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The Effect of Curcumin in the Recovery of Severe Traumatic Brain Injury: A Double Blind Randomized Controlled Trial

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Abstract

Background: Traumatic brain injury is one of the most important causes of death in trauma patients among the different types of trauma worldwide. In this study, the effect of Nano curcumin on the outcome of severe traumatic brain injury, which was performed in humans for the first time, was investigated.

Methods: This was a double blind and paralleled randomized controlled study that was conducted on 128 patients aged 18 to 70 with severe brain trauma. Patients were randomly assigned to two control groups (Standard care treatment+placebo) and an intervention group (Standard care treatment+oral Nano curcumin with the dose of 500 mg every 8 hours for three weeks). Changes in the level of consciousness, cerebral edema, kidney function, liver enzymes, sodium and potassium electrolytes, and brain function of patients in both groups were followed up and compared until 6 months after discharge.

Results: The mean and standard deviation of age (Mean+SD) for the intervention group (14.44 ± 31.86 years) and control patients (14.86 ± 33.34 years) had no significant difference (p=0.543). Both groups were similar in terms of gender (p=0.669). The average level of consciousness of patients in the intervention group increased by about 3 units (p=0.004) and more than 2 units (p=0.002) at the time of discharge compared to the control group. By comparing the optimal performance of patients in the first (p=0.389) and second (p=0.309) trimesters after discharge, no significant difference was observed between the intervention and control groups. The amount of brain edema caused by severe brain trauma on the 7th day of treatment was lower in the intervention group than in the control group (p=0.038). The two intervention and control groups did not differ in terms of coagulation factors, liver enzymes, kidney function, and sodium on the 3rd and 7th days of hospitalization (P ≥ 0.05).

Conclusion: Administration of oral Nano curcumin supplement in patients with severe brain trauma along with their routine treatment is effective in improving brain edema and their level of consciousness without causing coagulation, and liver and kidney complications. These findings are not only statistically significant but also clinically important.

Keywords: Trauma • Curcumin • Nano curcumin • Brain • Consciousness • Brain injury

Introduction

Traumatic Brain Injury (TBI) has affected approximately 50% of the world's population at some stage of life [1]. Trauma is one of the most important causes of death and disability in the active population in developing countries [2,3] and studies indicate that attention to trauma is less in these countries [4]. In 2016, 27.08 million new cases of brain trauma were registered in the world, which has increased the standardized prevalence of sense TBI in the world from 1990 to 2016 [5]. According to a report published by BMJ in 2017, TBI caused 8.1 million years of lost life in the world in 2016, which is a significant increase compared to the total number of years of life lost in 1990 [5].

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Traumatic Brain Injury (TBI) is defined as an acquired brain disease caused by an external force in the form of mechanical, chemical, thermal, or electrical energy or a combination of these [6]. According to US statistics, 43% of severe TBI survivors are likely to suffer long term disability [7]. On the other hand, it should be noted that the burden of severe brain trauma extends to the patient's family and the health care system [8]. The direct and indirect economic and social costs caused by trauma to families are relatively high so the estimated cost of brain trauma is approximately 400 billion US dollars per year [9] and about 11% of the years of life lost due to disability. It is caused by trauma.

To date, there is no complete and effective treatment for traumatic brain injury, as most injuries occur due to secondary effects through various pathophysiological pathways [1]. In addition, the main approach in the treatment of brain trauma is measures such as damage control, surgery, and post-operative care [10]. In the control of damage caused by severe brain trauma, measures aimed at targeting multiple pathways are needed for more effective treatment of this disease. Previous studies have shown that several natural products and herbal medicines have been tested for their ability to improve disorders such as neuron inflammatory conditions characterized by impaired redox balance and excessive inflammation [11-13].

There is evidence that curcumin can be traditionally used as a natural treatment for many diseases including diabetes, inflammatory diseases, and neurological disorders [14]. Some pharmacological studies also indicate the

effect of curcumin in the treatment of brain trauma and injuries caused by it, but it seems that these results are not enough and more extensive research should be done in this field [1].

Curcumin is considered a poly phenolic that, in addition to its anti-inflammatory, thrombolytic and anti-cancer effects, can be used in the treatment of several diseases such as Alzheimer's disease and injuries caused by trauma by inhibiting the accumulation of amyloid protein [15].

The effect of curcumin on endogenous neuron regeneration in rats after TBI has been confirmed, so the apoptotic cells in the damaged area of rats that had TBI and received curcumin were significantly less than in the control group [16]. In addition to the animal studies that have shown curcumin's therapeutic effect on brain trauma, they have not shown any toxicity at a dose of 500 mg [17]. On the other hand, the anti-inflammatory effect of curcumin with low molecular weight has been of interest for centuries [18], despite various studies on curcumin in laboratory animals and the lack of studies on humans considering the published literature, this study is aimed to the effect of curcumin in the treatment of severe brain injuries in patients.

Methods

The current study is a controlled double blind clinical trial study that was conducted on 128 patients (Figure 1). In this study, the patients were divided into two control groups by a simple randomization method (recipients of Standard care treatment i.e. treatment according to Yeoman's treatment protocol and treatment with prophylactic anticonvulsant drugs and antibiotics if needed and placebo) and intervention group (i.e. recipients of Standard care treatment and oral Nanocurcumin as orally or through a nasogastric tube in the amount of 500 mg every 8 hours and for 3 weeks). In this study, patients suffering from severe brain trauma referred to the special care department of neurosurgery and specialized and sub-specialized in Hamadan Besat hospital, West Iran from 2019 to 2021 were selected.

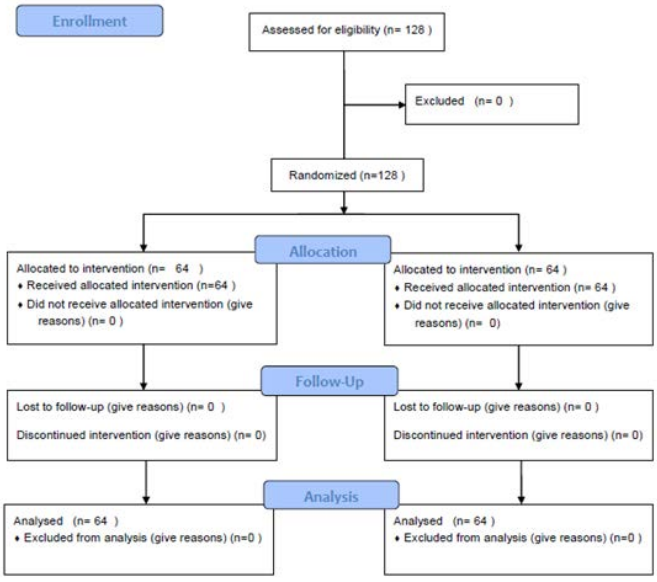

Figure 1. Follow-up chart of patients based on Consort 2010 guidelines.

The included patients were randomized using a computer random number generator to select random permuted blocks with a block size of 8 and an equal allocation ratio. Sequentially numbered, opaque, sealed envelopes were used to ensure concealment. Three members of the study team recruited, enrolled, and assigned participants to a computer-generated randomization sequence, held by an independent observer.

Inclusion criteria were people between the ages of 18 and 70 years, duration of concussion less than 24 hours, level of consciousness (GCS) 8 or less, not candidates for craniotomy surgery, and pregnant and lactating women. The exclusion criteria were those who had an unstable systemic condition, the presence of multiple and severe organic injuries, lack of brain stem reflexes, kidney failure, and the need for any type of surgery in the early days of hospitalization.

If a complication occurs and is observed by the attending physician, the treatment with curcumin was stopped. The patients in both groups were subjected to mechanical ventilation if needed, and no patient received barbiturate treatment. Consciousness level, blood pressure, the reaction of pupils to light, movement, and strength of organs were checked daily. Brain CT scan was performed on the 1st, 3rd, and 7th days based on the patient's condition. To investigate drug side effects, parameters such as serum biochemistry, platelet count, hemoglobin, PT, PTT, serum electrolytes, and liver tests were measured on the 1st, 3rd, and 7th days after hospitalization. To classify patients at discharge, GOS was used in 3 month and 6 month follow ups. Patients with good recovery or moderate disability were included in the favorable outcome group, and those with severe disability or vegetative life, as well as those who died, were included in the unfavorable outcome group.

This study was approved and registered by the Research Ethics Committee of the Hamadan University of Medical Sciences at the address IR.UMSHA.REC.1398.010 and the IRCT code is IRCT20120215009014N305.

Informed consent was obtained from all participants in this study. Participants' privacy and data confidentiality were guaranteed.

Analysis

We used an intention-to-treat analysis approach and include all randomly assigned participants. In this study, mean and standard deviation were used to describe quantitative variables, and number and percentage were used to describe qualitative variables. To compare the level of alertness and biochemical factors of patients in two groups of control and intervention from the variance analysis of repeated data, to determine the relationship between the performance of patients after discharge in the two groups using the chi-square test, to compare the frequency of edema in the two groups using the exact-Fisher test. The significance level in this study is less than 0.05 and SPSS version 21 software was used.

Results

This study was conducted on 128 severe brain trauma patients who were randomized into two intervention and control groups. The number of men in the intervention and control groups was 51 (79.7%) and 49 (76.7%) respectively. The Chi-square test showed that the gender distribution between the two groups was not statistically significant (p=0.669). Patients in the intervention (14.44 ± 31.86) and control (33.34 ± 14.86) groups did not differ in terms of age (p=0.543). The frequency of the cause of severe brain trauma among patients is shown in Table 1. Although Table 1 shows that the performance 6 months after discharge based on the GOS score was not significantly different between the two intervention and control groups, the frequency of optimal performance in the 3rd month after discharge in the intervention group was significantly higher than in the control group (p=0.034). Brain CT scan findings on the 1st and 3rd day showed no difference in terms of edema between the two groups, but on the 7th day, a score of 1 in the intervention group and a score of 3 in the control group were significantly observed p=0.038 (Table 1).

The findings of the present study showed that although there was no significant difference in the level of consciousness of patients in the two groups on the 1st day of hospitalization, the level of consciousness of patients in the intervention group was significantly higher than the control group on the 3rd (p=0.004) and 7th (p=0.001) days.

Also, the analysis of the variance of the repeated data showed that the changes in the level of consciousness of the patients in the intervention group were significantly different from the control group, p=0.003 (Table 2).

According to the findings in Table 2, there was a significant difference in

Table 1. Frequency and percentage of the cause of severe brain trauma, function, edema, and other biochemical characteristics of patients in two intervention and control groups.

Variables	Levels	Control (n=64) Number (%)	Control (n=64) Number (%)	P Value
Cause of trauma	Accident	55(85.9)	60(93.8)	0.114
	Fall from height	5(7.8)	4(6.2)	
	Head hit with a heavy object	4(6.3)	0(0.0)	
First quarter performance	Favorable	40(69.0)	28(60.2)	0.389
	Unfavorable	18(31.0)	18(39.1)	
Second quarter performance	Favorable	41(70.7)	35(79.5)	0.309
	Unfavorable	19(29.3)	9(20.5)	
The amount of cerebral edema based on the findings of brain CT scan	**1st day of visit**			0.955
	Score 1	44(68.8)	41(66.1)	
	Score 2	4 (6.2)	5(5.1)	
	Score 3	16(25.0)	16(25.8)	
	Score 4	0(0.0)	0(0.0)	
	3rd day of visit			0.615
	Score 1	48(77.4)	41(66.1)	
	Score 2	7(11.3)	9(14.1)	
	Score 3	7(11.3)	9(14.1)	
	Score 4	0(0.0)	0(0.0)	
	7th day of visit			The amount of cerebral edema based on the findings of brain CT scan
	Score 1	50(82.2)	46(74.2)	
	Score 2	6(10.3)	5(8.1)	
	Score 3	2(3.4)	11(17.7)	
	Score 4	0(0.0)	0(0.0)	

Table 2. Comparison of the level of consciousness and biochemical parameters in intervention and control group patients.

	Control group	Intervention group	P	Comparison	Comparison	Comparison	Comparison
Parameters	**1st day**	**3rd day**	**7th day**	**1st day**	**3rd day**	**7th day**	
Level of consciousness	6.14 ± 2.16	7.07 ± 3.09	8.79 ± 4.77	6.03 ± 2.14	8.70 ± 3.38	11.33 ± 3.90	0.003
PT	17.24 ± 4.51a	18.86 ± 7.45b	18.05 ± 14.87c	14.25 ± 3.47a	15.41 ± 2.40b	14.88 ± 1.91c	0.021
PTT	30.46 ± 7.93	34.02 ± 15.10	31.13 ± 6.63	35.48 ± 19.97	32.87 ± 8.74	32.98 ± 10.38	0.185
INR	1.34 ± 0.17	1.22 ± 0.53	1.26 ± 0.31c	1.14 ± 0.18	1.15 ± 0.15	1.11 ± 0.19c	0.023
Na	144.19 ± 18.17	148.11 ± 18.08b	143.00 ± 7.42	140.10 ± 3.91	142.27 ± 5.04b	135.85 ± 26.39	0.007
Urea	15.95 ± 6.27a	11.0 ± 7.62	16.18 ± 9.30c	12.16 ± 4.60a	11.0 ± 7.65	12.77 ± 5.46c	0.660
Creatinine	1.06 ± 0.28	1.12 ± 0.98	1.54 ± 3.46	0.96 ± 0.30	0.92 ± 0.30	0.84 ± 0.2	0.073
White blood cells (in thousands)	16.48 ± 11.91	12.46 ± 3.91b	11.64 ± 4.79c	13.34 ± 5.04	11.79 ± 3.74b	9.03 ± 3.49c	0.016
SGOT	65.27 ± 35.00	84.60 ± 35.58	44.54 ± 27.41c	67.97 ± 50.86	51.36 ± 38.95	70.18 ± 30.10c	0.313
SGPT	60.25 ± 22.84	79.86 ± 46.42	79.86 ± 46.41	104.78 ± 166.68	118.82 ± 182.84	118.82 ± 182.84	0.600
ALK	287.23 ± 201.32	208.00 ± 57.15	245.43 ± 48.57	332.99 ± 332.88	501.74 ± 321.57	282.20 ± 282.20	0.203
a, p<0.05; b, p<0.05; c, p<0.05							

the PT values of patients in the intervention and control groups on the 1st (p<0.001), 3rd (p=0.002), and 7th (p<0.001) days of hospitalization. The comparison of PT sizes in two groups showed that this parameter is different between the two groups over time (p=0.021) and the PT of patients in the intervention group is always lower than the control group.

In addition, there is no statistically significant difference in the PTT value between the patients of the two groups. The average INR in the intervention group was lower than the control group in all three stages, i.e. the 1st, 3rd, and 7th days of hospitalization. Variance analysis of repeated data also showed that there is a significant difference between these averages during the measurements made in the two groups, p=0.023 (Table 2). The biggest difference in INR between the two groups was observed on the seventh day of hospitalization.

During the follow up of the patients, there is a significant difference in sodium changes between the intervention and control groups (p=0.007), so the biggest difference was observed on the third day of follow up (p=0.019) between the two groups. According to the results of Table 2, no significant difference was observed in the changes in blood urea and creatinine between the two groups. The results of this study showed that although there is no difference in the general trend of urea changes between the patients of the intervention and control groups, that is, they had almost a slight increase (p=0.660), but in the two by two comparison of the groups on the 1st day (p=0.009) and the 7th day (p=0.015) statistically significant difference was evident.

According to the findings, there was no difference between the creatinine levels of the patients in the two groups (p=0.073), while the average white blood cell count was significantly lower in the patients of the intervention group (p=0.016). The findings show that the difference between the white blood cells between the two groups was on the 3rd day (p=0.004) and the 7th day (p=0.009). The average SGOT of patients in the intervention group was about 1.6 times higher than the control group, and this difference was significant (p=0.024). However, there was no difference between the SGOT of control and intervention group patients on the first and third days. In addition, the variance analysis of repeated data also did not show a significant difference between the two groups in terms of SGOT changes in general (0.313). In both intervention and control groups, there was no significant difference between the average SGPT (p=0.600) and ALK (p=0.203) during the hospitalization period of the patients.

This study showed that the rate of blood pressure reduction (p=0.028) and death (p<0.001) was significantly lower in patients who received routine+curcumin treatment compared to the control (Table 3). Pupil reactions of the right and left eyes were checked on the seventh day of hospitalization in both groups and no difference was observed between the two groups.

Table 3. Comparison of the frequency of blood pressure reduction, eye reaction, and mortality in patients with severe brain trauma in the intervention and control groups.

Variable	Levels	Intervention number (%)	Control number (%)	P value
Decreased blood pressure	Yes	0 (0)	6 (9.4)	0.028
	No	64 (100)	58 (90.6)	
Death	Yes	6 (9.4)	28 (43.8)	<0.001
	No	54 (90.6)	36 (58.2)	
Right eye pupil reaction	R	59 (92.2)	58 (90.6)	0.752
	NR	5 (7.8)	6 (9.4)	
Left eye pupillary reaction	R	57 (89.1)	58 (90.6)	0.770
		7 (10.9)	6 (9.4)	

Discussion

In the current study, considering the beneficial properties of curcumin in relieving inflammation [14], it was used to treat severe brain trauma patients in comparison to routine treatment in a clinical trial study. We focused on curcumin because it is a spice with multiple pharmacological properties, very low toxicity, and availability.

Cerebral edema and subsequent increase in ICP as well as decreased level of consciousness are serious complications of brain trauma that contribute to increased patient mortality and long term disability [18]. The present study clearly shows that doses of 500 mg every 8 hours of nano curcumin reduce cerebral edema and its mortality, especially from the 7th day onwards, reducing the frequency of hypotension, and the level of cerebral function in the first trimester. And secondly, it improves post-discharge, which improper performance can cause death, and improves some biochemical factors.

The therapeutic properties of curcumin in the intervention group reduced the amount of brain edema caused by severe brain trauma compared to the control group. Such a result with the study of Samini et al. [19] which was conducted on rats with traumatic brain injury with doses of 50 mg/kg and 100 mg/kg and also with the results of the study of Laird MD et al. [18] with three doses of 150 mg/kg-300 mg/kg was done. Siahaan et al.'s study [20] on rats with mild brain damage reported that the use of turmeric extract is not effective in improving neurological function caused by repeated mild brain damage in rats. It should be noted that the present study was conducted on humans and the maximum dose was 10 mg/kg. The difference between the results of this study and siahaan may be due to the severity of the trauma.

One of the results of this study was a significant increase in the level of consciousness of patients receiving curcumin compared to the control on the third day of treatment and at the time of discharge. Such a result is not far from expected, because Smal et al. [21] conducted a clinical trial study and confirmed the effect of curcumin bioavailability on memory and brain amyloid over 18 months. Previous studies emphasized that curcumin can relieve inflammation and apoptosis by modulating the involved molecular signaling pathways [22]. On the other hand, Shu et al. [16] also showed that curcumin is effective on endogenous neuron regeneration in an animal model after brain trauma. Therefore, the chemical mechanisms at the level of the brain also confirm the results of this study.

Another important result of this study was a reduction in the death rate among curcumin recipients compared to controls. This result is also reasonable because Ahmadi et al. [23] showed in a clinical trial that curcumin as an adjunctive treatment with riluzole can increase the survival of patients with amyotrophic lateral sclerosis. They reported this significant difference with the Kaplan-Meier survival plot. Although the present study was conducted on patients with severe brain trauma, both our study and Ahmadi et al.'s study confirmed the effect of curcumin on patients' survival.

Another important result we achieved in this study was that we did not

observe any difference between severe brain trauma patients who received curcumin and controls in terms of coagulation factors, electrolytes, liver enzymes, and kidney function. This means that there is no additional risk of liver, coagulation, and electrolyte damage in patients taking curcumin. Regarding the safety of curcumin as a treatment or complementary treatment in other diseases, reports have been published [24,25], and in this study, it was also confirmed that it is without complications in severe brain trauma patients. In this study, we used a dose of 500 mg of curcumin per day, while some studies used doses of 1200 mg per day and did not report any toxicity [23,24]. Zhu et al. [26] during their study confirmed that curcumin as a phytochemical compound with anti-inflammatory properties reduces inflammation and accelerates the recovery of brain function.

Conclusion

This study showed that the administration of oral Nanocurcumin supplement at the rate of 500 mg every 8 hours in a 3 week treatment period in hospitalized patients with severe brain trauma can have an effective role in improving cerebral edema and increasing the level of consciousness of patients in addition to their routine treatment. and this is without any side effects such as disorders in the coagulation, liver, and kidney systems also it did not any interactions with other drugs drug.

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Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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