney function and dose of ingested baclofen were correlated to blood pressure of cases.

In the current study, the adult cases, who attempted suicide were younger than others. Pelissier et al evaluated baclofen exposures in alcohol-dependent patients. They also reported that the patients attempting suicide were younger than others [20]. Baclofen self-poisoning is much more common in patients with psychiatric co-morbidity or alcohol dependency [20-23]. In our study, 8 patients (17.40%) had a past history of depression. Seventy percent of BAI patients had suicidal attempts, however, none of them were addicts. Two of BAI had also a history of depression (20%).

Psychiatric comorbidity not only increases the prevalence of suicidal attempt, but also relates to the severity of Baclofen poisoning [23-25]. In the present study, past medical history of depression had no statistically significant effect on signs and symptoms of intoxicated patients (multidrug and BAI) such as APACHE score, baclofen ingested dose, first presented vital signs and LOS. Although we could not find any statistically significant difference on factors of severity of poisoning between BAI patients with and without depression (because of the small sample size), two BAI cases with depression had ingested the highest dose of baclofen (200 and 250 mg), had low primary GCS (8 and 4), longer length of unconsciousness (10 and 14 hours), the highest APACHE scores (20 and 17), and the highest PSS. They also had the longest LOS in comparison with other BAI (3 and 3 days). Therefore, it seems that in larger sample sizes, psychiatric comorbidity can be a risk factor for severity of baclofen intoxication. Some authors recommended that the psychosocial interventions is an essential part of management of baclofen intoxicated patients, , especially in patients with comorbid mental problems [22].

Based on our results, the APACHE score can indicate the LOS in both BAI and multidrug intoxicated patients (figure1). In this way, for every ten points increase in APACHE score, the patient is hospitalized for more than half a day and a BAI patient will be hospitalized for two more days. In contrast, there was no significant correlation between PSS of BAI patients and LOS. Sam et al [9] reported a linear relationship (r=0.557) between APACHE II scores and PSS in organophosphate poisoned patients, very similar to our results (R2=0.499, PV=0.03).

There is limited data on toxicokinetics of baclofen. Long plasma elimination half-lives have been discovered in the circumstance of baclofen poisoning [26]. The prolonged and less complete elimination may be because of ongoing absorption from the intestine and redistribution from fatty tissue [26]. Enterohepatic circulation or delayed release from other compartments may demonstrate a second concentration peak in plasma baclofen [27]. So, renal failure leads to drug accumulation and can emphasize a risk factor for baclofen intoxication. In the present cases, we registered patients with a history of chronic kidney disease, who ingested a therapeutic dose of baclofen. Increasing the clearance of creatinine and decreasing renal function could increase the elimination half-life of baclofen [22]. However, we could not find a statistical correlation between LOS and none of laboratory test results, especially renal function tests.

Also, baclofen in animal model showed dose-dependent sedation [28]. All BAI patients were unconscious on admission. Rahimi et al reported 135 cases of baclofen intoxication and most of them had loss of conciseness, that was significantly related to the dose of baclofen [8]. However, we could not find a significant correlation between the primary GCS or length of unconsciousness of BAI patients with the baclofen ingested dose, the patients' renal function, and other factors. Burenti and coworkers compared the elimination half-life of baclofen in baclofen intoxicated patients who had a normal renal function and underwent renal replacement therapy or not. They concluded that renal replacement therapy could not significantly increase baclofen clearance in patients with normal renal function [29]. Hence, it seems that renal function does not a predictor in patients when it is normal. We also could not find a correlation between creatinine and LOS of BAI patients.

None of BAI patients were hypotensive. Leung reported 23 cases of baclofen intoxicated that hypotension had occurred in only one case that ingested more than 200mg of baclofen [30]. Baclofen intoxication could induce both hypertension [31] and hypotension [30]. The systolic blood pressures of BAI were not related to the dose of ingested baclofen and kidney function. But, diastolic and mean arterial blood pressure were predictable with the dose of consumed baclofen and the state of renal function.

Baclofen is a respiratory depressant drug [28, 32, 33]. We found two apnotic BAI patients (20%). However, we could not find any correlation between dose of ingested baclofen or renal function with respiratory rate. Although baclofen induces dose dependent hypothermia, sedation, and respiratory depression, we could not reveal a statistical correlation between baclofen ingested dose and clinical manifestations. This may be related to our small sample size and pharmacodynamic and pharmacokinetic mechanisms, which contribute to the variability of baclofen-induced neurotoxicity in poisoning [28]. Anand et al revealed a positive correlations between the baclofen ingested dose and the presence of acute respiratory failure, as well as duration of mechanical ventilation [32]. Their sample size was 6 times more than the current research.

Leger et al reported 190 cases of baclofen intoxicated cases. 42% of their cases required mechanical ventilation and 60% of them had GCS≤12. Seizures happened in 26% of their patients [34]. In the current research, 20% of cases required mechanical ventilation and any of the cases had seizures.

CONCLUSION

Baclofen ingested dose is not correlated to the clinical manifestation of baclofen intoxication, except diastolic and mean arterial blood pressure. We could not find a significant effect of comorbid depression and severity of intoxication. APACHE score had a positive correlation with LOS of all patients (multidrug and BAI). The renal function correlated to APACHE score of patients. Other clinical and preclinical parameters and baclofen ingested dose were not estimated the APACHE score. Although PSS correlated with APACHE score, it could not predict the LOS of BAI cases. Similar to other cases of poisoning, the adults, who attempted suicide with baclofen were younger than others and self-harm was the main cause of baclofen intoxication. In the current

research, 20% of BAI needed mechanical ventilation. All BAI cases were unconsciousness, however, none of them had significant hypotension, hypertension, bradycardia, or tachycardia. The length of unconsciousness also did not relate to other clinical and preclinical variables. To confirm or reject these relationships, studies with a larger sample size are needed.

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