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Research Paper

The Effect of Curcumin on the Recovery of Severe Traumatic Brain Injury: A Double-blind Randomized Controlled Trial

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ABSTRACT

Background and Aim: Traumatic brain injury (TBI) is one of the critical causes of death in trauma patients. In this study, the effect of nanocurcumin on the outcome of severe TBI was investigated for the first time in humans.

Methods and Materials/Patients: This randomized, double-blind, and paralleled controlled study included 128 patients aged from 18 to 70 years with severe brain trauma. Patients were randomly assigned to control group (standard care treatment+placebo) and intervention group (standard care treatment+oral nanocurcumin). Changes in the level of consciousness, cerebral edema, kidney function, liver enzymes, sodium and potassium electrolytes, and brain function were followed up and compared until 6 months after discharge.

Results: The Mean±SD in the intervention (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 in the intervention group increased by about 3 units (P=0.004) and more than 2 units (P=0.002) at discharge compared with the control group. By comparing the optimal performance of patients in the first (P=0.389) trimester and second (P=0.309) trimester 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 seventh day of treatment in the intervention group was lower than that in the control group (P=0.038).

Conclusion: Administrating oral nanocurcumin 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 vital.

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Highlights

• Administration of nanocurcumin supplement along with routine treatment is effective in improving edema and increasing the level of consciousness of patients with severe brain trauma.

• Administration of nanocurcumin supplement along with routine treatment is effective in reducing the mortality of these patients.

• Administration of nanocurcumin at a dose of 500 mg every 8 hours in a three-week treatment period in patients suffering from severe brain trauma causes no complications.

Plain Language Summary

Injuries and tissue damage caused by mechanical, physical, or chemical factors are called trauma which is the first cause of death and one of the main causes of disability. Traumatic brain injury is a crucial cause of death of trauma patients in the world. This damage leads to cerebral edema and increased intracranial pressure, reducing brain blood flow and causing brain damage. The existing medical treatments are not enough to control cerebral edema, and the use of brain surgery methods is limited. Thus, finding new methods to treat cerebral edema is required. Curcumin, one of the substances mentioned in this context, is the active component of turmeric spice with inflammatory properties. It is a strong antioxidant. In this research, considering the beneficial properties of curcumin in relieving inflammation, we decided to investigate the effect of this substance on the treatment of severe brain injury patients. The patients were admitted to the intensive care unit due to severe brain damage. They were divided into two control groups receiving routine treatment and the other intervention group receiving standard routine treatment+nanocurcumin for three weeks. The results of this study showed that the administration of oral nanocurcumin supplement at the rate of 500 mg every 8 hours in a three-week treatment period and the follow-up of the patients in the three-month and six-month periods improved the edema and increased the level of consciousness and reduced the symptoms. Along with routine treatment, it is effective without side effects.

1. Introduction

Traumatic brain injury (TBI) affects 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, increasing the standardized prevalence of observation 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 life lost in the world in 2016, a significant increase compared with the total years of life lost in 1990 [5].

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]. Moreover, 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 caused by trauma.

To date, no complete and effective treatment exists for traumatic brain injury, since most injuries occur due to secondary effects through various pathophysiological pathways [1]. In addition, the main approach in the treatment of brain trauma is measured, 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].

Evidence shows 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 these results seem to be insufficient, 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 anticancer 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; therefore 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, it has 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 according to the published literature, this study was conducted to examine the effect of curcumin in the treatment of severe brain injuries in patients.

2. Methods and Materials/Patients

The current study is a double-blind controlled clinical trial study 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 (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 three weeks). In this study, patients suffering from severe traumatic brain injuries who were admitted to the special care department of neurosurgery at Besat Hospital in Hamadan from 2019 to 2021 were selected.

The included patients were randomized using a computerized random number generator to select randomly permuted blocks with a block size of eight 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 computerized randomization sequence, held by an independent observer.

The inclusion criteria included being between the ages of 18 and 70 years, duration of concussion of less than 24 hours, level of consciousness of Glasgow coma scale (GCS) 8 or less, not being a candidate for craniotomy surgery, and being pregnant and lactating. The exclusion criteria were having 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 first, third, and seventh days based on the patient's condition. To investigate drug side effects, parameters such as serum biochemistry, platelet count, hemoglobin, prothrombin time (PT), partial thromboplastin time (PTT), serum electrolytes, and liver tests were measured on the first, third, and seventh days after hospitalization. To classify patients at discharge, the Glasgow outcome score (GOS) was used in three-month and six-month follow-ups. Patients with good recovery or moderate disability were included in the favorable outcome group, and patients with severe disability or vegetative life, as well as those who died, were included in the unfavorable outcome group.

Analysis

We used an intention-to-treat analysis approach and included all randomly assigned participants. In this study, Mean±SD 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 Fisher's exact test. A $P<0.05$ was identified as significance and SPSS software, version 21 was used.

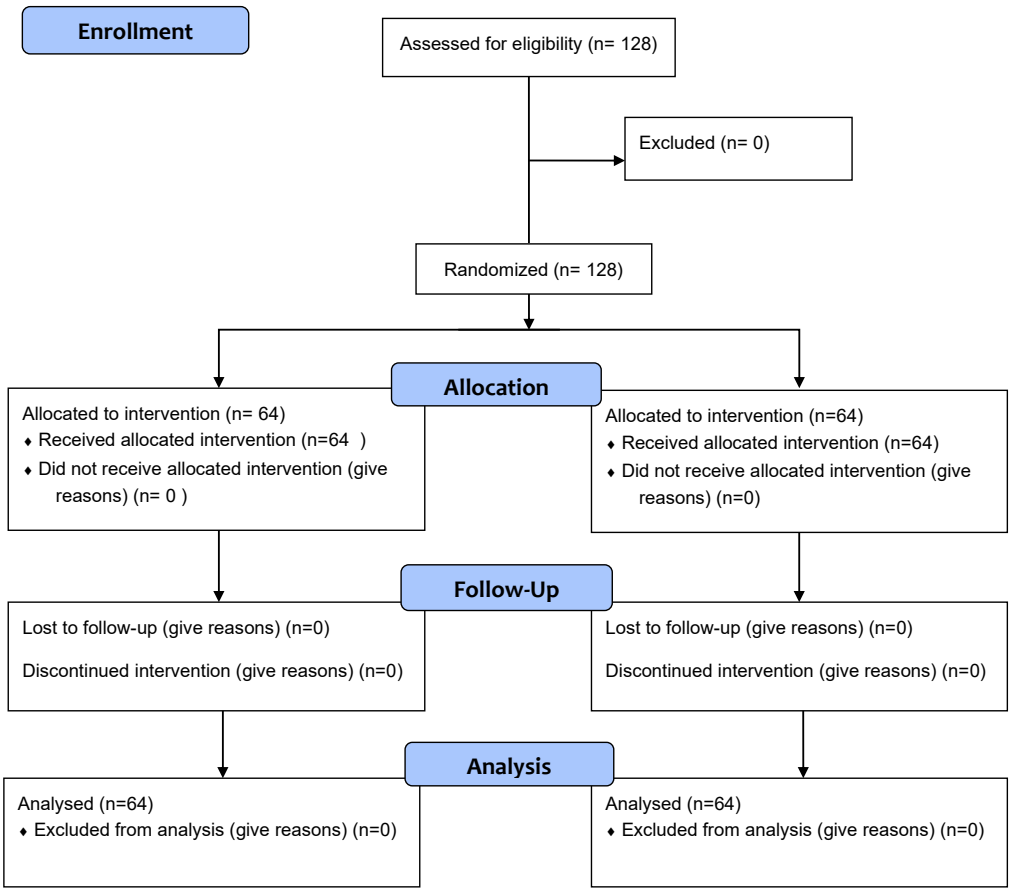

Figure 1. Follow-up of patients based on consort 2010 guidelines

3. Results

This study was conducted on 128 patients with severe brain trauma who were randomly divided 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. Based on the Chi-square test, 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). Table 1 presents the frequency of the cause of severe brain trauma among patients. Although Table 1 displays that the performance six months after discharge based on the GOS was not significantly different between the two intervention and control groups, the frequency of optimal performance in the third month after discharge in the intervention group was significantly higher than that in the control group (P=0.034). Brain CT scan findings on the first and third day suggested no difference in terms of edema between the two groups, but on the seventh day, a score of 1 in the intervention group and a score of 3 in the control group were significantly observed (Table 1, P=0.038).

The findings of the present study showed that although no significant difference was observed in the level of consciousness of patients in the two groups on the first day of hospitalization, the level of consciousness of patients in the intervention group was significantly higher than that of the control group on the third (P=0.004) and seventh (P=0.001) days.

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

According to the findings in Table 2, a significant difference was observed in the PT values of patients in the intervention and control groups on the first (P<0.001), third (P=0.002), and seventh (P<0.001) days of hospitalization. The comparison of PT sizes in the two groups revealed that this parameter was different between the two groups over time (P=0.021) and the PT of patients in the intervention group was always lower than that of the control group.

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	Days	Levels	No. (%)		P
			Intervention (n=64)	Control (n=64)	
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)	
1st quarter performance		Favorable	40(69.0)	28(60.2)	0.389
		Unfavorable	18(31.0)	18(39.1)	
2nd 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	Score 1	44(68.8)	41(66.1)	0.955
		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	Score 1	48(77.4)	46(21.9)	0.615
		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	Score 1	50(82.2)	46(74.2)	0.038
		Score 2	6(10.3)	5(8.1)	
		Score 3	2(3.4)	11(17.7)	
		Score 4	0(0.0)	0(0.0)	

In addition, no statistically significant difference was observed in PTT value between the patients of the two groups. The average international normalized ratio (INR) in the intervention group was lower than that in the control group in all three stages, i.e. the first, third, and seventh days of hospitalization. Variance analysis of repeated data also indicated a significant difference between these averages during the measurements made in the two groups (Table 2, P=0.023). The biggest difference in INR between the two groups was observed on the seventh day of hospitalization.

During the follow-up of the patients, a significant difference was noticed 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 exhibited that although no difference was observed 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), in the two-by-two comparison of the groups on the first day (P=0.009) and the seventh day (P=0.015) statistically significant difference was evident.

According to the findings, no difference was observed 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

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

Parameters	Control			Intervention			P
	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±4.51[a]	18.86±7.45[b]	18.05±14.87[c]	14.25±3.47[a]	15.41±2.40[b]	14.88±1.91[c]	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±0.31[c]	1.14±0.18	1.15±0.15	1.11±0.19[c]	0.023
Na	144.19±18.17	148.11±18.08[b]	143.00±7.42	140.10±3.91	142.27±5.04[b]	135.85±26.39	0.007
Urea	15.95±6.27[a]	11.0±7.62	16.18±9.30[c]	12.16±4.60[a]	11.0±7.65	12.77±5.46[c]	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±3.91[b]	11.64±4.79[c]	13.34±5.04	11.79±3.74[b]	9.03±3.49[c]	0.016
SGOT	65.27±35.00	84.60±35.58	44.54±27.41[c]	67.97±50.86	51.36±38.95	70.18±30.10[c]	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.

Abbreviations: PT: Prothrombin time; PTT: Partial thromboplastin time; INR: International normalized ratio; Na: Sodium; SGOT: Serum glutamic-oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; ALK: Alkaline phosphatase.

intervention group (P=0.016). The findings show that the difference between the white blood cells between the two groups was on the third day (P=0.004) and the seventh day (P=0.009). The average serum glutamic-oxaloacetic transaminase test (SGOT) of patients in the intervention group was about 1.6 times higher than that of the control group, and this difference was significant (P=0.024). However, no difference was observed between the SGOT of patients in both control and intervention groups on the first and third days. In addition, the variance analysis of repeated data also did not manifest a significant difference between the two groups in terms of SGOT changes (0.313). In both groups, no significant difference was observed between the average SGPT (P=0.600) and ALK (P=0.203) during the hospitalization period of the patients.

This study discovered 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 with the controls (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).

4. Discussion

In the current study, due to its beneficial properties in relieving inflammation [14], curcumin was used to treat patients with severe traumatic brain injuries, and its effects were compared with routine treatment in a clinical trial study. We focused on curcumin because it is a spice with multiple pharmacological properties, very low toxicity, and high availability.

Cerebral edema and subsequent increase in increased intracranial pressure (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].

This study showed that curcumin administration of 500 mg every 8 hours for a period of three weeks can reduce cerebral edema and mortality in patients with severe brain trauma. It also reduces the frequency of low blood pressure and improves brain function in the first and second trimesters during hospitalization and after discharge from the hospital, and it can be useful in improving some biochemical factors.

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

Variables	Levels	No.(%)		P
		Intervention	Control	
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
	NR	7(10.9)	6(9.4)	

The therapeutic properties of curcumin in the intervention group reduced the amount of brain edema caused by severe brain trauma compared with that of the control group. Such a result is consistent with the study of Samini et al. [19] which was conducted on rats with traumatic brain injury with doses of 50 and 100 mg/kg, as well as with the results of the study of Laird MD et al. [18] with three doses of 300-150 mg/kg.

Siahaan et al.'s study [20] on rats with mild brain damage reported that the use of turmeric extract is not effective on 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's research 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 with that of the control on the third day of treatment and at the time of discharge. Such a result is not far from expected, because Smal G 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]. Similarly, Shu Y et al. [16] also reported 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 the reduction of mortality among curcumin recipients compared with that of the control group. This result is also reasonable because, in a clinical trial, Ahmadi et al. [23] proposed 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 critical result we achieved in this study was that we did not observe any difference between patients with severe brain trauma who received curcumin and controls in terms of coagulation factors, electrolytes, liver enzymes, and kidney function. This means that no additional risk of liver, coagulation, and electrolyte damage exists 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 patients suffering from severe brain trauma. 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.

5. Conclusion

This study concluded that the administration of oral nanocurcumin supplement at the rate of 500 mg every 8 hours in a three-week treatment period in hospitalized patients with severe brain trauma can have an effective role on 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 as well as any interactions with other drugs.

Ethical Considerations

Compliance with ethical guidelines

This study was approved and registered by the Research Ethics Committee of the Hamadan University of Medical Sciences, Hamedan, Iran (Code: IR.UMSHA.REC.1398.010). The Iranian Registry of Clinical Trials (IRCT) Code is IRCT20120215009014N305. Informed consent was obtained from all participants in this study. Participants' privacy and data confidentiality were guaranteed.

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Authors' contributions

Conceptualization and design: Mohammadreza Saatian, Ebrahim Jalili and Sara Ataei; Data collection: Mohammadreza Saatian, Masoumeh Roustaei, Sara Ataei and Ali Abdoli; Data analysis and interpretation: Ali Poormohammadi, Maryam Farhadian, Masoumeh Roustaei and Ebrahim Jalili; Drafting, critically revising, reviewing the submitted version of the manuscript and approving the final version of the manuscript: All authors.

Conflict of interest

The authors declared no conflict of interest.

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