

Effects of citicoline on level of consciousness, serum level of fetuin-A and matrix Gla-protein (MGP) in trauma patients with diffuse axonal injury (DAI) and GCS \leq 8

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ABSTRACT

BACKGROUND: Citicoline, a neuroprotective drug, has been suggested to improve level of consciousness, mitigating secondary to brain damage and ectopic vascular calcification, following post-traumatic neurogenesis and angiogenesis, inducing calcification modulators, like fetuin-A and matrix Gla-protein (MGP). This study aimed to investigate effects of citicoline on levels of consciousness, serum levels of fetuin-A and MGP in patients with severe traumatic brain injury.

METHODS: This double blind randomized controlled trial (RCT) was conducted on patients with diagnosis of diffuse axonal injury (DAI) and GCS \leq 8. The cases were treated with citicoline (500 mg every 6 hours) intravenously for fifteen days. Daily GCS assessment and intermittent blood sampling were done for both cases and controls.

RESULTS: Fifty-eight patients were included in the study and during the study period, mean GCS levels improved in both groups; however, the difference was inconsiderable ($p>0.05$). Serum levels of fetuin-A, a negative phase reactant, increased in the group treated with citicoline ($p=0.012$), while these changes were insignificant for the controls ($p=0.455$). Serum levels of MGP, a calcification inhibitor, increased in the cases ($p=0.046$). The alterations were inconsequential in the control group ($p=0.405$).

CONCLUSION: The findings of this study suggest neutral effects of citicoline on level of consciousness and GCS. Through increasing levels of fetuin-A and MGP, citicoline may have protective effects against inflammatory damage and vascular calcification secondary to head trauma.

Key words: Citicoline; GCS; fetuin-A; level of consciousness; matrix Gla protein; traumatic brain injury.

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality.^[1] Based on available data, head trauma is the main reason of death due to trauma and the majority of victims are young men.^[2-4]

TBI is classified, based on timing of injury, to primary and secondary forms, and diffuse and focal types according to the extent of damage.^[5,6] Secondary (vs. primary) TBI occurs minutes to hours after primary assault, which is preventable and also treatable with hemodynamic or pharmacological strategies. In order to halt vicious cycle of cellular damage, pharmacological therapies has focused on the usage of calcium channel blockers, free radical scavengers, and membrane-restorative agents.^[7]

Fetuin-A or α 2-Heremans Schmid glycoprotein (AHSG), a circulatory negative acute phase reactant and anti-inflammatory protein, inhibits ectopic precipitation of Ca PO₄ ions, vascular calcification, and inflammatory cytokine production.^[8] Fetuin deficiency results in inflammation, vascular calcification, accelerated atherosclerosis, and higher cardiovascular mortality rate in uremic patients.^[9,10]

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Matrix Gla protein (MGP) is a vitamin K-dependent inhibitor of extracellular matrix calcification. MGP-deficient mice have developed progressive precipitation of hydroxyapatite crystals on arterial walls and died within two months.^[11]

Cytidine-5'-diphosphocholine, also known as Citicoline or CDP-choline, an essential intermediate substance for synthesis of phosphatidylcholine and acetylcholine neurotransmitter (ACh), has been suggested to have neuroprotective and neurorestorative effects.^[12]

Considering the burden of TBI and importance of halting secondary brain damage following trauma, preventing life-long disabilities of the victims, and lack of data on effects of citicoline as neuroprotective agent in this condition, this study aimed at investigating effects of citicoline on level of consciousness and GCS in patients with severe head trauma. In order to evaluate impact of citicoline on suppression of inflammation and secondary vascular calcification, fetuin-A and MGP were assessed as quantitative markers of inflammation status and ectopic calcification.

MATERIALS AND METHODS

This double blind randomized controlled trial (RCT) included patients admitted to the trauma department of Emam-Reza Research and Training Hospital affiliated by Tabriz University of Medical Sciences with the diagnosis of diffuse axonal injury (DAI) and GCS \leq 8 between September 2011 and March 2012.

The inclusion criteria were: age between 18 and 65 years, giving informed written consent by first degree relatives, absence of major traumatic lesion of the chest, abdomen or limbs, absence of focal brain lesions such as contusion or hematoma mandating surgical drainage admission within 24 hours after trauma, absence of heart disease, negative history for cardiovascular diseases, hyperlipidemia, diabetes, and hypertension. The patient was excluded in the case of not having inclusion criteria, pregnancy, surgery (including orthopedic, gynecologic and etc.) within the first 24 hours following trauma, cardiopulmonary resuscitation (CPR) within the first 24 hours after trauma, death or discharge before study completion.

The patients were divided into two groups, case and control, using a randomized parallel-group design and were randomly allocated to the case group receiving citicoline and the control group not receiving the drug.

The diagnosis was made based on CT findings including, single or multiple small intraparenchymal hemorrhages in cerebral hemispheres (<2 cm in diameter), intraventricular hemorrhage, hemorrhage in the corpus callosum, small focal areas of hemorrhage adjacent to the third ventricle (<2 cm in diameter), and brain stem hemorrhage. Written informed consent was taken from first degree family members after explaining

the goals and the whole process of the study. The study duration was fifteen days. Patients were randomly assigned to either groups. A thorough physical and neurological examination was done and the acquired GCS score was recorded immediately on admission to the trauma department; A 10 cc blood sample was taken and the samples were investigated for serum levels of fetuin-A and MGP. Citicoline was administered to the case group (500mg every 6 hours) intravenously by a nurse blinded to the study process. For both groups, blood-sampling was repeated on the sixth and twelfth days of admission, re-evaluating serum levels of fetuin-A and MGP. The results were recorded on related forms for each patient by the examiner (resident of neurosurgery), who remained unchanged during the whole study period and was blinded to the grouping of the patients. Meanwhile, the patients were examined by the resident on daily basis and the assessed GCS scores were recorded.

For the purpose of analysis, SPSS (Statistical Package for Social Sciences) version 21 was used. The results were reported as mean \pm Standard Deviation (SD). Analysis of variance (ANOVA) was utilized for cohort evaluation of each group. Considering data homogeneity, independent sample T-test was used for comparison between groups; a p value <0.05 considered to be statistically significant.

This research project was conducted after the approval of the Research Ethics Committee of Tabriz University of Medical Sciences.

RESULTS

Fifty-eight patients (13 female and 45 male patients), equally divided into case and control groups, were included into the study. The mean (\pm standard deviation) age of the patients was 30.94 \pm 8.6 years (maximum, 53; minimum, 18). The average GCS scores of the case group revealed statistically significant changes on various days of admission, which was highest on the fifteenth day (p <0.001). Corresponding values for the control group, also, had considerable alterations and were highest on the fifteenth day (p =0.000). Mean GCSs were comparable on each test day (p >0.05) (Table 1). The mean levels of serum fetuin-A for the case group were 45 \pm 9.26 ng/ml on admission, 48.80 \pm 6.5 ng/ml on the sixth day and 51.73 \pm 6.8 ng/ml on the twelfth day of admission, which had notable increment (p =0.012). These values for the control group were 42.39 \pm 13.54 ng/ml on admission, 44.10 \pm 12.60 ng/ml on the sixth day and 46.76 \pm 13.80 on the twelfth day of admission. The variation was not substantial in the control group (p =0.455) (Table 2). The average levels of MGP for the case group were 30.84 \pm 20.32 ng/ml on admission, 38.20 \pm 21.48 ng/ml on the sixth day and 44.86 \pm 21.58 ng/ml on the twelfth day of admission. These values for the control group were 25.95 \pm 5.92 ng/ml, 34.82 \pm 36.41 ng/ml and 31.11 \pm 17.65 ng/ml on admission, the sixth and twelfth days, respectively. The increment in serum levels of MGP was con-

Table 1. Mean (\pm Standard deviation) Glasgow Coma Scale (GCS) scores of the patients within the study period

	On Admission	1st Day	6th Day	12th Day	15th Day	p [Cohort evaluation]
Case	5.80 \pm 1.47	6.30 \pm 1.12	8.1 \pm 2.29	10.10 \pm 2.88	10.95 \pm 3.21	<0.001
Control	6.40 \pm 0.82	6.50 \pm 1.0	9 \pm 2.20	10.15 \pm 3.16	11.55 \pm 3.26	=0.000
P value	>0.05	>0.05	>0.05	>0.05	>0.05	

Table 2. Mean (\pm Standard deviation) serum levels of Fetuin-A (ng/ml)

	On Admission	6th Day	12th Day	p [Cohort evaluation]
Case	45 \pm 9.26	48.80 \pm 6.5	51.73 \pm 6.8	0.012
Control	42.39 \pm 13.54	44.10 \pm 12.60	46 \pm 13.80	0.455
P value	0.29	0.08	0.08	

Table 3. Mean (\pm Standard deviation) levels of Matrix Gla Protein (MGP) (ng/ml)

	On Admission	6th Day	12th Day	p
Case	30.84 \pm 20.32	38 \pm 21.48	44.86 \pm 21.58	0.046
Control	25.95 \pm 15.92	34.82 \pm 36.41	31.11 \pm 17.65	0.405
P value	0.31	0.66	0.01	

siderable in the case group ($p=0.046$) while this variance was statistically insignificant for the control ($p=0.405$) (Table 3). As shown in Tables 2 and 3, both groups were similar regarding serum levels of fetuin-A and MGP.

DISCUSSION

TBI, a leading cause of morbidity and mortality worldwide, has two main mechanisms for primary and secondary damage to the neurons. Instantaneously, after trauma, a series of biochemical reactions get started, final products of which can cause clinical presentations such as intensification of vascular calcification, local macrophage-activity, and ultimately, vascular atherosclerosis.^[13]

TBI can make changes in anatomical and functional structures of the brain like considerable brain volume loss and parenchymal degradation secondary to severe head trauma.^[14]

Since the nervous tissue doesn't have regenerative ability and the damage persists lifelong, therapeutic approaches have focused on banning secondary nerve damage through extracting free radicals from the region.^[15] This is, especially, a matter of concern in patients with severe and critical TBI with $GCS\leq 8$ and DAI, since, pre-hospital neurologic deterioration and lower level of consciousness are independent factors of poor prognosis.^[16,17]

Severe traumatic brain injury is an isolated predisposing factor for succeeding posttraumatic cerebral infarction (PTCI),^[18,19] in this setting, besides acute reperfusion strategies such as thrombolysis or mechanical clot removal, practically all available therapeutic protocols focus on palliation and use of neuroprotective agents for mitigation of secondary damage to the nervous system. Citicoline has been reported to have protective and restorative effects on the central nervous system (CNS) by inducing Na^+/K^+ ATPase activity, decreasing lipid peroxidation, preserving mitochondrial membrane cardiolipin, suppressing phospholipase A_2 activity, improving neuroplasticity and synthesis of neurotransmitters like acetylcholine (ACh) or dopamine.^[20-22] The drug has protective impact on cell membrane through accelerating re-synthesis of structural phospholipids, stabilizing the membrane, and attenuating free radical synthesis.^[23]

Pre-ischemic administration of citicoline attenuated glutamate and LDH release, banning corticostriatal depletion of high energy phosphates through improving ATP restoration and glutamate uptake, secondary to oxygen-glucose deprivation.^[24]

Study on experimental stroke models have revealed increased amount of activated microvessels of the infarct area after 21-24 days of citicoline treatment, compared to the controls,

citicoline had pro-angiogenic and protective effects on human brain microvessel endothelial cells of the infarct region.^[25,26]

Citicoline has been proposed to improve cognitive function, increasing cerebral blood flow, especially in conditions with vascular and degenerative etiology such as Alzheimer's disease,^[27,28] organic brain syndromes, like autism,^[29] decreasing cerebral edema, neuronal loss and cortical contusion.^[30] Citicoline has been reported to be as beneficial as methylprednisolone on spinal cord injury model of rats.^[31]

Citicoline has dose-dependent protective impacts on extravasation and water content of affected lobe and ipsilateral hippocampus (known to be susceptible to injury) in head trauma patients.^[32] The agent reduces post-traumatic hippocampal neuronal death, decreases cortical contusion volume and improves neurological recovery.^[33] Serum levels of malondialdehyde (an indicator of oxidative stress) has diminished after fifteen days of citicoline treatment in DAI cases, compared to the controls.^[34]

Citicoline improved neurological recovery of severe TBI, especially when administered within 24 hours after trauma,^[35] which was not in concordance with our findings. On the basis of our results, mean GCS levels increased considerably in both, case and control groups, temporally ($p < 0.001$ and $p = 0.000$, respectively) but the difference between groups was insignificant until the fifteenth day of admission ($p = 0.27$); According to available data, the difference may reach a considerable amount by extending the treatment period, especially up to twenty-one days.^[36]

In a study on patients with mild TBI, the outcome was comparable between citicoline and placebo-treated series.^[37]

Role of fetuin-A, a negative acute phase plasma protein, was evaluated in sepsis and endotoxemia. Serum level of fetuin decreased temporally, while increasing the concentration of HMGB1, a late inflammatory mediator of sepsis; fetuin-deficient rats were remarkably susceptible to lethal systemic inflammation. Exogenous administration of fetuin reduced HMGB1 levels considerably.^[38] In an experimental model of ischemic stroke, exogenous fetuin-A reduced infarct volume 24 hours after ischemia. Proposed mechanisms were activating Spermine-mediated anti-inflammatory processes, decreasing release of HMGB1 from ischemic tissue, suppressing central microglia and peripheral immune cells, diminishing TNF production from ischemic region, and on the whole attenuating inflammatory response secondary to ischemic insult.^[39,40] Macrophage-mediated phagocytosis induction by fetuin may prevent accumulation of HMGB1-containing apoptotic cells which can undergo late-onset necrosis and substance release.^[41]

Levels of fetuin, along with other inflammation and acute-phase indicators, can predict outcome in patients with acute coronary syndrome or end stage renal disease (ESRD).^[42,43]

In the current study, serum levels of fetuin-A increased in the group treated with citicoline, within the study period, which was statistically significant ($p = 0.012$), while these changes were inconsiderable in the controls ($p = 0.455$). These findings suggest possible anti-inflammatory (via fetuin-A increment)^[44] and protective effects against trauma-related vascular calcification and related morbidity and mortality.^[45]

A study on familial mediterranean fever (FMF) has showed down-regulation and inverse correlation of fetuin during attack phases, suggesting possible efficacy of fetuin as an indicator of acute phase and disease activity.^[46]

Patients with migraine had lower levels of fetuin in comparison to healthy controls. Considering the role of neurovascular inflammation, in pathophysiology of migraine attacks, lower fetuin-A may have a possible role in this inflammatory process.^[47]

Neurogenesis, accompanied with angiogenesis, after TBI and stroke has an important role in restoring motor and cognitive function.^[48-51] Angiogenesis, along with vasculogenesis, is seen 3-4 days after ischemic insult or TBI, in injured tissue, as a result of endothelial progenitor cells (EPC) invasion.^[52,53]

Angiogenesis, as an inevitable component of calcification, especially of blood vessels, heart valves and skeletal muscles, triggers ectopic calcification process.^[54]

Possible underlying mechanisms for angiogenesis-induced calcification are as follows: Firstly, vascular progenitor cells can act as a channel for osteoprogenitor cells invasion. Secondly, endothelium-derived cytokines (such as, BMP-4 and BMP-2) stimulate osteoprogenitors and calcification, as the production of these cytokines are up-regulated during inflammation or mechanical forces.^[55,56] Inflammatory response and mechanical stresses can result in calcification in certain settings.^[57,58] Thirdly, many angiogenic factors like fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) can also induce differentiation and migration of osteoblasts, osteoclasts, and chondrocytes.^[59]

As a potent inhibitor of vascular calcification, MGP, synthesized by vascular smooth muscle cells,^[60] may have a protective role against ectopic calcification following angiogenesis, especially in patients with chronic kidney disease^[41] and β -thalassemia.^[61]

Higher levels of MGP are related with lower cardiovascular events or mortality in patients with stable coronary artery disease,^[62] mandating more aggressive treatment strategies in patients with specific MGP-genotypes.^[63]

In our study, serum levels of MGP increased considerably in the case group ($p = 0.046$). These changes were inconsequential for the controls ($p = 0.405$). Increased amounts of MGP,

inhibiting calcification process following inflammation, and angiogenesis, can prevent vascular damage in affected cases.^[64]

According to our findings, citicoline may have a protective role against inflammation and following vascular calcification in secondary-TBI through increasing fetuin-A and MGP. Due to lack of similar papers, comparing findings of this study with other data was impossible.

Limitations of our study included the small number of the cases followed up for a short (15-day) period. For further elucidation of the effects of citicoline in patients with severe TBI, studies with larger case-series and long-term follow up should be conducted. In this context, Glasgow Outcome Scale (GOS) can be used overtime to determine impact of citicoline-treatment on final outcome.

The current study evaluated neuroprotective effects of citicoline in patients with severe TBI using quantitative indicators, while previous researches mostly investigated qualitative factor. To our knowledge, this is the first research on possible effects of citicoline on fetuin-A and MGP and their role against inflammation and ectopic calcification in severe TBI.

Conclusion

On the basis of our findings, citicoline, having neutral effects on levels of consciousness, may have a protective role against inflammation and, following vascular calcification, in secondary-TBI through increasing serum levels of fetuin-A and MGP.

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Conflict of interest: None declared.

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DENEYSEL ÇALIŞMA - ÖZET

Yaygın akson hasarı ve GKS ≤ 8 olan travma hastalarında sitikolinin bilinçlilik durumu, serum fetuin-A ve matriks Gla-protein (MGP) düzeyleri üzerine etkileri

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AMAÇ: Bir sinir koruyucu ilaç olan sitikolinin fetuin-A ve matriks Gla-protein (MGP) gibi kalsifikasyon modülatörlerini tetikleyerek posttravmatik nörojenез ve anjiyogenез sonrası bilinçlilik düzeyini iyileştirdiği, ikincil beyin hasarını ve ektojik vasküler kalsifikasyonu hafiflettiği ileri sürülmüştür. Bu çalışma ağır travmatik beyin hasarlı hastalarda sitikolinin bilinçlilik, serum fetuin-A ve MGP düzeyleri üzerine etkilerini araştırmayı amaçlamıştır.

GEREÇ VE YÖNTEM: Bu çift-kör randomize kontrollü çalışma (RKÇ) yaygın aksonal hasar tanılı GK skoru ≤ 8 olan hastalarda yapıldı. Olgular 15 gün sitikolinle (6 saatte bir 500 mg i.v.) tedavi edildi. Hem hastalar hem de kontroller günlük GCS değerlendirmesinden geçti, belli aralarla kan analizleri yapıldı.

BULGULAR: Çalışmaya 58 hasta katıldı. Çalışma dönemi boyunca her iki grupta Glaskov Skala skorları iyileşmiş olduğu gibi gruplar arasındaki farklılık hatırı sayılır derecede değildi ($p > 0.05$). Sitikolinle tedavi edilen grupta bir negatif faz reaktanı olan serum fetuin-A düzeyleri artmışken ($p = 0.012$), kontrollerde bu değişiklikler anlamlı değildi ($p = 0.455$). Bir kalsifikasyon inhibitörü olan serum MGP düzeyleri hastalarda yükselmişti ($p = 0.046$). Kontrol grubundaki değişiklikler anlamlı değildi ($p = 0.405$).

TARTIŞMA: Bulgularımız sitikolinin bilinçlilik düzeyi ve GKS üzerine nötr etkileri olduğunu düşündürmektedir. Sitikolin fetuin-A ve MGP düzeylerini yükselterek kafa travmasına bağlı enflamatuvar hasar ve vasküler kalsifikasyona karşı koruyucu etkilere sahip olabilir.

Anahtar sözcükler: Bilinçlilik düzeyi; fetuin-A; GKS; matriks Gla protein; sitikolin; travmatik beyin hasarı.

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