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ORIGINAL ARTICLE

Comparison of two different doses of citicoline in patients with traumatic brain injury

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Abstract

Introduction: The ever increasing and common occurrence of head traumas highlight the importance of adopting therapeutic measures for the reduction of the associated morbidity and mortality. Citicoline, as a safe medicine with positive effects on improving traumatic injuries, has been proven to be useful in various studies. However, there are still no data on the specific standard method and dosage of citicoline for the treatment of patients with traumatic head injuries. Regarding this, the present study was performed to determine the effective therapeutic dosage of citicoline and its impact on patients with traumatic head injuries.

Methods: This double-blind clinical trial was performed on 30 patients with traumatic concussion (a Glasgow coma scale [GCS] of ≤8) admitted to the intensive care unit and neurosurgery department. The patients were randomly divided into three groups of A (control), B (citicoline with a dosage of 0.5 g/twice a day), and C (citicoline with a dosage of 1.5 g/twice a day). The GCS, degree of muscle strength, Glasgow outcome score (GOS), contusion volume, and cerebral edema (based on brain CT scans) were calculated at specific times and intervals. In addition, the patients' dependency on a ventilator and their length of ICU stay were registered.

Results: Mean GCS on the first day of stay, GCS changes on the third and fourth days of stay, first and seventh days of stay, seventh and fourteenth days of stay, and first and fourteenth days of stay in the three study groups showed the significant statistical difference ($P<0.05$). Significant statistical differences were seen between the GOS of the 30th day of stay in the three study groups ($P<0.05$). The contusion volume difference was only significant between the first and seventh day of stay in groups A and C ($P<0.05$). No significant difference was observed in the mean length of stay in ICU and duration of dependency on a ventilator in the three study groups ($P<0.05$). The mean degree of muscle strength was only significantly different on the first day of stay between groups B and C ($P=0.008$).

Conclusions: In contrary to similar studies, the results of the current study revealed that citicoline had no positive effect on patient healing. This result may be due to the small sample size and the inconsistent first-day GCSs of the patients in all three groups. Therefore, given the confirmation of the effectiveness of citicoline even at higher dosages in other studies in future studies, it is recommended to use populations with a larger number of patients.

Key words: Brain edema, Concussion, Glasgow coma scale, Ventilator

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Introduction

Trauma is one of the most common causes of patient referral to emergency departments (EDs). In all age groups, the third leading cause of human deaths (preceded by heart disease and cancer) is trauma (1). The head is one of the most common parts involved in most of multiple trauma patients (2). Almost 50% of the mortality in trauma cases are due to head traumas (3). Traumatic brain injury (TBI) decreases the amounts of phospholipids in cell membranes, thereby leading to defects in the sodium-potassium pump and the subsequent accumulation of intracellular fluid.

This edema gets added to the vasogenic edema caused by damage to the blood-brain barrier (4, 5). In addition to the edema, other disorders in the brain metabolism, such as hyper glycolysis and brain acidosis, are some of the consequences of severe TBI. Moreover, ischemia defined as insufficient cerebral blood flow (CBF) to respond to brain metabolic needs, is one of the important mechanisms of secondary damage in patients with severe TBI (3). Furthermore, many patients suffer from hypoxia because of hyperventilation, airway obstruction, aspiration, hemothorax, and pneumothorax immediately after the traumatic event which will increase the morbidity and mortality rates (3).

Various agents are used to decrease or eliminate the effect of above-mentioned disorders. Some of these agents include osmotic agents, dopamine agonists, barbiturates, venous and arterial vasoconstrictors, and calcium channel antagonists (6). Citicoline is another medication recommended in this respect. It is derived from choline and cytidine and has a role in lecithin biosynthesis, a well-known medication for the treatment of stroke complications (7). Citicoline increases CBF and oxygen consumption (8). Furthermore, it stimulates phosphatidylcholine synthase, which facilitates the recovery and protection of cell membrane (9).

Studies have shown that citicoline accelerates the absorption of cerebral edema by strengthening the activity of mitochondrial ATPase and membrane Na^+-K^+ ATPase. According to the literature, citicoline is well tolerated and is very rarely accompanied by dangerous side-effects (mainly gastrointestinal upset) (10). Several studies have been performed to prove the effectiveness of this medication on patients with brain concussion.

Lazowski et al. (2003) observed that citicoline increased Glasgow coma scale (GCS) and improved Glasgow outcome scale (GOS) in patients. Moreover, it was reported to be accompanied by a positive effect on patients' neurological outcome (11). The results obtained by Aniruddha et al. (2009) showed that citicoline when used for a mild concussion could not decrease concussion symptoms or the number of lost working days. In addition, there was no difference between the two groups regarding the quality of life in the patients receiving citicoline (12).

Generally, it seems that citicoline accelerates coma by improving neurological, memory, and cognitive defects following trauma. However, given the prevalence of head trauma and the ever-increasing number of the incidents leading to head trauma, it is essential to investigate therapeutic measures and appropriate medicines to decrease morbidity and mortality in patients with trauma. None of the studies mentioned above have identified a specific standard method and dosage for the application of citicoline in patients with head trauma. Regarding this, the present study was conducted to assess the effect of citicoline on patients with severe TBI by comparing the effects of two different dosages of citicoline in these patients.

Methods

The study protocol was approved by the Ethics Committee of Birjand University of Medical Sciences (IR.BUMS.Rec.1394.438). Moreover, this study was registered on the Iranian clinical trial site (IRCT20140611018063N7).

The present study was conducted on 30 patients, aged 5-60 years, with isolated head trauma and severe brain injury (GCS≤8) referred to the ICU and Neurosurgery Department of Imam Reza Hospital of Birjand, Iran, from the 21st of May 2016 to the 6th of February 2017. The sampling was performed until reaching enough sample size (n=30). The exclusion criteria were: 1) history of severe cognitive disorders (e.g., dementia, Alzheimer's disease, and other degenerative nervous diseases) and severe underlying systemic disorder (e.g., previous stroke or any previous neural tube defects, heart disease, and respiratory diseases), 2) affliction with penetrating skull injury or open skull fracture and severe chest trauma, 3) subdural or large epidural hematoma requiring surgery, and 4) pregnancy. During the study, 5 (16.7%) patients died due to the severity of injuries (Figure 1). All patients were distributed into three groups of A, B, or C by randomly choosing one card marked with A, B, or C.

This study was double-blind; therefore, only the doctor was aware of group allocation. However, the

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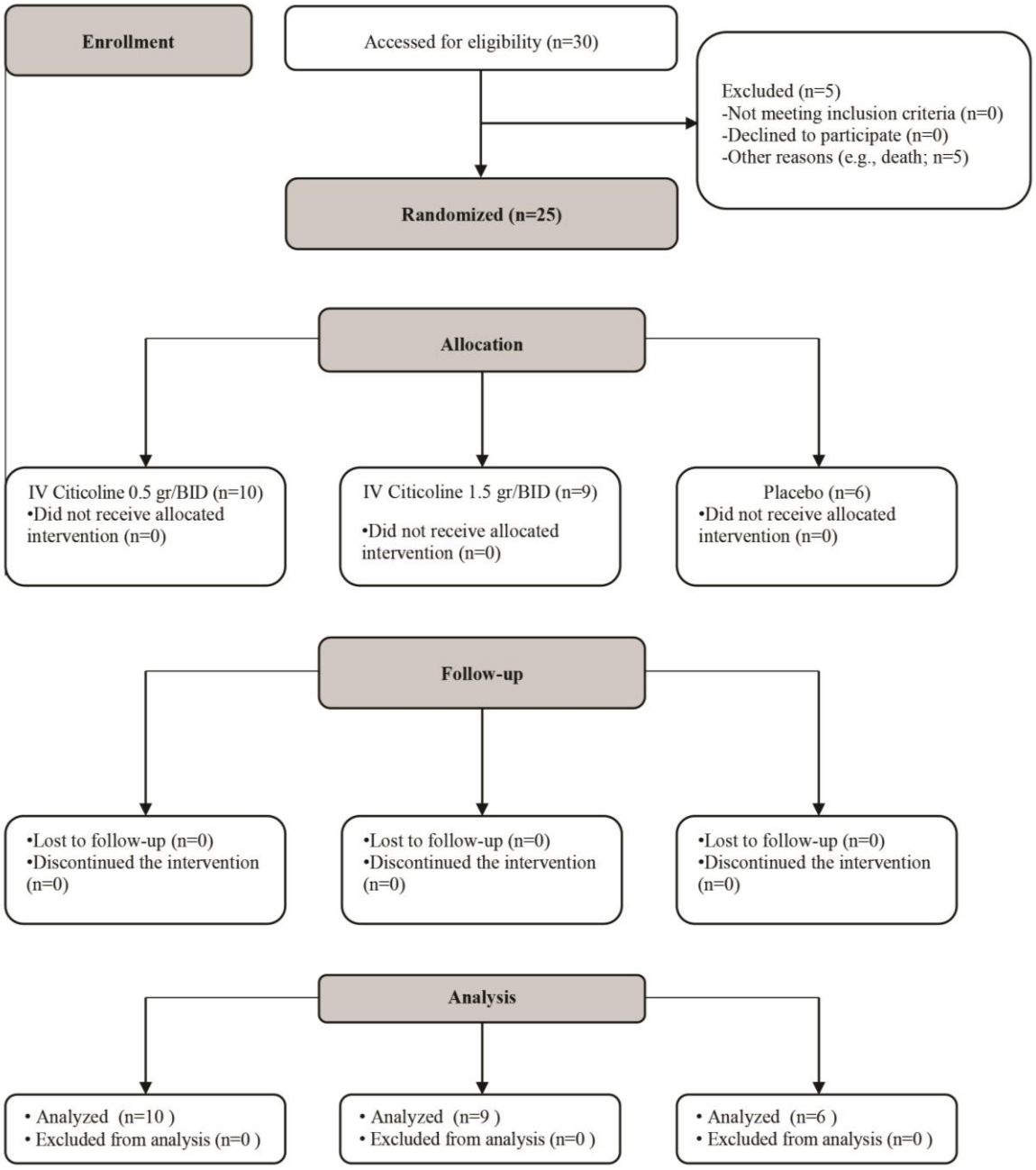

Figure 1: Flow diagram of patient recruitment and data collection during the study

patients, nurses, and researchers who collected the data were uninformed in this regard. The study population was assigned into three groups of 'A' receiving intravenous (IV) citicoline at a dosage of 0.5 g/twice a day, 'B' receiving IV citicoline at a dosage of 1.5 g/twice a day, and 'C' receivinginstilled sterile water as placebo (Figure 1). The treatment period of all patients was 14 days

The GCS of the patients was estimated on the first 7 days and 14th day of hospitalization. Furthermore, the muscle strength degree of the patients was calculated in the first week and on days 14, 21, and 30 of hospital stay. Additionally, the GOS of the patients was assessed on the 30th day of hospitalization. All patients were subjected to brain computed tomography (CT) scans on days 1, 3, 5, and 7 to estimate the contusion volume and cerebral edema. The lengths of dependency on a ventilator and ICU stay were documented for each patient.

The data were analyzed in the SPSS software using Mann-Whitney U, Fisher's exact, Tukey's

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exact, and Kruskal Wallis tests. Descriptive data were reported as mean±SD, frequency, and percentage. A p-value less than 0.05 was considered statistically significant.

Results

The mean ages of groups A, B, and C were obtained as 29.1±12.8, 22.3±8.9, and 26.3±18.6 years, respectively. A total of 27 (90%) patients were male. In terms of gender distribution, groups A, B, and C consisted of 9 (90%), 10 (100%), and 8 (80%) males, respectively.

The cause of head traumas in all three groups was car accident. In all three study groups, no statistically significant differences were observed in terms of age and gender (Table 1). The GOS on the 30th day of hospitalization showed statistically significant differences among three study groups (P=0.001; Table 2). The contusion volume difference was only significant between the first

Table 1: Comparison of the distribution frequency of demographic indicators in patients

		Group A	Group B	Group C	Significance
Age (Mean±SD)		29.10±12.78	22.30±8.99	26.30±18.63	F=0.59 df=2.27 P=0.56
Gender	Male	9 (90%)	10 (100%)	8 (80%)	Fisher's=0.33
	Female	1 (10%)	0 (0%)	2 (20%)	

Table 2: Comparison of the mean Glasgow outcome scale among three groups of patients over the 30-day follow-up

	Group A N=10	Group B N=10	Group C N=10	ANOVA and Tukey's test results
GCS on the 1st day	7.1+-0.87	6.1+-1.2	5.8+-1.3	F=3.53 df=2.27 P=0.04
GCS on the 1st and 2nd days	1.1+-1.8	0.9+-0.74	0.2+-1.2	F=1.27 df=2.27 P=0.29
GCS on the 2nd and 3rd days	0.9+-1.66	0.5+-1.2	0.1+-0.56	F=1.1 df=2.27 P=0.36
GCS on the 3rd and 4th days	0.1+-0.32	0.6+-0.97	0.2+-0.42	X=64 df=2 P=0.04
GCS on the 4th and 5th days	0.3+-0.48	0.5+-1.9	0.22+-0.67	X=4.8 df=2 P=0.09
GCS on the 5th and 6th days	0.2+-1.7	0.1+-0.57	0.44+-0.73	F=0.84 df=2.27 P=0.44
GCS on the 6th and 7th days	0.3+-0.67	0.1+-1.1	0+-0.71	F=0.31 df=2.26 P=0.74
GCS on the 1st and 7th days	2.9+-2.8	2.7+-3.5	0.56+-2	F=4.2 df=2.26 P=0.03
GCS on the 7th and 14th days	2.2+-2.25	0.6+-1.1	0.43+-0.97	F=3.44 df=2.24 P=0.049
GCS on the 1st and 14th days	5.1+-2.9	3.6+-1.1	1.9+-0.77	F=3.53 df=2.27 P=0.046
GOS on the 30th day	4.2±0.79	3.7±1.25	2.2±1.13	F=9.34, df=2.27 P=0.001

GCS: Glasgow coma scale, GOS: Glasgow outcome score

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Table 3: Mean brain edema changes on different days of hospitalization among three groups of patients

	Group A (n=10)	Group B (n=10)	Group C (n=10)	ANOVA and Kruskal-Wallis test results
	Mean ± SD			
Changes in brain edema between the first and third days of hospitalization (cm)	N=8 0.8±0.44	N=3 0.73±0.64	N=6 0.43±0.33	Kruskal-Wallis test X^2=2.68 df=2 P=0.26
Changes in brain edema between the third and fifth days of hospitalization (cm)	N=8 0.05±0.3	N=3 0.27±0.64	N=6 0.42±0.51	Kruskal-Wallis test X^2=1.43 df=2 P=0.49
Changes in brain edema between the fifth and seventh days of hospitalization (cm)	N=8 -0.26±0.49	N=3 0.23±0.46	N=6 -0.02±0.04	Kruskal-Wallis test X^2=2.39 df=2 P=0.3

Table 4: Length of dependency on ventilator and stay in intensive care unit among three groups

	Group A N=1	Group B N=2	Group C N=5	Kruskal-Wallis test
Length of dependency on ventilator (days)	0.1±0.32	2±5.1	6.7±14.1	X2=2.99 dF=2 P=0.22
Length of stay in ICU	13.3±5.9	15.5±7.1	18.8±12.5	F=0.95 dF=2.27 P=0.4

and seventh days of hospital stay in groups A and C (P<0.05; Table 3). However, the mean lengths of dependency on a ventilator and ICU stay in the three groups were not significantly different (Table 4). In addition, significant differences were observed in the mean degree of muscle force on the first day of hospital stay among the three study groups. Based on the results of the Tukey's test, this difference was statistically significant between groups B and C (P=0.008).

Moreover, changes in the degree of muscle strength did not show any statistically significant difference on various days (Table 5). In group A, none of the patients deceased; however, 1 (10%) and 4 (40%) patients passed away in groups B and C, respectively. The Fisher's exact test showed significant differences in this respect among all three study groups (P=0.04).

Discussion

This study was conducted to investigate the effect of two different dosages of citicoline on the healing process of patients with TBI. The results of the present study differ from those reported in most of the similar investigations because in most of the investigated cases, citicoline was observed to exert no positive effect on the patients. With respect to changes in the alertness level of the patients (GCS changes), the results of the daily investigations did not differ among the three study groups. Nonetheless, the GCS changes between days 1 and 7, days 7 and 14, and days 1 and 14 were statistically significant among the three groups. Although these results apparently show a better improvement of alertness level (GCS) in the control group and inefficiency of citicoline in the improvement of the patients, this may be attributed to the dissimilarity of the patients studied in these three groups.

In the current study, the GCS differences of the patients in the three groups were high on the first day of hospitalization. The numbers of patients with a GCS of 3-5 on the first day of hospitalization in the control, low-dosage citicoline, and high-dosage citicoline groups were 0, 3, and 5, respectively. Among the other studies, only in the study performed by Lazowski et al., the GCS changes on days 7 and 14 of treatment did not differ. However, in the mentioned study, the GCS changes between days 21st and 30th were better in the group receiving citicoline, indicating the protective effect of this medication (11).

Almost in all the studies performed, citicoline

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Table 5: Changes in the degree of muscle strength in the three study groups

	Group A (n=10)	Group B (n=10)	Group C (n=10)	ANOVA and Kruskal-Wallis test results
	Mean ± SD			
The degree of muscle strength on the first day of hospitalization	N=10 4.1±1.1	N=10 4.8±0.63	N=10 3.4±1.1	ANOVA F=5.31 P=0.01
Changes in the degree of muscle strength on days 1 and 2, 2 and 3, and 3 and 4 of hospitalization	0	0	0	P=1
Changes in the degree of muscle strength on days 4 and 5 of hospitalization	N=5 0	N=1 0	N=7 -0.57±1.1	Kruskal-Wallis test X^2=1.86 P=0.39
Changes in the degree of muscle strength on days 5 and 6 of hospitalization	N=5 0.2±0.45	N=1 0	N=7 -0.43±0.79	Kruskal-Wallis test X^2=2.82 P=0.24
Changes in the degree of muscle strength on days 6 and 7 of hospitalization	N=5 0	N=1 -3	N=7 -0.57±1.1	X^2=5.1 P=0.08
Changes in the degree of muscle strength on days 7 and 14 of hospitalization	N=5 0.2±0.45	N=1 0	N=4 -0.25±0.5	X^2=5.1 P=0.36
Changes in the degree of muscle strength on days 21 and 30 of hospitalization	N=5 0.4±0.55	N=0 -	N=4 0	Mann-Whitney test 1035=Z P=0.41

was reported to be effective in the improvement of GCS level in patients (13-15). The results obtained about the patient status after one month calculated based on the GOS criterion showed no significant difference among the three study groups. However, these results were better in the control group, which once again showed the ineffectiveness of citicoline. Similarly, Lozano et al. concluded that citicoline does not have any effect on GOS in patients (12, 16). In the studies performed by Lazowski and Calatayud, patients receiving citicoline had better GOS (11, 13). In this study, the patients were investigated regarding the number of ICU stay duration and the length of dependency on a ventilator, revealing no differences among all the three groups.

On the other hand, Calatayud and Cohadon reported that citicoline had a positive effect in this regard by decreasing patient need for ICU stay (13, 17). However, it should be noted that various countries use different criteria for patient admission to ICU; accordingly, this issue must have certainly influenced the study results. In the present study, the improvement of patients' neurological defects through the enhancement of their motor functions in organs having motor impairment were investigated and compared with each other. In this regard, no differences were observed between the study groups.

This result, like the rest of our results, is in contrast with the other reports, which were mostly indicative of the effectiveness of citicoline in the improvement of motor status in patients (13, 14, 17, 18). The reason may be ascribed to the fact that in the present study, the number of patients with motor impairment was low, and that they were not equally distributed among the three groups (five cases in the control group, one case in the low-dosage citicoline group, and eight cases in the high-dosage citicoline group). The results of this study did not support the positive effect of citicoline on the reduction of cerebral edema in patients following a severe head concussion. However, this effect was indicated in other studies both in humans and rats (16-18).

Dempsey et al. observed the effectiveness of citicoline in rats (18). In the mentioned study, perilesional edema was investigated; however, the cerebral edema may have been measured by another method in other studies. Regarding the present study, two aspects must be considered. Firstly, the sample size in the three groups was

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small. Even in some cases, such as the investigation of motor status, all patients did not have motor impairment; accordingly, this issue could have influenced the results. Secondly, the mean score of the primary GCS of patients among three groups was very different. Although all the patients suffered from a severe concussion and were randomly placed in three groups, this grouping method was performed in a way that patients with better conditions were placed in the control group, while those with more severe conditions were placed in the intervention groups.

The results of this study revealed the inefficacy of citicoline in the treatment of patients with severe head concussion. However, the results of other studies are indicative of the role of this medication in the acceleration of cerebral edema absorption, improvement of alertness level and neurological disorders, and reduction of the length of hospital stay in patients with severe head concussion, particularly in those with a primary GCS of 5-7 (15). In a study investigating the effect of citicoline on patients with brain trauma, it was found that GCS in patients on the 15th day of hospitalization treated with 500mg of citicoline every 6 hours compared to the first day of hospitalization, it was associated with an increase in the degree of GCS (19). In another study investigating the patients with brain trauma with a GCS of < 13 using a 6-month follow-up, citicoline administration was reported to cause a marked decrease in mortality rate among people admitted to the ICUs (20). In an investigation including 1,213 patients with brain trauma between 2007 and 2011, no changes were observed in the GCS level in the intervention and control groups after 90 days of treatment with citicoline (two g per day) (21). In a study performed on 58 patients with diffuse axonal injury and GCS of ≤ 8, both groups showed an increase in GCS levels after receiving citicoline (500 mg) every 6 h for 15 days. In addition, serum matrix gla protein levels as an inhibitor of calcification following injury were reported to elevate in both groups (22).

Conclusions

Our study did not prove or support the positive effect of citicoline on the healing process of patients with severe head trauma. However, given the reports regarding the effectiveness of this medication even at higher dosages, it is required to perform more accurate studies in this regard. Future studies are recommended to employ a greater sample size.

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Conflict of Interest

There is no conflict of interest to be declared.

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