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Amantadine Effect on Neurorecovery of Patients with Traumatic Brain Injury: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

The increasing number of Traumatic Brain Injury (TBI), mostly due to accidents, greatly contributes as one of the major cause of long-term disability in the world. The brain injury causes neurological dysfunction *via* direct tissue disruption and delayed pathophysiological changes in the molecular and cellular level resulting to neuronal death. The pathophysiological changes seen play an important role in chronic neurodegeneration leading to neurological impairment. Reversing this pathophysiological change may help reduce significant morbidity and mortality.

Keywords: Traumatic Brain Injury • Neurological Impairment • Disability Rating Scale

Introduction

This neuroprotection principle is one of the reasons why different pharmacologic therapies are being studied for their possible neuroprotective properties. One example of that drug is Amantadine. Amantadine is an indirect dopamine agonist and N-methyl-D-aspartate antagonist [1]. It is currently being used for treatment of influenza and dyskinesia in Parkinson's disease. At present, it is also being used off-label to enhance the behavioral responsiveness and arousal *via* improving the injury-induced derangements in the dopaminergic and noradrenergic neurotransmitter systems [2].

A multiple-regression analysis evaluating the effect of Amantadine at 16 weeks after head injury showed better scores on the Disability Rating Scale (DRS). DRS is a measure of functional outcome specific to traumatic brain injury. Despite the small size population of the available studies, we aim to make a generalization thru systematic review and meta-analysis on the effect of Amantadine in the functional improvement of patients diagnosed with traumatic brain injury [3].

Objectives

This study aims to provide generalization on the effect of amantadine in the functional recovery of patients diagnosed with traumatic brain injury thru systematic review and meta-analysis.

Methodology

Overview

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for meta-analyses of healthcare interventions.

Eligibility criteria

Studies included in the meta-analysis are as follows: 1) randomized controlled trials comparing Amantadine to placebo with functional recovery as assessed by the Disability Rating Scale (DRS) as outcome measure and 2) study participants which fulfill the following criteria: a. >16 years old patients with TBI, b. Glasgow Coma Scale score of 10 or less within the first 24 hours of injury, c. No moribund identity.

Data sources and search strategy

The following databases were searched for eligible published and unpublished studies in English language on or before August 30, 2019: PubMed, Cochrane Library, Central, BMJ Journals, Web of Science, PLOS, ClinicalTrials.gov and Herdin. The following search terms were used: "amantadine", "outcome assessment", "neurorecovery", "traumatic brain injury", and "rando mized controlled trial".

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Study selection

The study selection process followed the PRISMA guidelines. Excluded in the selection were the following: 1) duplicate studies 2) systematic reviews and 3) studies that were abstracts only, non-randomized clinical trials and not in the English language. Two authors reviewed independently the titles, abstracts, and full articles to determine whether the studies met the inclusion criteria. Complete articles were obtained for all titles and abstracts that appear to meet the inclusion criteria. The reasons for the exclusion were coded as one or more of the following: inappropriateness in the: 1) study population 2) intervention 3) comparison 4) outcome(s) and 5) study design. Conflicting assessment between reviewers were resolved by agreement. A flow diagram that depicts the search process was shown in Figure 1.

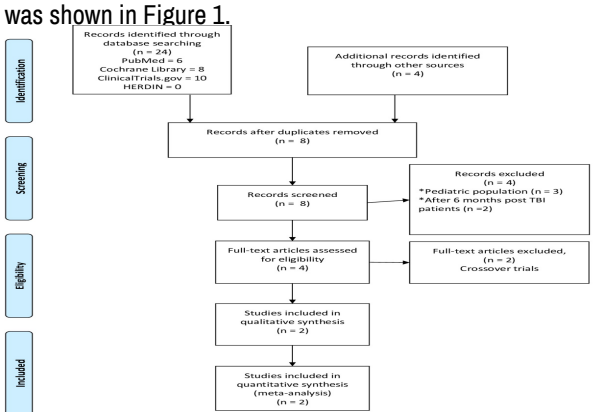

Figure 1. PRISMA flow diagram of study selection process.

Data extraction

The two authors independently abstracted data on the characteristics of the study, participants, intervention and outcome of improvement in the functional status as shown in Table 1 [4] .

Quality assessment

The randomized controlled trials were graded using the Quality Scale for Meta-Analytic Reviews The risk for bias for each randomized controlled trials were assessed using the Cochrane Risk of Bias instrument. The bias in randomized controlled trials was evaluated for six domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, and selective reporting. Sequence generation was considered adequate if the central randomization or tables of random numbers were used. For the allocation concealment, if the central randomization or sealed envelopes were used, it is considered adequate. Blinding is adequate if the participants, outcome assessors and statistician were blinded to the group assignment. The rest of the domains were evaluated based on the criteria of the risk of bias tool. The studies were classified based on whether they have a high, low or unclear risk of bias. The overall risk of bias is categorized as high even if only one of the domains is considered as high risk. The two authors independently assessed the risk of bias in the included studies. If there are discrepancies, it is immediately resolved by consensus. The risk of bias assessment is summarized in Table 2. Sequence generation, allocation concealment, and blinding were considered as key essential domains to score the overall quality of a trial.

Table 1. Summary characteristics of included randomized controlled trials.

Study	Year	Country	Sample size	Study design	Age of cases (years old)	Treatment protocol	Timing from injury to study
Giacino et al. [5]	2012	USA	184	Double-blind, placebo-controlled RCT	16-65	4 weeks Amantadine (200-400 mg/day) 4 weeks placebo	4-16 weeks after surgery
Ghalaenovi et al. [6]	2017	Iran	40	Double-blind, placebo-controlled RCT	16-80	6 weeks Amantadine (100 mg twice a day) 6 weeks placebo	Post-trauma, as soon as the feeding started (1-10 days)

Table 2. Quality scale rating and assessment of risk of bias of included randomized controlled trials.

Study	Quality Scale Rating (Grade)	Sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Giacino et. al., 2012	A	+	+	+	+	+	+
Ghalaenovi et al., 2017	A	+	+	+	+	+	+

Note: +indicates low r isk

Data synthesis and analysis

The meta-analysis was done using Review Manager Version 5.3. Inverse-variance method was used for the analyses of continuous outcome data. The Disability Rating Scale (DRS) was used to evaluate the effect of Amantadine on the functional status of the patients. It consists of the following: 1) eye opening, 2) verbalization, 3) motor response, 4) cognitive understanding of feeding, dressing, and grooming, degree of assistance and supervision required and 5) employability. The score ranges from 0 to 29 and higher scores indicate greater disability. The continuous outcomes were pooled with mean difference and its corresponding 95% Confidence Intervals (CIs). The statistical heterogeneity was assessed using I2 test, wherein I2>50% was considered as significant heterogeneity. The random-effects model was applied to address the heterogeneity among studies.

Sensitivity analyses

The random-effects model and study exclusion were applied to address the heterogeneity among studies.

Results

Search results

The literature search generated a total of 28 abstracts. Two randomized clinical trials met the inclusion criteria. The detailed process of study selection is shown in Figure 1.

Study characteristics

A total of 224 patients diagnosed with an acute/recent traumatic brain injury treated in the three randomized clinical trials published from 2002 to 2017 were included. Majority of the patients were male (75.9%) with a mean of 36.4. The Disability Rating Score of all included patients were obtained at baseline and after treatment with Amantadine.

Quality assessment of included studies

The quality of the studies and risk of bias assessment is shown in Table 2. The included randomized controlled trials have low risk of selection, performance, detection, attrition and reporting biases.

Efficacy outcome

The intended outcome was analyzed using the inverse-variance random-effects model. The pooled data of the two randomized clinical trials comparing Amantadine to placebo revealed thatAmantadine has no effect on functional recovery of patients with traumatic brain injury (SMD=-0.06, 95% CI=-0.76, 0.64, P=0.88; I2=76%, P=0.04) shown in Figure 2.

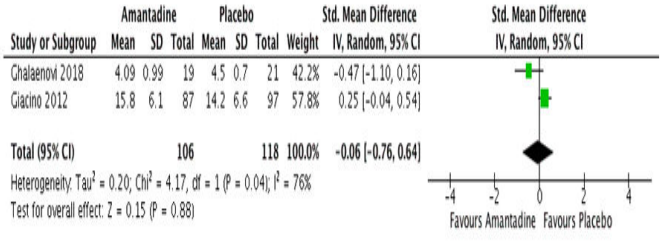

Figure 2. Effect of Amantadine versus placebo in the functional status of patients with TBI after 4 to 6 weeks of treatment.

Risk of bias across studies

The substantial heterogeneity observed in all the analyses may be partly due to within-study bias in smaller studies. Publication bias was less likely given the result of funnel plot of the included studies; both studies are within the 95% confidence interval as shown in Figure 3.

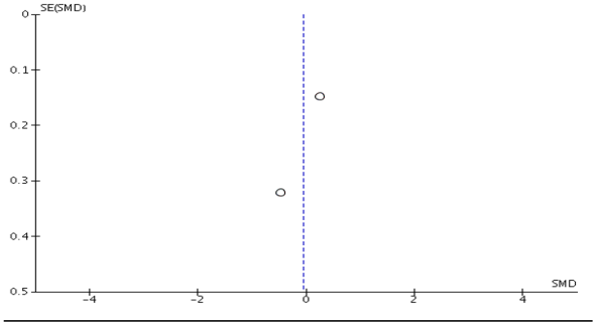

Figure 3. Funnel plot of the meta-analysis of published studies.

Discussion

The faster recovery of the Amantadine group was not documented in this meta-analysis, likely because of the significant heterogeneity of the randomized trials. This meta-analysis supports the available studies that investigate the effects of Amantadine on patients with traumatic brain injury. The results were conflicting, probably because of its small sample size. Nonetheless, small sample size crossover in the randomized controlled trials has different results. It was reported a better disability rating scale score in the Amantadine group than in the placebo group [7]. Conversely, in the study no significant difference was noted between the two groups [8].

This meta-analysis showed that Amantadine may have no effect at all or may not show rapid functional improvement among patients with traumatic brain injury [9].

Study limitations

There are several limitations in our meta-analysis that must be emphasized. First, the included randomized controlled trials in the

meta-analysis have small sample size, increasing the risk for bias. Second, the dose and the duration of the included trials were not homogenous leading to a confounding bias.

Conclusion

Traumatic Brain Injury (TBI) caused by high-speed transportation accident results in mechanism of injury described as Diffuse Axonal Injury (DAI), which is associated with reduction in dopamine turnover in brain. The effect of Amantadine on functional improvement in patients with traumatic brain injury is not apparent at 4 to 6 weeks of treatment. There was a consistent trend toward a more rapid functional improvement regardless of when a patient with DAI-associated TBI was started on amantadine in the first 3 months after injury. Studies with large sample size are needed to establish its neuroprotective effect.

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