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Original article

Role of bromocriptine in multi-spectral manifestations of traumatic brain injury

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ABSTRACT

Purpose: Despite the prevalence and cost of traumatic brain injury related disabilities, there is paucity in the literature on modern approaches to pharmacotherapy. Medications may promote recovery by enhancing some neurological functions without impacting others. Herein we discussed the role of bromocriptine in neurorehabilitation for patients with traumatic brain injury.

Methods: A cohort comprising of 36 selective nonsurgical cases of traumatic brain injury in minimally conscious state were enrolled in the study. After hemodynamic stability, bromocriptine was given at paediatric dose of 3.75 mg/d and adult dose of 7.5 mg/d. It was administered through a naso-gastric (NG) feeding tube in the patients with minimally conscious state, then changed to oral route after proper swallowing and good gag reflex were ensured in the patient. The drug was slowly reduced over three weeks after neurological improvement in the patients. Positive result was determined by improved GCS score of 2 and motor power by at least 1 British Medical Council (BMC) motor score. Improvement of deficits was evaluated in terms of fluency of speech for aphasia, task switching, digit span double tasking and trail-making test for cognition and attention, and functional independence measure score for motor functioning and self-independence.

Results: Accelerated arousal was seen in 47.0% of cases (8/17) in 4–40 days. In 41.2% of cases (7/17), Glasgow outcome score (GOS) was improved to 4/5 in 90 days. Improvement in hemiparesis by at least 1 BMC score was seen in 55.6% of cases (5/9) in 40 days. Aphasia was improved in 80% of cases (4/5) in 7–30 days. Moderate improvement in cognitive impairment was seen in 66.7% of cases (2/3) in 14–20 days. Improvement in memory was observed in 50% of cases (1/2) in over 30 days. No cases were withdrawn from the study because of adverse reactions of the drug. There was no mortality in the study group.

Conclusion: Bromocriptine improves neurological sequelae of traumatic brain injury as well as the overall outcome in the patients. If medication is given to promote recovery and treat its associated disabilities, clinicians should thoroughly outline the goals and closely monitor adverse effects.

Introduction

Traumatic brain injury (TBI) is a critical health concern and global socio-economic burden. It is a major cause of death, especially in young adults, leading to multi-spectral disabilities among the survivors.[1] TBI can hinder quality of life in numerous ways, thereby incapacitating interpersonal, social and occupational functioning of victims. It also has negative impact on families and the economy of a nation. TBI is termed as a silent epidemic.[2]

With new armamentarium and advances in the neurocritical care, an increasing number of patients with head injuries are surviving, but with major residual neurological impairments. The situation gets even worse in developing countries where one can hardly find trauma rehabilitation centres and only a few patients can have access to these centres, which are located in the capital cities only. Therefore, they are becoming an abandoned subset of population, laying uncomfortably in their beds or wheelchairs and receiving minimal basic supports.

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It is high time to understand the pathogenesis of chronic disability following TBI and develop new strategies assisting in speedy recovery. Though substantial progress has been made, considerable work still needs to be done. Herein we discussed the role of bromocriptine as an imperative means to provide rehabilitation in patients with TBI.

Materials and methods

We enrolled 36 TBI patients admitted in the Department of Neurosurgery, College of Medical Sciences, Bharatpur, Nepal from December 2013 to May 2015 in the study. The study was approved by the board of institutional ethical committee. Both written and verbal consent were taken from the patients and their relatives regarding the initiation of drug therapy following detailed counselling. Adverse events during the treatment course were noted.

Inclusion criteria were as follow: (1) TBI patients were in a minimally conscious state with no indications for surgical intervention; (2) all patients were hemodynamically stable with normal electrolytes and endocrine function; (3) written consent was obtained from the patients and their relatives.

Exclusion criteria were as follow: (1) pure surgical lesions; (2) significant polytrauma; (3) sepsis; (4) medical sequela of TBI such as deep vein thrombosis and pulmonary embolism; (5) traumatic spinal cord injuries; (6) autonomic dysregulation (dysautonomia); (7) active seizure; (8) cardiovascular instability; (9) electrolyte imbalance; (10) endocrinopathies; (11) coagulopathy.

Clinical evaluation of Glasgow coma scale (GCS) and neurological examination for any focal neurological deficits (FNDs) were daily charted in the intensive care unit (ICU) via the resident doctor and counterchecked by the consultant on duty. The drug dosage was modified with regards to the clinical improvement in the patients from 2.5 to 20 mg daily in divided doses.

After hemodynamic stability, bromocriptine was given at paediatric dose of 3.75 mg/d and adult dose of 7.5 mg/d. It was administered through a naso-gastric (NG) feeding tube in the patients with minimally conscious state. It was changed to oral route (from NG route) once proper swallowing and good gag reflex were ensured in the patients. The drug was slowly reduced over three weeks after neurological improvement in the patients.

Responses were charted and tallied daily for the first 2 weeks on the basis of GCS and FNDs. Positive result was determined by improved GCS score of 2 and motor power by at least 1 British Medical Council (BMC) motor score. Improvements of deficits were evaluated in outpatient clinic in the 1st, 3rd and 6th months with regards to speech fluency for aphasia, task switching, digit span double tasking and trail-making test for assessment of improvement in cognition and attention, and functional independence measure (FIM) score for motor functioning and self-independence.

Results

Age group

Adults compromised of 33 (91.7%) of the study group whereas only 3 (8.3%) were in the paediatric age group.

Severity of injury

There were moderate head injury in 72.20% of the patients, severe head injury in 22.20% and mild head injury in 5.60%, respectively.

Diagnosis

Most of the patients in our study had diffuse axonal injury (60%), followed by contusions in 30% and hypoxic brain injury in 10%.

Neurological deficits

Among the study group, no arousal was seen in 47.20% of patients followed by hemiparesis in 25.00%, aphasia in 13.90%, cognitive impairment in 8.30%, and memory impairment in 5.60%, respectively.

Morbidity improvement

Accelerated arousal was seen in 47.0% of cases (8/17) in 4–40 days. In 41.2% of cases (7/17), Glasgow outcome score (GOS) was improved to 4/5 in 90 days. Improvement in hemiparesis by at least 1 BMC score was seen in 55.6% of cases (5/9) in 40 days. Aphasia was improved in 80% of cases (4/5) in 7–30 days. Moderate improvement in cognitive impairment was seen in 66.7% of cases (2/3) in 14–20 days. Improvement in memory was observed in 50% of cases (1/2) in over 30 days. No cases were withdrawn from the study because of adverse reactions of the drug. There was no mortality in the study group. The different deficits and the overall improvements during the 6-month follow-up are shown in Fig. 1.

Discussion

Despite the prevalence and economical burden of TBI-related disabilities, there is paucity in studies which provide new insight into pharmacological rehabilitation. There is growing evidence that medications may speed up recovery through modulations in neurotransmitters on the central nervous system.

The main aim of neuro-pharmacological rehabilitation is to assist in transition from disability to full neurological recovery.[3] Neuro-stimulation can specifically modify and enhance neural transmission via increasing neurotransmitters in the synaptic junctions.[4–10] The spectrum of gains ascribed includes enhanced arousal, wakefulness, awareness as well as improvement in attention, memory, mental and motor processing.[3,4]

Many studies have verified the implication of dopamine in TBI. Dopamine has a significant role in the cognitive processing, attention and memory functions.[11] It also modulates motivation and sleep–wake cycle.[12] Anoxia associated with TBI alters dopaminergic pathways in the mesencephalon, which activates the striatal and medio-basal frontal cortex, and these disorders could be partially improved after drugs activate the dopaminergic pathway.[13] In a double-blinded placebo controlled study, McDowell

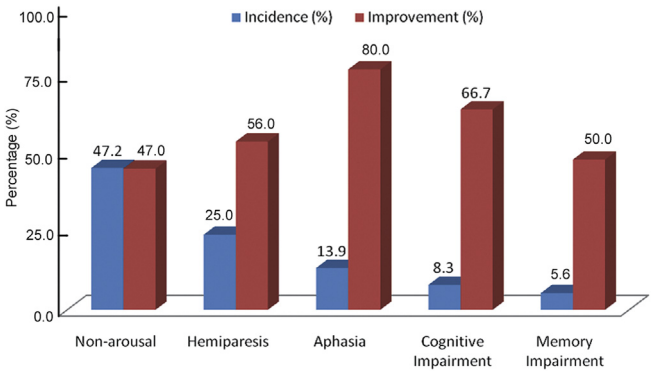

Fig. 1. The incidence of different deficits and overall improvement of traumatic brain injury patients during the follow-up.

et al[14] found significant improvement in executive functioning of their patients after drug therapy, which activated dopaminergic pathways. In a study by Whyte et al,[15] most of the patients in their study cohort had to be withdrawn following moderate to severe drug reaction. None of the patients in our group had to be withdrawn because of side effects of the drug.

Most of the studies in humans were performed in well-selected small groups, thus they served as a proof-of-principle study only. To date, there is only limited evidence supporting drugs for neurorehabilitation.

There are a few limitations in our study. First is the relatively small size of our cohort study. Secondly, there is confounding bias from associated factors such as hypoxia, hypotension and associated medical co-morbidities in the patients. Plasticity of the brain, especially in children, also has a significant impact on the outcome of patients with head injury.

In rural countries like ours, there is a significant time delay in the transfer of patients to a proper neurosurgical centre. The prehospital basic management in such patients is also dismal. These may produce significant prognostic effect on the outcome of patients. We thereby included the patients who were hemodynamically stable. We also needed to have in-depth knowledge on the natural development of diffuse axonal and hypoxic brain injuries. A multi-centric randomized controlled trial with large sample size and long-term follow-up is needed to assess the efficacy of similar neuro-stimulants in patients with TBI. It will provide insights into current pharmacological rehabilitation in management of such patients.

Bromocriptine enhances the arousal of TBI cases and improves neurological sequelae of TBI as well as the overall outcome. If medication is given to promote TBI recovery and treat its associated disabilities, clinicians should thoroughly outline the goals and closely monitor adverse effects. Further research is undoubtedly needed to solve this problem.

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