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Comparative study of therapeutic response to baclofen vs tolperisone in spasticity

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ABSTRACT

Background: Spasticity from the upper motor neuron syndrome can result from a variety of conditions affecting the cortex or spinal cord. Some of the more common conditions associated with spasticity include spinal cord injury, cerebral palsy, and post-stroke syndrome. In this study we compared the efficacy and safety of baclofen vs tolperisone in spasticity. One hundred fifty patients with cerebral palsy or post stroke or spinal cord injury associated spasticity were enrolled in present study. Group I comprised of Seventy-five patients receiving baclofen and group II comprised of 75 patients receiving tolperisone. For efficacy measurement 4 evaluation methods were used, 1) Modified Ashworth Scale for muscle tone, 2) Medical research council scale for muscle strength and 3) Barthel Index for functional outcome 4) Coefficient of efficacy. In efficacy evaluation, both groups showed significant improvement in muscle tone, muscle strength and functional outcome at week 6 (Group I, 1.55 ± 0.053, $2.79 + 0.032$, 59.31 ± 1.32; Group II, 1.57 ± 0.053, 3.04 ± 0.032, 73 ± 1.32 respectively). In between the group analysis, there was no significant difference in muscle tone improvement in both the groups after 6 weeks (Group I, 1.055 ± 0.053 vs Group II, 1.57 ± 0.053, $p > 0.05$). Group II showed non-significant but greater improvement in muscle strength (Week 6; Group I, 2.79 ± 0.032 vs Group II, 3.04 ± 0.032, $p > 0.07$). Improvement in functional outcomes was greater in group II as compared to group I (Group I, 59.31 ± 1.32 vs Group II, 73 ± 1.32, $p < 0.05$). Overall efficacy coefficient was greater for group II (3.6) as compared to group I (2.3). Baclofen showed more side effects compared to tolperisone in, asthenia being the most frequent. Tolperisone offers greater improvement in activities of daily living compared to baclofen. Tolperisone is more tolerable drug as compared to baclofen.

1. Introduction

Spasticity is a clinical sign of upper motor neuron dysfunction. It occurs due to defects in inhibitory descending spinal motor pathways [1]. The characteristic features of spasticity appear occurring due to hyper excitability of the stretch reflex including exaggerated tendon jerks and a velocity dependent increase in tonic stretch reflexes (muscle tone) [1]. Over 12 million patients are suffering from spasticity globally. Neurological disorders such as cerebral palsy (CP) and stroke are commonest causes of spasticity [1]. About 30% of stroke patients exhibit symptoms of spasticity which usually occurs within the first few days or weeks [2]. Approximately 90% of children with CP present with clinical symptoms of spasticity [3].

Several mechanisms are reported for spasticity. These include damage of descending inhibitory pathways and creation of new synapses by motor neurons which have lost their supraspinal innervations [4]. Depending upon the upper motor neuron signs, spasticity can be classified into positive and negative. Positive spasticity includes hyperreflexia, clonus, spasms, and postural abnormalities while loss of dexterity, loss of strength, fatigue, and pain are signs of negative spasticity. The spasticity treatment is usually focused on the positive upper motor neuron signs [5].

The aim of the treatment of spasticity is to facilitate rehabilitation, increase daily activities, prevent contractures and relieve pain. Sometimes the treatment may overshoot its goal if muscle deficit is aggravated by a too rigorous control of spasticity: in fact the maintenance of a certain level of spasticity may be beneficial in some patients in order to support near to normal posture. Since decades several treatment options have been made

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available to the patients and some new therapeutic approaches have been developed. Different *meta*-analyses have been published in an attempt to assess the efficacy of treatments in spasticity [6]. The reviews from trials showed limited evidence to assess the effects of the range of drugs used to relieve spasticity. Besides methodological limitations, this may also be explained by the low validity and reliability of the commonly used rating scales, the (daily) fluctuations of the clinical picture of spasticity and concurrent disabling deficits. This often prompted the authors of reviews to call for more research and make recommendations as to how this research should be conducted. [7].

Oral baclofen is one of the most common drug used for the treatment of spasticity on a long term basis [8]. Baclofen is a gamma aminobutyric acid receptor B (GABA-B) agonist. Despite the fact that there is wide distribution of GABA-B receptors on the spinal cord [9], baclofen preferentially binds to pre-synaptic receptors which are lower in concentrations than post-synaptic receptors and causes a decrease in release of neurotransmitters [10]. Baclofen, post synaptically acts by increasing the total persistent inward current in motoneurons as it increases more of sodium current compared to the calcium flow reduction. [11]. It has been reported that baclofen causes reduction in hyperreflexia, muscle tone and contractions of paralyzed muscles [12,13]. A reduction in spasticity benefits the patients by virtue of enhancement in carrying their daily tasks easily and decreases the dependence on others. The muscle activity reductions though suggest induction of long-term disuse effects in muscle by baclofen. Infact, it has been reported that patients with SCI or multiple sclerosis have complaints of muscle weakness and reduced voluntary functions after few weeks [14]. But, just 1 week treatment with baclofen shows positive impact on voluntary muscle strength in people with multiple sclerosis [15]. Short term and long term use of baclofen in the treatment of spasticity is unpredictable as very few trials are available to show a clear picture of this drug.

From last few years, tolperisone has presented itself as a very effective and safe muscle relaxant in all types of spasticities. It stabilizes nerve membrane and inhibits pathologic mono- and polysynaptic reflex activity in the formation reticularis and spinal cord [16,17]. Tolperisone has different pharmacological properties than other myotonolytic agents viz. absence of sedation or withdrawal phenomenon. [16–19]. Additionally, unlike other centrally acting skeletal muscle relaxants, it has no substantial affinity to cholinergic, serotonergic, dopaminergic or adrenergic receptors in the central nervous system. On the other hand, the existing dataset is indicative of a modest effect of tolperisone in the treatment of spasticity caused by neurological disorders, but it is important to note that the evidence is mainly based on the results of the Stamenova study – which only included patients with post-stroke spasticity [2,21]. For the remaining indications (rehabilitation after orthopaedic and trauma surgery, treatment of obliterate vascular diseases as well as syndromes due to impaired vascular innervation, and Little's disease and other encephalopaties accompanied by dystonia) there is extremely limited evidence of efficacy with inadequate design and include a heterogeneous population [22–24]. There are very few trials available which ensures the efficacy and safety of tolperisone. Relevant studies also exist in the locomotor indication, the majority of which failed to demonstrate the efficacy of the drug [24]. Moreover, only few studies are available evaluating the safety and efficacy profile of tolperisone in post-stroke spasticity and no reports are available for SCI and CP related spasticity [20,21].

In spite of sufficiently wide list of proposed drugs for normalization of muscular tone in the post stroke patients, there is no single opinion regarding highest efficacy of any one of them among investigators and clinical experts. For comparision of these two drugs, only one comparative trial available in international context and none in Indian context. The aim of this study is comparative evaluation of efficacy and safety of baclofen vs tolperisone in cerebral palsy, stroke and spinal cord injury patients.

2. Materials and methods

2.1. Subjects

One hundred fifty patients with spasticity due to post stroke and cerebral palsy were enrolled in the present open label parallel randomised study. We have used Simple parallel randomization design with block procedure to ensure balance between the two treatment groups. Patients were enrolled from June 2011 to Dec 2015. We have established 3 centres, 2 centres (Sparsh rehabilitation centre and Divya physiotherapy & rehabilitation) were in Ahmedabad and 1 centre in Jaipur (Institute of pain and paralysis rehabilitation centre). The study protocol was approved according to the requirements of Good Clinical Practice & Indian Council of Medical Research (ICMR) guidelines including the Declaration of Helsinki in its latest version as and by Institutional Ethics Committee of Nirma University, Ahmedabad, Gujarat. Informed consent was obtained from parents or their legal guardians, for performing the study. The subjects were enrolled into two groups randomly: group I – patient receiving baclofen and group II – patients receiving tolperisone. The major signs that collectively led to a diagnosis of spasticity included delayed motor milestones, abnormal neurologic examination and abnormal postural reactions.

2.2. Inclusion criteria

Patients with CP and stroke were eligible to participate if they had: a) Parents and legal guardians ready to provide consent for the study, b) Diplegic CP patients with lower limb muscles spasticity (medial hamstring and hip adductors muscle) c) diagnosis of severe chronic spastic hypertonia in the lower extremities (although the upper extremities could also be involved) of at least 6 months' duration d) the degree of spasticity had to be level 3 or more in most affected muscle of flexors and extensors as rated on the Ashworth Scale, e) muscle strength on medical research council scale (MRC) lesser than or equal to 2, f) functional outcomes measured on Barthal Index (BI) lesser than or equal to 50.

2.3. Exclusion criteria

Following were the exclusion criteria: a) children with CP born preterm before 37 weeks gestational age, b) any CP children with history of seizures, c) patients with severe language and cognitive deficit which made them unable to follow the instructions, d) Concomitant neurological disease, orthopaedic illness or any other disease likely to alter muscle tone, hamper motility, or influence the aim of the trial otherwise, e) hypersensitivity to tolperisone or baclofen f) women in reproductive age without safe contraception, pregnancy or lactation period, g) known or suspected alcohol or drug abuse, h) treatment with any investigational drug within the last 3 months, i) legal incapacity and/or other circumstances rendering the patient unable to understand the nature, scope, and possible consequences of the study or to cooperate, and evidence of an uncooperative attitude.

2.4. Procedure

The degree of spasticity in the most severely affected joint region (target joint) was determined at the initial visit and was assessed at all subsequent visits. In group I, the starting dose of baclofen was 5–10 mg two or three times per day, and the dosage can be increased by 5–10 mg per week. Dosing up to 80 mg per day