

Traumatic brain injury pharmacological treatment: recommendations

Tratamento farmacológico do traumatismo cranioencefálico: recomendações

Renato Anghinah¹, Robson Luís Oliveira de Amorim², Wellingson Silva Paiva², Magali Taino Schmidt¹, Jéssica Natuline Ianof¹

ABSTRACT

This article presents the recommendations on the pharmacological treatment employed in traumatic brain injury (TBI) at the outpatient clinic of the Cognitive Rehabilitation after TBI Service of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil. A systematic assessment of the consensus reached in other countries, and of articles on TBI available in the PUBMED and LILACS medical databases, was carried out. We offer recommendations of pharmacological treatments in patients after TBI with different symptoms.

Keywords: guideline; therapeutics; brain injuries, traumatic.

RESUMO

Este artigo apresenta as recomendações sobre o tratamento farmacológico empregado para o traumatismo cranioencefálico (TCE) em pacientes ambulatoriais de Reabilitação Cognitiva pós-TCE no Serviço do HCFMUSP. Foi realizada uma avaliação sistemática dos consensos publicados em outros países e dos artigos sobre TCE disponíveis nas bases de periódicos médicos como PUBMED e LILACS. Recomendamos tratamentos farmacológicos em pacientes pós-TCE com diferentes sintomas.

Palavras-chave: guia; terapêutica; lesões encefálicas traumáticas.

Traumatic brain injury (TBI) is an insult to the brain due to an external mechanical force. There is a potential temporary or permanent occurrence of cognitive, physical and psychosocial deficits, associated with, or without, a decrease or alteration of the level of consciousness¹. It is one of the most frequent causes of morbidity and mortality worldwide, with an important impact on quality of life².

In Brazil, TBI is responsible for high mortality rates, the main cause of which is traffic accidents, and is more prevalent in young males². In 1993, in the state of São Paulo, 57,000 deaths from TBI were reported³. Brazilian data indicate that around 700,000 to 1.1 million people are victims of TBI, of whom 20-30% have moderate to severe TBI.

Therefore, guidelines for management of the person who has had a TBI are of paramount importance to guide the health team at all stages of the care and rehabilitation process. In this article, the emphasis on the motor component of rehabilitation will not be addressed, as it has already been covered in another guideline⁴.

The aim of this article is to update the practice parameters regarding late TBI care for outpatients, focusing on the question: *Is pharmacological treatment effective in treating the cognitive-behavioral symptoms of TBI patients?*

This guideline's target audiences are neurosurgeons, neurologists, physiatrists, psychiatrists, ophthalmologists, neuropsychologists, psychologists, speech therapists, occupational therapists and nurses, to guide and provide information on the treatment of adults with traumatic brain injury, with emphasis on outpatient care.

METHODS

We systematically reviewed the literature (MEDLINE database) from 1966 to December 2016 for pertinent evidence. We assessed the evidence for quality and synthesized this into conclusions using the Grading of Recommendations Assessment, Development and Evaluation process. For some

¹ Universidade de São Paulo, Hospital das Clínicas, Faculdade de Medicina, Divisão de Neurologia, Serviço de Reabilitação Cognitiva pós-TCE, São Paulo SP, Brasil;

² Universidade de São Paulo, Hospital das Clínicas, Faculdade de Medicina, Divisão de Neurocirurgia, Serviço de Emergência, São Paulo SP, Brasil.

Correspondence: Renato Anghinah; Divisão de Neurologia do Hospital das Clínicas / FMUSP; Rua Conselheiro Brotero, 1505 / 9º andar; 01232-011 São Paulo SP, Brasil; E-mail: anghinah@terra.com.br

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topics, we accessed papers from 2004 to April 2014, using organized questions based on “Patients”; “Intervention”; “Controls” and “Outcome”. As key words we used: TBI, head trauma, treatment, pharmacological treatment. We have organized the presentation of this paper according to the most frequently-asked questions in this area.

Is pharmacological treatment effective in treating the cognitive-behavioral symptoms of TBI patients?

With these descriptors, cross-references across databases were made according to the theme proposed in each topic of the questions. After analysis of this material, the articles with the most available scientific information were selected, and the evidences that based the guidelines of this document were established. For available randomized and controlled studies, the classification of the strength of evidence was based on the Jadad scale. Work done on children (under 16 years of age) and those written in languages other than Portuguese, English, French and Spanish were excluded. The recommendations regarding the questions in this guideline were prepared by the experts in their respective areas of activity and reviewed by all members in a forum created for this purpose (consensus). The preparation of this document was based on the methodological strategies advocated by the Appraisal of Guidelines for Research & Evaluation (AGREE II).

All the authors contributed equally to this work. Approved by the Guideline Development Subcommittee on May 31, 2014, specialists and several health professionals met in São Paulo, SP, to define the consensus for outpatient treatment of TBI patients. Neurologists, neurosurgeons, psychiatrists, ophthalmologists, occupational therapists, neuropsychologists, speech therapists and nurses were present.

Degree of recommendation and strength of evidence:

- A) Experimental or observational studies of greater consistency.
- B) Experimental or observational studies of less consistency.
- C) Case reports (uncontrolled studies).
- D) Opinion that is not critically-based on consensus, physiological studies or animal models.

Perspectives of the target population

Research was conducted with open questions among patients suffering from TBI and their relatives, at a specific outpatient clinic of a tertiary hospital. The main concerns were collected and the domains of greatest interest were selected.

RESULTS AND DISCUSSION

Is pharmacological treatment effective in treating the cognitive-behavioral symptoms of TBI patients?

The drug-based approach is based on the functional anatomical knowledge of the encephalic region affected by TBI⁴.

Therefore, it is necessary to know the pathophysiology of the different types of TBI, assessing lesion location and specific clinical findings⁴.

Methylphenidate

In a study of 40 patients with moderate-to-severe TBI in the rehabilitation phase, the primary goal of which was to assess care, the administration of methylphenidate (3 mg/kg, 2x daily) increased the speed of information processing in several neuropsychological tests, when compared to the use of placebo⁵ (B).

Agomelatine

The use of agomelatine (25 mg every night) leads to greater sleep efficiency, with a lasting effect⁶ (C).

Modafinil

Modafinil promotes an increase in alertness by the activation of noradrenergic and dopaminergic systems. Two controlled clinical studies, totaling 115 patients, evaluated the use of modafinil for excessive drowsiness and fatigue in patients with severe TBI for longer than a year^{7,8}. A meta-analysis of these studies showed a therapeutic effect of modafinil on fatigue (evaluated by a fatigue severity scale), with a mean difference of -0.82 (95%CI -1.54– -0.11 p = 0.02, I² = 0%)⁹. Regarding excessive daytime sleepiness, the meta-analysis revealed no significant difference between the modafinil group and the placebo group. To assess this outcome, the heterogeneity between the two studies was very high (I² = 70%) (A).

Amantadine

Amantadine is a dopaminergic and serotonergic agonist, and acts by blocking NMDA receptors. In a controlled study of 76 patients over six months of their TBI, the use of amantadine (100 mg, 2x daily for 28 days) was shown to be safe and effective in reducing the frequency and severity of irritability symptoms (-4.3 points in the irritability domain of the neuropsychiatric inventory, in the amantadine group, P = .0085)¹⁰. In this study, aggression symptoms were also reduced when 18 patients who had minimal or no symptoms of aggression were excluded (-4.5 points in the aggression domain of the neuropsychiatric inventory in the amantadine group, P = .046) (A). In a study of 184 patients in a persistent vegetative state or minimal state of consciousness between four and 16 weeks after TBI, the use of amantadine (200-400 mg / day) accelerated the rate of functional recovery during the first four weeks of treatment, compared to placebo (p = 0.007)¹¹ (A).

Venlafaxine

One study on venlafaxine use was included in our guideline. A case report demonstrated that the use of venlafaxine (75 mg twice daily) in a post-obsessive-compulsive disorder might improve obsessive behaviors, irritability and sadness symptoms¹²(C).

Valproate

Two studies on valproate use were included in our guideline. Valproate appears to have benign neuropsychological effects, and is a safe drug to control established seizures or stabilize mood. However, it should not be used as a prophylactic measure in post-traumatic seizures as it does not prevent these¹³ (B). Valproate therapy showed no difference when compared with phenytoin therapy. Valproate should not be used routinely to prevent post-traumatic seizures¹⁴ (B).

Antidepressants

Five studies on antidepressant use were included in our guideline. The use of citalopram was not indicated for the prevention of relapse of major depression (measured by the Hamilton Depression Rating Scale) after TBI¹⁵ (B). The use of sertraline did not seem to prevent the development of cognitive and compartmental problems after TBI¹⁶ (B). There was no evidence that early administration of sertraline decreased the expression of depressive symptoms after discontinuation of the drug¹⁷ (B). The use of fluoxetine for six months in patients with post-traumatic stress decreased relapse rates, as measured by the Clinical Global Impressions Scale¹⁸ (B). Methylphenidate and sertraline had similar effects on depressive symptoms (evaluated by the Beck Depression Inventory and the Hamilton Depression Rating Scale). However, methylphenidate appeared to have more improvements in cognitive functions and was also beneficial in keeping the patient alert during the day. In addition, methylphenidate showed better tolerability than sertraline¹⁹ (B).

Dopaminergic agonist

One study on dopaminergic agonist use was included in our guideline.

The use of bromocriptine (5 g, 2 x daily) in post-TBI subjects with attentional problems did not improve alertness skills and may have been associated with a number of adverse effects²⁰ (B).

Rivastigmine

One study on rivastigmine use was included in our guideline.

The use of rivastigmine demonstrated safety and was well tolerated by patients with TBI. Rivastigmine appeared promising in the subgroup of patients with moderate/severe memory impairment. The Cambridge Automated Neuropsychological Assessment Battery and Hopkins' Verbal Learning Test were used as evaluation measures²¹ (B).

Galantamine

One study on galantamine use was included in our guideline.

Acetylcholinesterase inhibitors have great potential in the treatment of chronic phase TBI, improving fatigue, memory, attention and initiative. However, there were no significant differences between the drugs galantamine, rivastigmine and donepezil²² (B).

Donepezil

Two studies on donepezil use were included in our guideline.

The use of donepezil in chronic traumatic encephalopathy patients with cognitive impairment promoted clinical improvement (observed in the Mini-Mental Status Examination, Wechsler Memory Test, Boston Naming Test and Color Progressive Matrix Test) and improved metabolism in the frontal, parietal, occipital and temporal lobes²³ (B). The drug improved neuropsychological test scores (measured by the Wechsler-III Memory Scale and the Serially Paced Auditory Test) related to short-term memory and sustained attention²⁴ (B).

Recommendations

The use of amantadine to improve functionality between four and 16 weeks is recommended. Although several drugs are being tested to improve the chronic symptoms of TBI, there is a lack of high quality data to testify to the benefits of these drugs. Even so, as long as they are used in a specific way for the symptoms as reported above, the drugs methylphenidate to ameliorate cognitive impairment; agomelatine to improve sleep; modafinil for fatigue; fluoxetine to alleviate depressive symptoms; and rivastigmine and donepezil for memory impairment; may be used in an individualized approach.

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