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Outcome of Traumatic Dysarthria and Lingual Problems of Understanding with Creatine Administration. An Open Label Randomized Pilot Study

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Abstract

Background: The most common cause of death and disability after severe trauma in childhood is traumatic brain injury (TBI). Of all trauma deaths, 25% are caused by head injury.

Objectives: The complex pathobiology of traumatic brain injury (TBI) offers numerous targets for potential neuroprotective agents. We evaluate the clinical benefit after creatine administration in children and adolescents.

Methods: A prospective, randomized, comparative, open – labeled pilot study of the possible neuroprotective effect of creatine was carried out on 39 children and adolescents, aged between one to eighteen years old, with (TBI). The creatine was administered for 6 months at a dose of 0.4gr/kg in an oral suspension form every day. For categorical variables, we used the χ^2 test (Chi-square test) to identify differences between controls and cases. Statistical significance was defined as a p-value<0.05 and not statistically significant if p-value >0.1.

Results: The administration of creatine to children and adolescents with TBI improved results in several parameters, including duration of post-traumatic amnesia (PTA), duration of intubation, intensive care unit stay. Significant improvement was recorded in the categories of dysarthria (p<0.001) and lingual problems of understanding (p<0.001) aspects in all patients. No side effects were seen due to creatine administration.

Conclusions: More specific examinations for in vivo evaluation of creatine must be performed, in order to draw conclusions for the optimal duration and manner of creatine supply, as well as its possible role for the prevention of TBI complications, in double blind studies.

Keywords: Creatine; Traumatic brain injury; Pediatric; Outcome

Introduction

The most common cause of death and disability after severe trauma in childhood is traumatic brain injury (TBI). Of all trauma deaths, 25% are caused by head injury. The cost to society is enormous because of the long recovery and disability involved, the comparatively long hospital stays and 5-10% requires discharge to a long-term care facility [1]. Severe head injuries usually are associated with motor vehicle crashes, height falls and child abuse. Much is yet to be learned regarding the effects of severe head trauma on brain development, but available studies suggest that neuropsychiatric recovery after significant head injury takes a long time following resolution of the immediate effects of the injury. Functional deficits result from primary and secondary mechanisms after traumatic brain injury. The primary damage occurs at the time of impact and results from the mechanical insult itself. The secondary injury, defined as cellular damage not immediately apparent after the trauma but developing within minutes, hours, or even days, seems to be related to mitochondria dysfunction associated with the disruption in cellular calcium homeostasis that is known to occur after TBI. Maintenance of cellular calcium homeostasis is intimately related to adenosine triphosphate (ATP) use and synthesis, which are key to proper brain functioning. Enhanced neuron survival may be improved by providing an adequate supply of ATP immediately after trauma [2]. Creatine (a-methyl-guanidinoacetic acid) [Cr] is an amino acid endogenously produced from glycine, methionine and arginine in the liver, kidney and pancreas [2]. Creatine supplementation increases intramuscular and cerebral stores with both creatine, and its phosphorylated form, phosphocreatine [PCr] [3]. The increase of these stores may offer therapeutic benefits by stimulating protein synthesis or reducing protein degradation, stabilizing biological membranes, and preventing ATP depletion, which occurs in patients with traumatic brain injury [4]. Recent findings in animal models have demonstrated that creatine affords significant neuroprotection against experimental brain injury [5,6] Based on these experimental facts, we studied administration of creatine to patients with traumatic brain injury. Precedent to this study included clinical studies of neurologic illnesses such gyrate atrophy, mitochondriopathies, myopathies and myocardiopathies in which no serious side effects were observed after the administration of creatine [7-13].

Materials and Methods

The institutional ethics committee of the University Hospital of Heraklion approved the study protocol. A prospective study was conducted in the Pediatric Surgical Department of the University Hospital of Heraklion from February 2000 to March 2004. Thirty

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nine children and adolescents were enrolled after obtaining informed consent from their parents. They were randomized to study and control groups, with the study group receiving creatine using Glasgow Coma Scale (GCS) scores as the randomization factor [3-8]. Pearson's chi-square test showed that there is no statistically significant difference between the two groups p=0.835. We assessed power estimation for categorical variables (disability or death vs. good recovery). Initial considerations were: Type I error was set at 0.05 and 20 patients per arm were selected. The probability for a disability outcome was set at 85%. This percentage was estimated from previously published studies [4,9,10]. The disability outcome for creatine group was set at 0.50. The power of this estimation was calculated at 66, 8%.

Entry and exclusion criteria

Patients eligible for the study had to satisfy the following inclusion criteria: 1) age between 1 and 18years, 2) Glasgow Coma Scale (GCS) on admission between 3 and 9, 3) Pediatric Trauma Score (PTS) on admission between (-4) and 12 and 4) treatment could be initiated within 4 hours from the time of injury. Exclusion criteria were 1) history of previous admission to hospital for head injury, 2) known psychiatric disorder or mental retardation, 3) received other medication within 30 days of enrolment. In general, patients were admitted directly to the hospital within 1-4 hours after injury. The GCS and PTS were assessed as part of the neurological examination.

Therap

According to random numbers, patients were allocated to receive either creatine at a dosage of 0.4gr/kg in an oral suspension form, every day for six months, or nothing. Creatine was mixed with water or apple juice then flushed through nasogastric tube or given with a spoon. Treatment could be stopped at the request of the patient's guardians or if the clinician or parent judged that treatment was having adverse effects.

Outcome assessment

The presence of post-TBI dysarthria or lingual problems of understanding was performed by a specially trained neurologist. Dysarthria was defined as the presence of either the following forms of dysarthria: ataxic, flaccid, spastic, hyperkinetic, hypokinetic, mixed. Lingual problems of understanding were defined as the presence of either signs or symptoms of semantic or pragmatic speech problems after conversation with the neurologist and/or after reading a piece of a book, designed for the age of the child, and afterwards discussing it with the neurologist.

Follow up

After discharge from the hospital, a follow up was scheduled at 6 months after injury by the same blinded surgeon in each hospital. During each visit a checklist of complaints was filled out, together with a structured interview and a neurological examination.

Statistical analysis

A parametric (student's t-test) and a non-parametric test (Mann-Whitney U-test) were used to identify if there were differences between selected continuous variables in controls and cases. For categorical variables, we used the χ^2 test (Chi-square test) to identify differences between controls and cases. Statistically significance was defined as a p-value<0.05, trend toward significant if 0.05<p-value<0.1 and not statistically significant if p-value>0.1.

Results

Forty-eight children with TBI were admitted to our hospitals during the study. Three children were not eligible and the parents of four children refused to have their children participate in the study. A total of 39 eligible children were randomly selected. There were 19 children (patients) in group I (controls) and 20 children in group II (creatine). Four children died during the time period of the study, (within 3 months), two from each group. Twenty of the children in the study group received creatine at a dosage of 0.4gr/kg in an oral suspension form every day for six months, and 19 children received nothing. There were no significant differences between the two study groups. The patient characteristics are given in Table 1 of reference [12]. There were no significant differences between the Computed Tomography (CT)/Magnetic resonance imaging (MRI) of brain and using the Chi Square test, no statistically significant differences were noted at concomitant injuries, electroencephalogram, whether an operation was carried out or not, the Glasgow Coma Score and the Pediatric Trauma Score between the two groups.

Outcome assessment (short term)

The mean duration of intubation, length of stay in intensive care (ICU), hospital stay and Post Traumatic Amnesia (PTA) was compared between the two groups and the results are given in Table 2 of reference [12].

Outcome assessment (long term)

There was a statistically significant difference between the controls and cases and the groups of "dysarthria" (x2=16.985; df=1; p<0.001). More specifically, the proportion of children having no problem of dysarthria is significantly higher in cases than controls (100.0% vs. 35.3%), while 11 children (64.7%) of the 17 controls appear to have dysarthria problems. (Figure 1) There was a statistically significant difference between the controls and cases and the groups of "lingual problems of understanding" (x2=14.824; df=1; p<0.001). More specifically, the proportion of children having no problem of lingual understanding is significantly higher in cases than controls (100.0% vs. 41.2%), while 10 children (58.8%) of the 17 in controls appear to have a lingual problem of understanding (Figure 2).

Discussion

Given the fact that many observations have been made that creatine may have beneficial effect in TBI, especially in experimental models the creatine supplementation in children with TBI represents an attempt

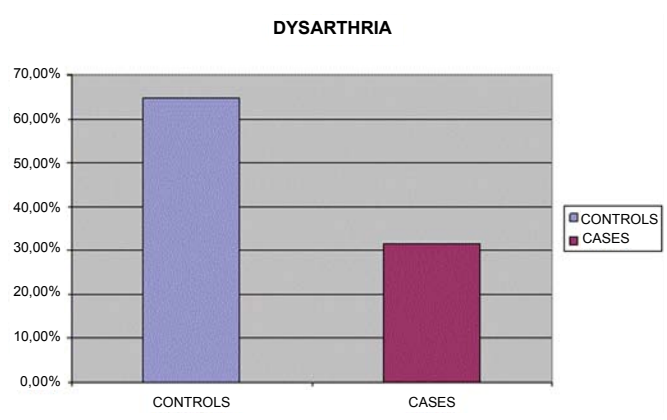

Figure 1: Bar chart for dysarthria of controls and cases.

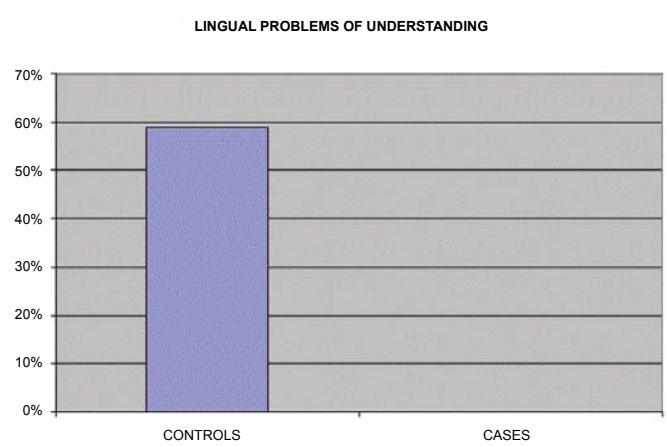

Figure 2: Bar chart for lingual problems of understanding of controls and cases.

to provide neuroprotection for these children [1,3,4]. In this study, the creatine administration gave encouraging results in several parameters, including post traumatic dysarthria and lingual problems of understanding which affect negatively the quality of life of both children and their families. Dysarthria is the abnormal articulation of sounds or phonemes because of abnormal activation of the oromandibular pharyngeal muscles. The speed, strength, timing, range, or accuracy of speech may be affected. Dysarthria can affect articulation, phonation, breathing, or prosody (emotional tone) of speech. In the diffuse, non-specific nature of TBI may result in damage to many areas of the central and peripheral nervous system (upper motor neuron, lower motor neuron, extrapyramidal or cerebellum). This leads to a wide variation in dysarthria type (ataxic, flaccid, spastic, hypokinetic) [14]. On the basis of perceptual analysis, the speech dimensions of prosody, resonation, articulation and respiration are significantly impaired but important is the fact that dysarthria types noted in groups of children subsequent to TBI are similar to those identified in adults with dysarthria subsequent to TBI, especially if the lesions are in the basal ganglia [15-17]. The fact that, at six months follow, the creatine group had a statistically significant difference regarding the post-traumatic dysarthria, provides evidence that the supply of creatine may be an adequate preventive treatment, as part of a multidimensional treatment programs, focusing in the perceptual speech assessment and an inappropriate speech sub-system, that planned by the speech pathologists [14]. As far as the lingual problems of understanding, children with TBI have semantic-pragmatic language problems that include difficulty in understanding and producing both literal and non-literal statements [18,19]. The deficits are expanded in almost all areas of language perception, for example understanding the information flow in texts and idiomatic expressions or making pragmatic inferences and producing speech acts or appreciating humor. Many children with severe TBI have injuries to the frontal lobes, where brain regions (particularly the orbitofrontal regions) have been implicated in tasks requiring awareness of mental states, beliefs, and intentions [20,21]. The variety of language deficits continue to be impaired many years after childhood TBI making the recovery incomplete. Children with mild or severe TBI without the ability to understand discourse-level language will be significantly disadvantaged not only in school but in their everyday communication. Creatine can play an important role as a neuroprotective agent for the prevention of these symptoms which are part of the post-traumatic syndrome, that affect the quality of life of children and their families [22].

How creatine works remains to be determined. Work done in animal models suggested that the mechanical basis for the neuroprotective effects of creatine might involve alterations of the insult-induced depletions of cellular ATP. Chronic ingestion of creatine results in increased brain levels of (PCr). In rat pups hypoxia produces seizures most frequently at 10-12 d of age. Brain cellular energy metabolism increases between 5 and 25 d of age in the rat, as indicated in vivo by the phosphocreatine (PCr)/nucleoside triphosphate (NTP) ratio measured by nuclear magnetic resonance (NMR) spectroscopy. Brain PCr/NTP ratios are approximately the same in 10-12-d-old rats and human term newborns, the ages of high seizure susceptibility. Thus, low Cr or PCr may be important in susceptibility to hypoxic seizures in the metabolically immature brain. To test this hypothesis, rat pups were injected with Cr for 3 d before exposing them to hypoxia on postnatal d 10 or 20. Before and during hypoxia, the electrocortical activity or P magnetic resonance spectra were measured. At 10 but not 20 d, Cr injections increased brain PCr/NTP ratios, decreased hypoxia-induced seizures and deaths, and enhanced brain PCr and ATP recoveries after hypoxia. Thus, Cr protects the metabolically immature brain from hypoxia-induced seizures and, perhaps, from cellular injury [12,23]. Similar results regarding maintenance of cellular ATP levels have been demonstrated in animal models receiving creatine before TBI, particularly the effect of chronic administration of creatine ameliorated the extent of cortical damage by such as 36% in mice and 50% in rats. Protection seems to be related to creatine-induced maintenance of mitochondrial bioenergetics. Mitochondrial membrane potential was significantly increased, intra-mitochondrial levels of reactive oxygen species and calcium were significantly decreased, and ATP levels were maintained. Induction of mitochondrial permeability transition was significantly inhibited in animals fed creatine [1]. Lactate and free fatty acids, which are markers of secondary cellular injury following traumatic brain injury, have been found to be lower in animals treated with creatine before TBI [3]. Other mechanisms underlying this neuroprotection may involve the maintenance of mitochondrial integrity. The cellular and molecular pathways initiated by traumatic brain injury (TBI) may compromise the function and structural integrity of mitochondria, thereby contributing to cerebral metabolic dysfunction and cell death [24,25]. The creatine action may prevent structural mitochondrial changes, as was shown in experimental work with adult rat cardiomyocytes cultured in creatine-deficient medium. The possible beneficial effect of creatine on mitochondrial function is also demonstrated in different clinical studies about creatine action on mitochondriopathies [24,25].

Conclusion

Creatine administration to patients with TBI plays a protective role for the prevention of post-TBI dysarthria and lingual problems of understanding, such as for more post-traumatic complications as shown in references [12,13]. The protective role of creatine administration needs further investigation, in a larger number of patients, with double blind studies and with longer follow-up. The best administration and dose scheme must be discovered and probable long time protective or adverse effects must be surveyed so as to determine whether it can be used as common practice after brain injury in hospitals. Furthermore, a set of extra examinations, such as brain spectroscopy, which can evaluate the function of brain in vivo, can be performed, to evaluate and define better the effect of creatine on brain tissue and making able to follow in detail the changes that PCr performs in order to possibly demystify the mechanism of its action.

References

1. Cakmakci H (2009) Essentials of trauma: head and spine. Pediatr Radiol 39: 391-405.
2. Sullivan PG, Geiger JD, Mattson MP, Scheff SW (2000) Dietary supplement creatine protects against traumatic brain injury. Ann Neurol 48: 723-729.
3. Scheff SW, Dhillon HS (2004) Creatine-enhanced diet alters levels of lactate and free fatty acids after experimental brain injury. Neurochem Res 29: 469-479.
4. Gasparovic C, Arfai N, Smid N, Feeney DM (2001) Decrease and recovery of N-acetyl-aspartase/creatine in rat brain remote from focal injury. J Neurotrauma 18: 241-246.
5. Schulze A, Bachert P, Schlemmer H, Harting I, Polster T, et.al. (2003) Lack of creatine in muscle and brain in an adult with GAMT deficiency. Ann Neurol 53: 248-251.
6. Tarnopolsky MA, Roy BD, MacDonald JR (1997) A randomized, controlled trial of creatine monohydrate in patients with mitochondrial cytopathies. Muscle Nerve 20: 1502-1509.
7. Berger R, Middelanis J, Vaihinger HM (1999) Creatine protects the immature brain from hypoxic damage: Dose-effect relationship. Brain Res 816: 124-130.
8. Balestrino M, Rebaudo R, Lunardi G (1999) Exogenous creatine delays anoxic depolarization and protects from hypoxic damage: dose-effect relationship. Brain Res 816: 124-130.
9. Felber S, Skladal D, Wyss M, Kremser C, Koller A, et al. (2000) Oral creatine supplementation in Duchenne muscular dystrophy: A clinical and 31P magnetic resonance spectroscopy study. Neurol Res 22: 145-150.
10. Gordon A, Hultman E, Kaijser L, Kristjansson S, Rolf CJ, et al. (1995) Creatine supplementation in chronic heart failure increases skeletal muscles creatine phosphate and muscle performance. Cardiovasc Res 30: 413-418.
11. Holtzman D, Togliatti A, Khait I, Jensen F (1998) Creatine increases survival and suppresses seizures in the hypoxic immature rat. Pediatr Res 44: 410-414.
12. Sakellaris G, Kotsiou M, Tamiolaki M, Kalostos G, Tsapaki E, et al. (2006) Prevention of complications related to traumatic brain injury in children and adolescents with creatine administration: an open label randomized pilot study. J Trauma 61: 322-329.
13. Sakellaris G, Nasis G, Kotsiou M, Tamiolaki M, Charissis G, et al. (2008) Prevention of traumatic headache, dizziness and fatigue with creatine administration. A pilot study. Acta Paediatr 97: 31-34.
14. Cahill LM, Murdoch BE, Theodoros DG (2002) Perceptual analysis of speech following traumatic brain injury in childhood. Brain Inj 16: 415-446.
15. Hirose H (1986) Pathophysiology of motor speech disorders (dysarthria). Folia Phoniatr (Basel) 38: 61-88.
16. Theodoros DG, Murdoch BE, Chenery HJ (1994) Perceptual speech characteristics of dysarthric speakers following severe closed head injury. Brain Inj 8: 101-124.
17. Aram DM, Rose DF, Rekate HL, Whitaker HA (1983) Acquired capsular/striatal aphasia in childhood. Arch Neurol 40: 614-617.
18. Dennis M, Barnes MA (2001) Comparison of literal, inferential, and intentional text comprehension in children with mild or severe closed-head injury. J Head Trauma Rehabil 16: 456-468.
19. Dennis M, Barnes MA (1990) Knowing the meaning, getting the point, bridging the gap, and carrying the message: aspects of discourse following closed head injury in childhood and adolescence. Brain Lang 39: 428-446.
20. Dennis M, Barnes MA, Wilkinson M, Humphreys RP (1998) How children with head injury represent real and deceptive emotion in short narratives. Brain Lang 61: 450-483.
21. McDonald S, Pearce S (1996) Clinical insights into pragmatic theory: frontal lobe deficits and sarcasm. Brain Lang 53: 81-104.
22. Ewing-Cobbs L, Brookshire B, Scott MA, Fletcher JM (1998) Children's narratives following traumatic brain injury: linguistic structure, cohesion, and thematic recall. Brain Lang 61: 395-419.
23. Klivenyi P, Ferrante RJ, Matthews RT, Bogdanov MB, Klein AM, et al. (1999) Neuroprotective effects of creatine in a transgenic animal model of amyotrophic lateral sclerosis. Nat Med 5: 347-350.
24. Lifshitz J, Friberg H, Neumar RW, Raghupathi R, Welsh FA, et al. (2003) Structural and functional damage sustained by mitochondria after traumatic brain injury in the rat: evidence for differentially sensitive populations in the cortex and hippocampus. J Cereb Blood Flow Metab 23: 219-231.
25. Borges N, Cerejo A, Santos A, Sarmento A, Azevedo I (2004) Changes in rat cerebral mitochondrial succinate dehydrogenase activity after brain trauma. Int J Neurosci 114: 217-227.