Baclofen in the Therapeutic of Sequele of Traumatic Brain Injury: Spasticity

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Abstract: Traumatic brain injury (TBI) is an alteration in brain function, caused by an external force, which may be a hit on the skull, rapid acceleration or deceleration, penetration of an object, or shock waves from an explosion. Traumatic brain injury is a major cause of morbidity and mortality worldwide, with a high prevalence rate in pediatric patients, in which treatment options are still limited, not available at present neuroprotective drugs. Although the therapeutic management of these patients is varied and dependent on the severity of the injury, general techniques of drug types are handled, as well as physical and surgical. Baclofen is a muscle relaxant used to treat spasticity and improve mobility in patients with spinal cord injuries, relieving pain and muscle stiffness. Pharmacological support with baclofen is contradictory, because disruption of its oral administration may cause increased muscle tone syndrome and muscle spasm, prolonged seizures, hyperthermia, dysesthesia, hallucinations, or even multisystem organ failure. Combined treatments must consider the pathophysiology of broader alterations than only excitation/inhibition context, allowing the patient's reintegration with the greatest functionality.

Key Words: baclofen, spasticity, traumatic brain injury

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Traumatic Brain Injury

Traumatic brain injury (TBI) is an alteration in brain function or other evidence of brain pathology caused by an external force, which may be a direct hit on the skull, rapid acceleration or deceleration, penetration of an object (firearm), or shock waves from an explosion.[1] The nature, intensity, direction, and duration of this force determine the pattern and severity of injury.[2]

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Traumatic brain injury is one of the major health and socioeconomic problems worldwide, ranking the fourth leading cause of death and the second cause of disability among young individuals.[3]

Clinical and Pathologic Characteristics

Traumatic brain injury can be classified into the following 3 types according to damage intensity: mild, moderate, and severe. The classification is made taking into account the level of consciousness measured according to the Glasgow Coma Scale (GCS).[4] The GSC evaluates the following 3 independent responses: visual, verbal, and motor. The clinical picture presented that the patient will depend on the intensity of the TBI.

In TBI, the following 2 types of lesions can be distinguished:

A. Primary lesion, which occurs at the moment of impact, is not reversible, including the tearing of white matter pathways, focal contusion (intracerebral and extracerebral) hematomas, and diffuse edema; the early events of neurotrauma at the cellular level include microporation of plasma membrane, ion channel mismatch, and protein conformational changes, and in the highest levels of damage, ripped blood vessels can be found, which may cause ischemic damage and cerebral microbleeds, which can be extended or more commonly perilesional.[2]

B. Secondary injury, which corresponds to late effects, is a potentially reversible process, through appropriate therapy.[5] It involves functional, structural, cellular, and molecular changes that cause neuronal damage, including neurotransmitter release, generation of free radicals, damage mediated by the influx of Ca^{2+} into neurons, gene activation, mitochondrial dysfunction, and inflammatory response.[2] Furthermore, ischemia causes decrease in O_2 and nutrients input, as well as the output of potentially toxic metabolites, and leads to biochemical changes in the brain affected area.[5]

In these lesions, there is a depletion of glucose and glycogen, failure of the Na^+/K^+-ATPase and other pumps, lowering the excitation threshold, increases the frequency of action potentials, release of excitatory neurotransmitters such as glutamate, massive influx of Ca^{2+}, activation of proteases, lipases, nitric oxide, and other enzymes,[5] and finally necrosis and/or apoptosis; however, neuroprotection responses, for example, the GABAergic pathways, are activated.[6,7]

Sequelae and Complications

The clinical consequences that can produce the TBI are diverse and depend on many factors. In first place, factors related to the injury are the following: (*a*) mechanism of injury (traffic incidents, falls, gunshot injuries); (*b*) severity of injury (mild, moderate, or severe according to GCS); (*c*) the type of brain injury (focal, multifocal, or diffuse); and (*d*) the topography and extent of the injury (frontal, temporal, brainstem). In second place, the individual-related factors are the following: age, education level, previous cognitive status, history of substance abuse, or comorbidities.[8,9] Clinical complications are highly variable from patient to patient; however, they can be grouped as the following: (1) motor (paresis, disorders of muscle

tone, amyotrophy, spasticity); (2) sensory (hypoesthesia, dysesthesia, neuropathic pain); (3) speech and swallowing disturbances (aphasia, dysphagia); (4) cognitive (posttraumatic amnesia, attention problems); (5) behavioral and neuropsychiatric symptoms (agitation, depression, impulsivity); (6) autonomic and neuroendocrine disorders; (7) balance and coordination problems (dizziness, ataxia); (8) sleep disorders (insomnia, sleep apnea) and other related complications. All these manifestations contribute in some extent to TBI-related disability.[8,9]

Clinical Sequelae in Patients With Mild TBI

Although the clinical sequelae of TBI are highly variable and depend on many factors, undoubtedly, one of the most important factors is the severity of the injury. Mild TBI is often defined as patient with a GCS score of 13 to 15 points assessed at 30 minutes after injury. Sometimes, the term brain concussion is used interchangeably to refer to a mild TBI; however, the American Academy of Neurology defined brain concussion as a trauma that produces a transient mental status changes (usually mental confusion) with or without loss of conscience, which resolve spontaneously and completely in few minutes.[10] In mild TBI, a stereotyped clinical picture that has been called postconcussion syndrome is observed, which includes cognitive disorders (problems with attention, short-term memory), headache, dizziness, sleep disturbances, irritability, depression, anxiety, and fatigue.[9] For example, in a recent study of patients with postconcussion syndrome, the most common symptom was headache (27%), followed by insomnia (18%), fatigue (17%), short-term memory disturbances (16%), and dizziness (16%).[11]

Motor Sequelae in Moderate to Severe TBI (Spasticity)

One of the most prevalent and disabling sequelae of TBI is motor disturbances, although the most obvious manifestation of these motor sequelae is the decreased muscle strength in any body segment (paresis or plegia); one of the most common complications is disorder of muscle tone. Spasticity in TBI is estimated to be between 17% and 50% of patients with moderate to severe TBI that presents increased muscle tone or spasticity.[12,13]

Spasticity is a disorder of sensorimotor control of spinal reflexes that results from injury to the central or upper motor neurons of the pyramidal tract. Upper motor neuron syndrome usually includes negative signs, such as muscle weakness or loss of motor dexterity, and positive signs, which are characterized by muscle hyperactivity; the spasticity is one of these manifestations but also includes increased muscle stretch reflexes, clonus, and flexor spasms.[14]

Spasticity is defined as the speed-dependent increase of the resistance to movement in response to tonic muscle stretching. This can result from injury to different levels along the corticospinal tract (pyramidal). This includes the motor cortex, internal capsule, brainstem, or spinal cord. Although it is commonly thought that spasticity is a result of direct injury of upper motor neurons or its axons, the anatomical and functional studies have shown that this disturbance is more related to interruption of the spinal reflexes control pathways, known collectively as "parapyramidal" tracts. Those pathways are classified into (1) inhibitory pathways, of which the most important is the dorsal reticulospinal tract, which has its origin in the ventromedial reticular formation, and (2) the excitatory pathways, of which the most important is the medial reticulospinal tract and the vestibulospinal tract (Fig. 1). Because these modulating pathways run through different anatomical locations, this creates the possibility of brain damage affecting 1 pathway and not

another, generating different patterns of involvement and severity of spasticity.[14]

However, the interruption of these regulatory pathways of the spinal reflexes can explain much of the pathophysiology of spasticity; in addition, it has been proposed that other mechanisms, such as hyperactivity of the cells of muscle spindles, hyperactivity of spinal motor neurons, segmental spinal interneurons hyperactivity, and even changes in the viscoelastic properties of muscles are also involved.[15]

In clinical practice, the relevance of spasticity is related to the negative effects that may produce in the patient. It can produce from mild discomfort to the presence of very painful spasms or dystonic movements, decreasing the patient mobility, inducing abnormal postures, and may favor the occurrence of deformities, muscle contractures, or pressure sores, hampering self-care activities, and interfering with bladder and bowel care, as well as with sexual function.[16] To clinically evaluate and measure spasticity and its repercussions, several methods have used and include the following: (1) physiological assessments, which involve parameters obtained by clinical electrophysiological studies as Hmax/Mmax ratio, the vibratory inhibitory ratio; (2) assessments based on passive activity, of which the most commonly used are the modified Ashworth scale and Tardieu scale; (3) assessments based on voluntary activity, as the Fugl-Meyer scale or analysis of spatiotemporal gait parameters; and (4) functional assessments, through the application of different scales such as the Functional Independence Measure and the Barthel Index among others.[17]

Therapeutically Strategies in the Treatment of Clinical Sequelae of TBI (Spasticity)

Currently, TBI is a major cause of morbidity and mortality worldwide, with a high prevalence rate in pediatric patients, where treatment options are still limited, not available at present neuroprotective drugs.[18] Although the therapeutic management of these patients is varied and dependent on the severity of the injury, general techniques of drug types are handled (Table 1), as well as physical and surgical.[18–21] The sequelae of TBI can manifest in different ways and produce a wide range of cognitive, behavioral, emotional, and sensorimotor alterations, and one of these consequences is spasticity, which is an integral therapeutic protocols addressing from physiotherapy techniques and the use of various drugs (Table 2).[22,23]

Using Baclofen in the Treatment of Spasticity After TBI

Baclofen Background

Baclofen is a muscle-relaxant agent used to treat spasticity and improve mobility in patients with spinal cord injuries, relieving pain and muscle stiffness.[54] This drug produces its effects through supraspinal level $GABA_B$ receptor activation, acting at the spinal cord level, blocking pathways polysynaptic and monosynaptic afferent transmission, and thus inhibits the transmission of impulses through these channels acting as a neurotransmitter inhibiting or inducing hyperpolarization primary nerve terminals, which alters the release of excitatory neurotransmitters such as glutamate or aspartate.[54] Disruption of the oral administration of baclofen or baclofen intrathecal therapy may cause withdrawal, increased muscle tone syndrome and muscle spasm, prolonged seizures, hyperthermia, dysesthesia, and hallucinations and may eventually cause rhabdomyolysis and multisystem organ failure.[55]
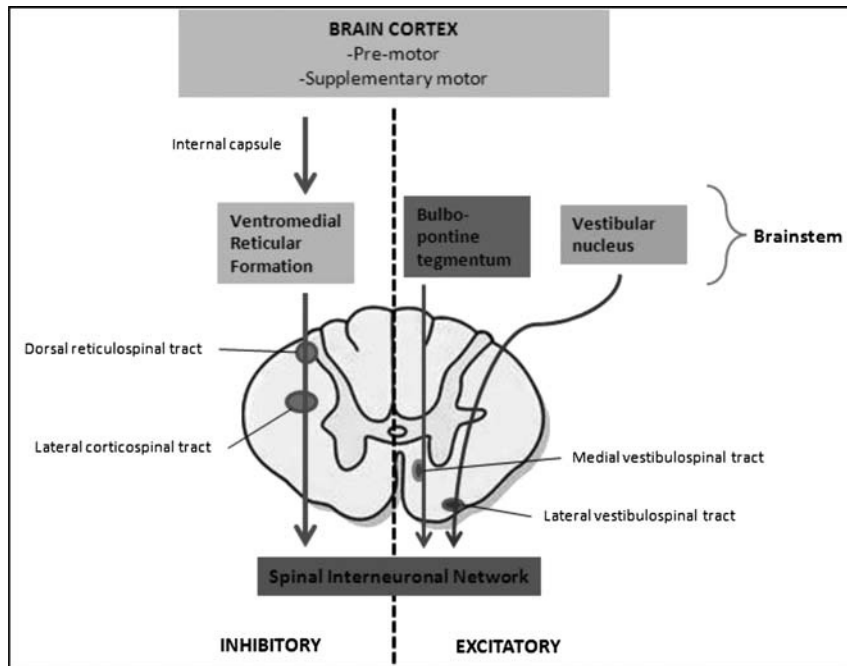
FIGURE 1. Schematic diagram of major excitatory and inhibitory pathways of the spinal reflexes.[14]

Therapeutical Effects of Baclofen in the Treatment of Spasticity

Pharmacological support with baclofen generates controversial results, which are summarized in Table 3.

New Drugs in the Management of Spasticity

Most currently available drugs for the pharmacological treatment of spasticity are focused on GABAergic (baclofen, diazepam, tetrazepan, gabapentin) or adrenergic receptors (tizanidine,

TABLE 1. Main Therapeutic Strategies for Handling TBI[20]

Therapeutical Strategy		Recommendation
DFH	Prophylaxis of seizures	Prophylactic treatment with DFH can be considered to reduce the risk of early seizures in pediatric patients with severe TBI.
Barbiturics	Treatment of intracranial hypertension	Treatment with high doses of barbiturates is considered to manage refractory to medical and surgical management in hemodynamically stable pediatric patients with intracranial hypertension in severe TBI.
Decompressive craniectomy	Treatment of refractoriness intracranial hypertension	Decompressive craniectomy with dural surgery can be considered for the treatment of intracranial hypertension refractory to medical management in pediatric patients with treatment in early stages of handling.
Cerebrospinal fluid drainage	Treatment of intracranial hypertension	The drainage of cerebrospinal fluid via an external ventricular drainage device may be considered for the treatment of intracranial hypertension in pediatric patients with TBI.
Steroids	Treatment of intracranial hypertension	Cortico steroid use has not shown improvement in outcome or reduction of intracranial hypertension in pediatric patients with treatment.
Hyperventilation	Treatment of intracranial hypertension	Avoid hyperventilation $P_{CO_2} < 30$ mm Hg should be considered in the first 48-h posttrauma. If hyperventilation is used as a treatment for refractory intracranial hypertension, you should consider neuromonitorization to avoid ischemia.
Analgesics, sedatives, and neuromuscular blockers	Treatment of intracranial hypertension	Etomidate, thiopental sedation, may be considered for control of severe intracranial hypertension. The use of continuous infusion propofol as sedation and/or treatment of severe intracranial hypertension is NOT recommended.
Temperature control	Treatment of intracranial hypertension	Moderate hypothermia (32°C–34°C) used within the first 8 h posttrauma treatment of intracranial hypertension should be considered in pediatric patients with TBI.
Hyperosmolar therapy (3% NaCl hypertonic solution)	Treatment of intracranial hypertension	The use of hypertonic solution NaCl 3% should be considered as treatment of intracranial hypertension in pediatric patients with trauma. Effective doses are in range of 6.5 to 10 mL/kg per d and infusions of 0.1 to 1 mL/kg per h.

Diphenylhydantoin indicates DFH.

TABLE 2. Main Pharmacological Strategies for Handling Spasticity After TBI

Pharmacological Strategy	Use in Spasticity After TBI	References
Baclofen	In severe spasticity with resistance to oral drugs and/or their adverse severe effects, intrathecal baclofen is used for clinical management of muscle hypertonia of spinal and supraspinal origin.	Azouvi et al, 1996[24]; Avellino and Loeser, 2000[25]; Albright et al, 2003[26]; Boviatsis et al, 2005[27]; Francisco et al, 2006.[28]
Diazepam	Diazepam enhances the efficacy of $GABA_A$ receptor-Cl^- channels, which is beneficial for mortality and cognitive impairment after TBI. This benzodiazepine is used for enhancing movement in patients with hypertonia and spasticity and for preventing the development of brain edema in craniocerebral injury in posttraumatic period.	Wroblewski and Joseph, 1992[29]; Novikov, 1996[30]; O'Dell et al, 2000[31]; Mathew et al, 2005[32]; Gibson et al, 2010[33]; Richter et al, 2012.[34]
Tizanidine	Tizanidine is an imidazoline central α-2-adrenoceptor agonist widely used to decrease excessive muscle tone in patients with cerebral or spinal injury or cerebrovascular lesions.	Wagstaff and Bryson, 1997[35]; Groves et al, 1998[36]; Gelber et al, 2001[37]; Meythaler et al, 2001[38]; Kamen et al, 2008.[39]
Dantrolene sodium	Dantrolene sodium is used in the treatment of spasticity. This drug is a muscle relaxant that inhibits ryanodine receptor Ca^{2+} channels located on the sarcoendo plasmatic reticulum in skeletal muscle and neuronal cells. It blocks calcium-induced calcium release from intracellular Ca^{2+} stores, preventing cytosolic Ca^{2+} overload. In addition, it has been shown to have anti-inflammatory and neuroprotective properties in several models of ischemia and TBI.	Meyler et al, 1981[40]; Frandsen and Schousboe, 1991[41]; Wei and Perri, 1996[42]; Elovic, 2001[43]; Büyükokuroglu, 2002[44]; Kobayashi et al, 2005[45]; Cherednichenko et al, 2008[46]; Gwah et al, 2008.[47]
Botulinum toxin	Botulinum toxin produces a dose-related muscular weakness by blocking the release of acetylcholine at the neuromuscular junction. The toxin binds to cholinergic terminals. Then, a decrease in the frequency of acetylcholine released at the synaptic cleft causes temporary muscle paralysis. It has been used for treatment for focal spasticity, posttraumatic headache, stereotyped posturing, oropharyngeal dysphagia, and bruxism produced by TBI.	Pavesi et al, 1998[48]; Terre et al, 2008[49]; Kemp et al, 2012[50]; Kesikburun et al, 2014[51]; Schnitzler et al, 2015[52]; Yerry et al, 2015.[53]

clonidine), which usually relate to the appearance of major side effects associated with their central nervous system depression properties. However, recently, there have been proposed new therapeutic targets. One is the use of agonists of the cannabinoid receptors. Since the 1980s, they have begun to propose the use of marijuana or its active principles to treat several symptoms, such as pain, ataxia, fatigue, and spasticity in multiple sclerosis.[67] However, only recently, they have begun to know the mechanism by which cannabinoid agonists exert their effect on spasticity. In a study using a mouse model of experimental allergic encephalomyelitis to induce spasticity in knock-out mice for the CB1 receptor, demonstrating that antispastic effects of agonists of cannabinoid receptors are mediated by the CB1 receptor, it was in addition noted that this receptor is also responsible for their psychoactive effects.[68] Multiple recent clinical studies support the effectiveness of different formulations of cannabinoid receptor agonists in multiple sclerosis spasticity, which is why even the American Academy of Neurology in a systematic review concluded that oral cannabis extract and tetrahydrocannabinol can be considered as effective in spasticity management.[69] However, despite that, clinical improvement obtained with cannabinoid agonist is interesting because it has not demonstrated significant effects on more objective parameters as electrophysiological assessments or studies of cortical excitability, so the efficacy and its final mechanism of action of these drugs in spasticity are still under study.[70,71]

Furthermore, there is experimental evidence that some antagonists of excitatory amino acid receptors may have muscle-relaxant properties. Among these, one that may be more promising is the kynurenic acid (KYNA), which is a product of tryptophan catabolism by kynurenine pathway, and it is the only endogenous N-methyl-D-aspartate antagonist known.[72] In previous studies, it has been able to increase the brain concentrations of KYNA using precursors and inhibitors of excretion, which has also been associated with neuroprotective effects.[73] However, there is still concern about potential long-term toxic effects because a recent study showed that chronic administration of intrathecal KYNA caused myelin damage in the spinal cord.[74]

On the other hand, for several decades, studies have shown the involvement of glycine A receptors in the origin of spinal spasticity. Experimental studies have shown that administration of glycine agonists, glycine or D-serine, can significantly decrease the electrophysiological responses associated with spasticity; in addition, they found that the application of antagonists such as strychnine on the contrary increased the spasticity.[75] The evidence of the involvement of glycine in spasticity also is strongly supported by the phenotype showing mutant spastic mouse, which besides seizures and myoclonic jerks, they have spasticity, and has been shown that its mutation produces a selective deficiency of a glycine receptor isoform during development.[76] Recently, it has been identified and isolated several new glycine receptor modulators from marine sponges, but still, it needs to verify their effects at preclinical and clinical level in spasticity.[77] All this evidence suggests that stimulation of glycine receptors (which is proposed to increase the inhibition of spinal interneurons) may be a promising therapeutic target in the management of spasticity.

Another group of drugs that have also been tried in the management of spasticity are serotonin antagonists, particularly cyproheptadine (5HT2 antagonist), and in the 1980s and 1990s, it

TABLE 3. Evidence-Based Results With the Use of Baclofen in Spasticity After TBI

Therapeutical Strategy	Population	Main Findings	References
Intrathecal baclofen for spastic hypertonia	Patients aged between 10, 18, and 35 y with TBI	At 4 h, baclofen administered was a significant decrease in Ashworth scales both upper and lower extremities, as well as scale and spasm reflex.	Meythaler et al, 1996[56]
Intrathecal baclofen for severe spasticity	Children with severe spasticity due to TBI or heart disease	Improved muscle tone, with adverse effects in 5 children (sedation, apnea, respiratory depression, bradycardia, hypotension). Report of 2 patients' deterioration. Impairment is reported in cortical damage.	Armstrog et al, 1997[57]
Intrathecal baclofen for hypertension spastic-dystonic	Patients with TBI	Significant improvement in the Ashworth scale pretreatment (lower and upper limbs) in all patients. Significant improvement in pretreatment of spasms and reflections scale.	Meythaler et al, 1999[58]
Baclofen intratecal in TBI to prevent severe spasticity	Patients aged 10, 20, 26, and 22 y with TBI (Glasgow 3–4), and autonomic disorders and poor response to conventional treatment for spasticity	Improvement in spasticity. The monitoring showed that 3 survivors had low Ashworth score 6 mo after TBI. Autonomic disorders significantly subsided in 3 patients, but persisted spasticity in 2 of them.	Francois et al, 2001[59]
Oral baclofen for spastic hypertonia postacquired brain injury	Patients with TBI (mean age of a 27 y, with a range of 6 to 65 y)	Significant improvement in the Ashworth scale (lower limbs) in all patients. Significant improvement in the level of spasms and reflexes in patients with TBI.	Meythaler et al, 2004[60]
Application of intrathecal baclofen	Patients aged 3 to 21 y with severe spasticity	The caregiver sees improvement and recommends the use of baclofen.	Gooch et al, 2004[61]
Intrathecal baclofen for spastic hypertonia	Case series. Three men, 2 aged 41 y and 1 age 36, who suffered TBI at 20, 14, and 17 y, respectively, before being treated with intrathecal baclofen	Improvement in the modified Ashworth scale of the 3 most hypertonic muscles in the lower limbs affected after intrathecal baclofen. There was no improvement in the measurement scale-independent mobility functionality.	Francisco et al, 2007[62]
Intrathecal baclofen for spastic hemiparesis.	Patients aged 11to 64 y with unilateral, hemorrhagic, or ischemic infarction and chronic severe spastic hypertonia with 6 mo	No improvement with intrathecal baclofen administration 6 patients aggravated after application.	Kofler et al 2009[63]
GABA agonists intrathecal (baclofen) in a vegetative state	Patients aged 8–18 y	Reducing spasticity, with subsequent recovery of consciousness administration of baclofen with serious adverse effects.	Taira, 2009[64]
Intrathecal baclofen therapy delivered by a pump implanted at a very early stage in acquired brain injury	Twelve patients participated in the study, 6 were implanted 3 mo and the other 6 between 3 to 6 mo. In 3 patients, their brain injury was caused by cerebral hemorrhage. In 1 case, the diagnosis was an anoxic encephalopathy and 8 patients had suffered from a TBI. Ten were males, mean age was 36 y (range, 17–65 y) and 2 female patients aged 48 and 45 y, respectively.	Spasticity and spasm frequency, 3 mo after the implant, significantly decreased in all patients. At the 1-y follow-up, available to 5 patients, there was no change in spasticity and spasms and further improvement was detected in some patients. The total spasticity decrease for every patient before and after the implant was very high for the upper and lower extremities.	Posteraro et al, 2013[65]

TABLE 3. *(Continued)*

Therapeutical Strategy	Population	Main Findings	References
Intrathecal baclofen bolus injection in patients with resting hypertonia after acquired brain injury.	Eleven patients with TBI (age, 28 [11] y; 48 [40] mo postonset) and 8 subjects with hemorrhagic stroke (6 intracerebral, 2 subarachnoid; age, 43 [8] y; 50 [43] mo postonset).	Decrease in the frequency and gain of significant positive electromyogram-legthening velocity slope in medial gastrocnemius muscle during stance and a shorter tibialis anterior and medial gastrocnemius muscles with coactivation during the entire gait cycle, primarily in the more-affected leg and lasting at least 6 h after intrathecal baclofen bolus injection.	Chow et al 2015[66]

was used in some small groups of patients who apparently showed positive effects.[78] However, in subsequent years, the clinical studies did not spread to larger populations but has now resumed its use in the treatment of symptoms that occur after withdrawal of chronic infusion of intrathecal baclofen.[79,80] At present, different substituted cyclic amines having action as 5HT2A receptor antagonists have been patented as potential drugs in the management of spasticity, but its biological effects are still unknown.[81]

Other therapeutic targets that have recently been tested are some principles of traditional Chinese medicine, as Gancao Shaoyao glycosides; an open clinical trial apparently showed positive effects in patients with hemiplegia secondary to stroke.[82] However, the mechanism by which this improvement occurs is still under study.

Clinical Relevance and Conclusions

The impact of TBI on health systems and the economies of countries is reflected in the last 2 decades with the increase in research in this field. However, the diversity of reasons why falls, traffic accidents, violence, sports, war, etc; the wide range of pathophysiological mechanisms involved in the injuries; lack of diagnostic biomarkers; and presence of prognosis in the initial management of TBI; and the absence of a specific therapeutic clinical treatment for this condition enables the development of sequels that limit patients, impairing their quality of life.

The absence of evidence does not necessarily mean a lack of effectiveness of drug treatment in the rehabilitation of functions. Thus, it is necessary to clarify the heterogeneity of sequelae of traumatic damage and the great variability of therapeutic response to different pharmacologic agents for each patient after TBI: (*a*) identify if there is a genetic predisposition that can affect recovery from traumatic consequences and thus explain individual susceptibility to traumatic impact and personal response to drug treatment; (*b*) the study of biomarkers with diagnostic and prognostic utility in TBI, enabling timely treatment of patients, especially those who show early signs of poor prognosis, to prevent the sequelae; (*c*) perform multicenter clinical trials, double-blind, controlled group, to demonstrate the effectiveness and efficiency of drug groups used in the rehabilitation of the affected functions after TBI; (*d*) define the clinical profile of patients most likely to benefit from the indication of one or more of the various groups of drugs mentioned; and (*e*) study the safety and effectiveness of these pharmacological agents in each population and strategies for optimal dosage. In particular, spasticity is a common presenting symptom in response to damage of the pyramidal system in the brain or spinal cord; this may be secondary to head trauma, stroke, spinal cord injury, multiple sclerosis or anoxia, and other pathologies. This also determines the severity, its clinical presentation, and the choice of treatment (conservative or surgical), even the accurate mechanisms for

induction of spasticity to TBI, because it is a multidimensional and dynamic process,[83] so that early intervention to prevent, treat, and decrease is unknown, in addition to the controversy on the effectiveness of drug therapy and speech therapy, as well as the unwanted effects of current treatments. A better and deeper understanding of the mechanisms responsible for the presentation of neuroplastic changes induced TBI, tracts involved in the development of spasticity, favor the design of treatments and therapies more effective in rehabilitation, allow access to the therapeutic goal with patients: (1) improve the functionality, (2) improve the quality of life and comfort, (3) provide care and activities of daily living, (4) prevent and treat musculoskeletal complications, and (5) improve body aesthetics.[23]

Other alternative strategies for spasticity management are nonpharmacologic options such as: (1) orthopedic management (reconstructive surgery of upper extremity, soft tissue operations or bony procedures for treatment of hip deformities, and surgical correction or orthotic treatment of foot abnormalities and spine abnormalities[84–87]); (2) selective dorsal rhizothomy (surgical resection of selected dorsal roots for reduce afferent input to the spinal reflex arc and dampen the muscle elongation[88–90]); (3) stretching, fitting of splints/braces or serial casting, ultrasound and thermotherapy, neuromuscular electrical stimulation, muscle strengthening, or use of robotics to perform stretching and movement training[91,92]; and others pharmacologic treatment options such as the following: (1) local injections of phenol (≥3%) or alcohol (≥50%) that induces chemical neurolysis and performed on motor nerves, which reduces the symptoms of spasticity[93]; (2) antiepileptic drugs, such as gabapentin or pregabalin, has been used as adjunct therapies particularly when central neuropathic pain is present[94,95]; (3) immunomodulators (interferon beta and glatiramer acetate), Sativex (agonist at cannabinoid receptors) and cannabis that have been used in some countries for treatment of spasticity only in multiple sclerosis[96–100]; and (4) Zolpidem, a nonbenzodiazepine approved for the treatment of insomnia, for treatment of neurological complications (including spasticity after of hypoxic ischemic in brain injury).[101] Others alternative used in spasticity management is the administration of natural agents as the oil of *Alpinia zerumbet*, which has been used in patients with clinical diagnosis of stroke who presented spasticity. This study showed that dermal application of this oil affected skeletal spastic muscle activity, presenting relaxing action, and improves contractile performance.[102]

Future research on the treatment should be directed toward the development of new drugs that do not require invasive procedures for administration and achieve cross the blood brain barrier, with greater bioavailability and fewer adverse effects; the development of combined therapeutic considering the pathophysiology in a broader alterations with only excitation/inhibition context; and

the consideration of using treatments for acute and chronic phase that promote neuroprotection and neurodegeneration, allowing the patient's reintegration with the greatest possible functionality.

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