Memantine

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Memantine is effective in blocking excessive activity of NMDA-type glutamate receptors and reduces the progression of dementia and may have benefits after TBI.

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1. Introduction

In 2016, more than 27 million new cases of traumatic brain injuries (TBIs) were diagnosed globally, while approximately an equal number of patients were suffering from the sequelae of older TBIs[1]. Several national studies have established that there is a significant financial burden related to TBIs due to associated healthcare costs and loss of earnings/productivity[2][3]. Financial losses for a proportion of TBI patients continue after their initial hospitalization period, as they suffer from the sequelae of traumatic brain injury[4]. The sequelae of TBI can include cognitive decline, behavioural changes, neurodegenerative disease processes, motor deficits, somnolence, hormonal dysfunction, increased risk of seizures and sensory disturbances[5][6][7][8]. Cognitive impairments after TBI can include disturbances of attention, memory and executive function, resulting in reduced global cognition, naming, incidental memory, immediate memory, learning and delayed recall[9][10][11][12][13].

In this systematic review, we focus on whether an Alzheimer's disease (AD) medication, memantine hydrochloride (memantine), produces benefits in TBI patients. TBI can be divided into three major categories: (i) closed head; (ii) penetrating; and (iii) explosive blast TBI[14][15]. Closed head TBI typically occurs after blunt impact incurred through motor vehicle accidents, falls and sporting activities and leads to immediate damage of the brain vasculature and neurons. Penetrating TBI results from foreign body penetration of the skull and brain parenchyma causing focal damage, intracranial haemorrhage, edema and ischemia[14][15]. Explosive blast TBI however, is prevalent in war-related casualties and compromises brain tissues due to the rapid pressure shock waves generated from explosions leading to widespread diffuse damage such as neuronal death, axonal injury, compromised blood–brain barrier and edema[14][15].

Excitotoxicity and apoptosis are two mechanisms of neuronal cell death that occur in TBI, with the N-methyl-D-aspartate (NMDA)-type glutamate receptors implicated in both mechanisms[16][17][18][19][20][21][22]. With moderate hyperactivity of glutamate receptors, there is an excessive influx of calcium (Ca^{2+}) which leads to apoptosis (programmed cell death)[16][17]. Whereas, in excitotoxicity, there is a massive release of glutamate resulting in the loss of Mg^{2+} within the glutamate receptor's ion channel[15]. Without the regulating effect of Mg^{2+}, there is an influx of calcium and sodium, which causes the neuronal cells to depolarize, swell and lyse (necrosis)[16][17]. With necrosis, there is a release of cellular contents that leads to neighbouring neuronal dysfunction or neuronal cell death by excitotoxicity. Neuronal dysfunction occurs secondary to ischemia caused by the increased energy demands needed to maintain ion gradients[16][17]. Similarly, activation of NMDA receptors by glutamate promotes the production of reactive oxygen species (ROS) and nitric oxide (NO) which further exacerbate secondary cell injury[17][18][19]. Memantine blocks excessive activation of NMDA-type glutamate receptors (NMDAR) since it is an uncompetitive open channel blocker which binds in the region of Mg^{2+}, but has a higher affinity than Mg^{2+}[17][18][19][20][21][22]. In normal physiological states, the NMDA-type glutamate receptor is not open long enough to allow memantine to accumulate in its active site. Being an uncompetitive antagonist, memantine's efficacy increases as the concentration of glutamate increases[17][18][19][20][21][22].

Memantine was not only neuroprotective in animal models of cerebral and spinal cord ischemia but also in models of TBI[23][24][25][26][27][28][29][30][31]. Studies have also shown that blocking NMDAR function with antagonists such as amantadine, improve cognitive outcomes after mild TBI[32][33]. Hence, randomized control trials (RCTs) have been carried out to assess whether memantine has similar benefits in patients with TBI.

2. Effects of Memantine in Patients with Traumatic Brain Injury

we identified four RCTs that met our inclusion/exclusion criteria related to the use of memantine in TBI and its potential benefits on outcomes, including cognitive functions. Due to the heterogeneity within studies related to parameters including the timing of TBI to treatment and the inclusion of all forms of TBI, meta-analysis was deemed not possible and hence the four RCTs were qualitatively analysed. Our results demonstrate that in TBI, one study reported reduced serum NSE levels by day 7 and marked improvements in their GCS scores on day 3 of the study. In addition, only one study demonstrated significant improvements in cognitive outcomes across 26 standardized tests for cognitive performance, whilst two studies demonstrated that patients in the memantine group underperformed in all cognitive tests.

Across the RCTs, there were 28 outcome measures, which assessed the severity of TBI, the extent of neuronal damage, memory, cognitive flexibility, information processing, attention, conceptualization, initiation, perseverance, praxis, impulse control, depression and anger. A single RCT by Mokhtari et al.[34] presented the neuroprotective effects of memantine in TBI patients with a significant reduction of NSE and significant day to day improvement in the Glasgow Coma Scale (GCS). NSE is a commonly used as a biomarker of TBI since NSE is abundant in neuronal tissues, and structural damage of these cells cause NSE leakage into the extracellular space and into the bloodstream[35][36][37]. Elevated NSE levels indicate the degree of brain cell damage and correlate with unfavourable outcomes and clinical complications in neuro-intensive care units[38][39][40][41][42][43][44]. However, NSE levels are not 100% specific since extracranial tissues can also contribute to total serum levels if the patient suffers from severe multi-trauma or even haemolysis[45][46]. Although NSE levels correlate with mild cognitive impairment in conditions such as diabetic retinopathy and post-operative cognitive dysfunction after cardiac surgery[47][48], no relationship to NSE levels and cognitive decline have been reported in TBI[49].

The severity of TBI is defined by the duration of loss of consciousness (LOC), altered mental state (i.e., confusion) or post-traumatic amnesia (PTA) and graded according to the GCS[50]. GCS is a 3- to 15-point scale used to assess the level of consciousness and neurological functioning and is scored on motor, verbal and eye-opening responses. In a recent study, moderate TBI patients with an initial GCS score of 9–10 exhibited greater cognitive dysfunction, compared to those with GCS scores of 11–12[51]. Cognitive outcomes from TBI not only depend on duration of LOC and PTA but also on the degree of diffuse axonal injury, as well as evidence of brain stem dysfunction at the time of injury and the presence and size of focal hemispheric injury[52]. Since memantine increased GCS scores and higher GCS scores relate to improved LOC, an indirect effect of memantine on cognitive dysfunction may be surmised. Hence, increasing initial GCS score may reduce cognitive decline in TBI patients. Despite the fact that the study by Mokhtari et al.[34] was underpowered, the *p*-value for the reduction in serum NSE in the therapeutic arm was low ($p = 0.009$), which is promising. This study did not follow up participants after their trial period which was only 7 days, so it is difficult to establish whether NSE levels would remain lower in the treated group and whether positive effects on increasing GCS would be sustained. Furthermore, no placebo was used in the control group and so a large multicentre trial, using placebo in the comparative arm would be beneficial to confirm these findings.

All assessments demonstrating significant improvements in cognitive function were from a single RCT by Litvinenko et al.[53], the source of funding for which was not declared. Two other RCTs were carried out in America looking into cognitive improvements in TBI patients from memantine, both these studies used placebos in the control group and employed double/triple blinding. One of these RCTs, was funded by a pharmaceutical company which produced and sold memantine[54]. However, both American RCTs[54][55] did not show significant improvements in cognitive function in the memantine groups. Although the American RCTs had a superior study design, they also had less than half the sample size than in the RCT by Litvinenko et al.[53]. Clearly, this is an area where further well-controlled, suitably powered studies are required to clear up these discrepancies.

The exact dose of memantine varied slightly across the studies assessing cognitive function[53][54][55]. For the most part, all three RCTs used a total daily dose of 20 mg of memantine in their therapeutic arm, with 2 of the RCTs titrating to 10 mg twice daily as the dose and frequency of choice. One study used 20 mg twice daily for 19 of the 168 days of the treatment course[55]. Across the RCTs, there was no mention of improvements in cognitive function associated with as higher dose of memantine. The available raw data did not measure for the effect of dose of memantine/placebo effects on cognitive function.

The duration of therapy varied from 7 to 168 days across the 4 RCTs. RCTs employing a longer course of memantine therapy did not report significant improvement in cognitive function, and across most outcome measures, cognitive function scores were lower in assessments taken closer to the end of the drug course. Duration from injury also ranged from 48 h to 20 years amongst RCTs assessing cognitive function, with no clear benefit demonstrated when treatment

with memantine was started earlier following TBI. Although in the RCT where TBI patients were treated within 48 h from the onset of TBI, only severe TBI patients were included. It is entirely possible that within this patient population there was little scope for improvements to occur.

The severity of TBI requirements across included RCT differed vastly, with the first RCT including only moderate TBI patients, the second RCT including all three severities, the third RCT excluding severe TBI patients and the final RCT selecting for severe TBI patients only. Clearly, different severities of TBI would affect the severity of cognitive decline and also the potential to recover. Closed (non-penetrating) versus open (penetrating) head injuries will also necessitate different interventions and treatments as well as different time points for intervention and hence a mixture of these patients in RCTs may confound eventual outcomes. In addition, the time from TBI event to treatment will also significantly affect the potential benefits of treatment. For example, memantine might be more effective in the acute stages after TBI in inhibiting current flow through the NMDA receptor, as a result of excessive activation by e.g., glutamate, whilst in chronic stages, memantine may not have any effects since glutamate levels may be lower. Memantine may contribute to cognitive improvements in TBI by decreasing the synaptic 'noise' resulting from excessive NMDA receptor activation[56], inhibition of β-amyloid mediated toxicity[57][58][59][60] and readjustment of the balance between inhibition and excitation on neuronal networks in the CNS. Moreover, 2 of the studies used some cognitive tests that were common to both studies[54][55] whilst the study reporting improvements in cognitive function used different cognitive tests[53]. This presents problems in comparing the apparent recovery as each test measures different types of cognitive functions. It is possible that memantine positively affected performance in the cognitive tests used by Litvinenko et al.[53] but had no effect on those used by Rupright and Johnstone[54] and Hamond[55]. Future trials assessing cognitive improvement in TBI patients would need to consider all of these important points as well as benefit from using standardized and sensitive tools for assessing cognitive outcomes after TBI.

Groups receiving memantine were reported to have exclusively had the following adverse events across RCTs reporting these events; nausea, vomiting, hematuria and dehydration. Since the target population is the same across included RCTs, several adverse events were common between both the therapeutic and control arms. These include: respiratory tract infections, neurostorming, headaches, insomnia, depression and anxiety. There is no significant difference in the frequency of those adverse events common to both the therapeutic and control arms of reviewed RCTs. This is a potential indicator that memantine has not inferred protection to TBI patients in the various therapeutic arms, although it is noted that the total number of participants enrolled in the trials were too few to draw concrete conclusions.

Limitations

The leading limitation of this article is that there was an inadequate number of RCTs (only 4 studies) and all RCTs included small sample sizes, rendering them underpowered. None of the articles reported alpha values, presumably for the reason that their sample sizes were too small. For this reason, a meta-analysis was not possible. Other limitations included variable time frames from TBI to treatment (48 h to 20+ years), differing severities of TBI (mild, moderate or severe) were often grouped together, demographic data when provided did not relate to the participants from whom results were generated and RCTs assessing cognitive function used different outcome measures that prevented meta-analysis from being carried out. In the future, investigators should pay more attention to performing high-quality, adequately-powered RCTs to test the effectiveness of memantine in TBI outcomes.

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