Effect of various anti-spastic medications on spasticity in spinal cord injury cases: An Interventional Study

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Abstract*—Spasticity following spinal cord injury (SCI) is a common symptom which negatively affects quality of life. Despite its prevalence, spasticity as a syndrome in the SCI population is not always managed effectively because it has various presentations. Different drugs are used to manage spasticity. A prospective interventional study in 20 acute spinal cord injury patients has been done to find out the effect of various anti-spastic medications like Baclofen, Diazepam, Tizanidine, Gabapentine, on spasticity and results were measured clinically on Modified Ashworth scale (MAS), Penn Spasm Frequency scale (PSFS) and Hmax/Mmax ratio. Baclofen in dose range of 15-37.5 mg/day showed highly significant reduction in mean Hmax/Mmax ratio and significant reduction in mean PSFS. Although mean MAS also showed reduction, but this was non-significant.*

Keywords: Spinal Cord Injury, Spasticity, Anti-spastic Medications.

I. INTRODUCTION

The word 'spasticity is derived from the Greek word 'spasticus', which means 'To pull' or 'To Tug'. Spasticity is defined[1] as 'Disordered sensory-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles'. In simple words, spasticity is stiffness of muscles that occurs after injury to the spinal cord or brain. Young has defined spasticity as a velocity-dependent hyperreflexia[2] while the Lance[3] defined it as 'a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon reflexes, resulting from excitability of the stretch reflex'.

Spasticity is the most common complication affecting the persons with spinal cord injury. 60% of the Stockholm Spinal Cord Injury had a spastic paresis and 40% of those, reported that their spasticity was problematic in their activities of daily living.[4] The prevalence of problematic spasticity has varied between 12% and 37% in different studies.[5-7]

The exact pathogenesis of spasticity following SCI in patients remains uncertain. The increased excitability of the stretch reflex in patients with spasticity directed research efforts toward investigating the spinal mechanisms modulating the excitability of this reflex and the potential alteration in its excitability after SCI.

Spasticity can severely impair normal daily functions such as walking, eating, dressing and all this contributes to patient disability. The therapeutic objective is to reduce the excessive muscle tone, with the aim of increasing patient's functionality and reducing discomfort.

Several anti-spastic drugs are available with various mechanisms of action, but none has been established as uniformly useful in reducing the spasticity. In addition, all drugs have potentially serious side effects. It is essential to weigh the benefit before considering starting them.

So this present study was designed to find out the effects of various anti-spastic medications on Modified Ashworth scale (MAS), Penn Spasm Frequency scale (PSFS) and Hmax/Mmax ratio.

II. METHODOLOGY

This prospective interventional study was conducted to find out the effect of various anti-spasmodic medication on spasticity in SCI cases at Department of Physical Medicine and Rehabilitation (PMR) of SMS Medical College, Jaipur (Rajasthan) India.

Study population: Study participants were SCI cases with spasticity and who complained off difficulty in performing activities of daily living, had pain or discomfort due to spasticity and had spasticity grade II or III on MAS. Patients having polytrama/ nociceptive stimulus like pressure sore, bladder stone, heterotrophic ossification etc. were excluded from study.

Thus, twenty patients with spasticity were recruited from 853 spinal cord injury patients admitted during 1st September 2004 to 30th August 2006. Spasticity was noticed in 148 (17.35%) patients, out of these 72 (8.44%) had pressure sore, 32 (3.75%) had grade I & I+ spasticity on MAS not interfering in activities of daily living, 18 (2.11%) had urinary tract infection & six ((0.7%) patients had non-recordable Hmax/Mmax ratio; and were excluded from the study.

These 20 patients were randomly divided into four drug groups i.e. Diazepam, Baclofen, Tizanidine & Gabapentin.

Clinical assessment: Neurological assessment was performed on all patients. Modified Ashworth scores[8] were obtained over knee joint because long lever arm associated with it, it is easy to monitor the effect of anti-spastic medication.

Penn Spasm frequency scale[9] was also used which is a self-report scale, which reflected the number of spontaneous sustained flexor and extensor muscle spasms per hour. The sensitivity of scale depends upon the particular patient group tested.

Hmax-to-Mmax ratio (also known as "EMG"**ratio**) is considered a suitable index for illustrating the level of reflex excitability of the motor pool, which, in turn, is dependent on the facilitation of the transmission between the Ia fibers and a-MN.[10]

Statistical analysis: Statistical analysis was done by using T-statistics with Pearson's correlation to find out the correlation between MAS, PSFS and Hmax/Mmax ratio, and to study comparative efficacy of various anti-spastic medications.

III. RESULTS

Of these 20 (2.34%) patients included in this study five (25%) patients were females and remaining 15 (75%) were males. Patients ranged in age from 17 to 55 years. The average interval between injury & study was 187 days. 12 patients in this study had cervical spine and eight patients had dorsal spine injury. Fourteen patients had complete injury (ASIA-A) and six patients had incomplete lesion (ASIA-B, C & D).

Five patients in the Diazepam group received drug in the dose range of 6-30 mg/day in three divided doses. Four out of five patients complained of sedation as side effects of the drug. Statistical analysis showed non-significant increase in mean Hmax/Mmax ratio after drug therapy. All the other parameters showed non-significant reduction in their value (Table 1).

Table 1
Effect (Mean ± SD) of Diazepam on Spasticity (N=5)

Parameters		Before Therapy	After Therapy	Mean Change	P Value LS
MAS Score	Right	3.00 ± 0.00	2.80 ± 0.400	0.20 ± 0.447	> .05 NS
	Left	3.00 ± 0.00	2.80 ± 0.400	0.20 ± 0.447	> .05 NS
PSFS Score	Right	3.80 ± 0.400	3.60 ± 0.490	0.20 ± 0.447	> .05 NS
	Left	3.80 ± 0.400	3.80 ± 0.400	0.00 ± 0.000	- -
Hmax/Mmax Ratio (%)	Right	48.90 ± 28.74	50.63 ± 28.60	1.73 ± 18.99	> .05 NS
	Left	44.33 ± 24.97	46.71 ± 26.88	2.38 ± 12.40	> .05 NS

Baclofen was given in five patients in the dose range of 15-37.5 mg/day in three divided doses. None of the patient in this group complained of any side effect of the drug. Statistical analysis showed significant reduction in mean Hmax/Mmax ratio and PSFS. Mean MAS also showed reduction, but this was non-significant (Table 2).

Table 2
Effect (Mean ± SD) of Baclofen on Spasticity (N=5)

Parameters		Before Therapy	After Therapy	Mean Change	P Value LS
MAS Score	Right	2.60 ± 0.490	2.00 ± 0.894	0.60 ± 0.548	> .05 NS
	Left	2.60 ± 0.490	2.20 ± 0.980	0.40 ± 0.548	> .05 NS
PSFS Score	Right	3.60 ± 0.800	2.60 ± 1.02	1.00 ± 0.707	**<0 .05 S**
	Left	3.60 ± 0.800	2.80 ± 0.748	0.80 ± 0.837	> .05 NS
Hmax/Mmax Ratio (%)	Right	60.22 ± 27.36	42.29 ± 29.36	17.93 ± 16.09	> .05 NS
	Left	86.50 ± 20.52	57.65 ± 20.42	28.85 ± 5.57	**<0.001 S**

Dose range in five patients in Tizanidine group was 6-30 mg/day in three divided doses. None of the five-patient complained of any side effect. Statistical analysis showed non-significant reduction in all the parameters in this group (Table 3).

Table 3
Effect (Mean ± SD) of Tizanidine on Spasticity (N=5)

Parameters		Before Therapy	After Therapy	Mean Change	P Value LS
MAS Score	Right	3.00 ± 0.00	2.25 ± 0.433	0.75 ± 0.500	> .05 NS
	Left	3.00 ± 0.00	2.50 ± 0.500	0.50 ± 0.577	> .05 NS
PSFS Score	Right	3.50 ± 0.500	3.50 ± 0.500	0.00 ± 0.00	- -
	Left	3.60 ± 0.490	3.40 ± 0.490	0.25 ± 0.500	> .05 NS
Hmax/Mmax Ratio (%)	Right	97.10 ± 62.31	80.14 ± 54.77	16.95 ± 22.48	> .05 NS
	Left	66.74 ± 33.80	51.82 ± 27.21	14.92 ± 28.52	> .05 NS

None of the five patients in Gabapentin group showed side effect of drug in the dose range of 300-1500 mg/day. Statistical analysis showed significant reduction in mean spasm scale, non-significant reduction in mean MAS & Hmax/Mmax ratio (Table 4).

Table 4
Effect (Mean ± SD) of Gabapentin on Spasticity (N=5)

Parameters		Before Therapy	After Therapy	Mean Change	P Value LS
MAS Score	Right	2.80 ± 0.400	2.40 ± 0.490	0.40 ± 0.548	> .05 NS
	Left	2.60 ± 0.490	2.00 ± 0.00	0.60 ± 0.548	> .05 NS
PSFS Score	Right	3.80 ± 0.400	3.20 ± 0.400	0.60 ± 0.547	> .05 NS
	Left	3.80 ± 0.400	3.00 ± 0.000	0.80 ± 0.447	**<0.05 S**
Hmax/Mmax Ratio (%)	Right	24.32 ± 12.22	40.19 ± 16.39	15.87 ± 23.97	> .05 NS
	Left	35.48 ± 23.35	38.78 ± 18.07	3.30 ± 34.52	> .05 NS

Correlation between clinical & electro-physiological parameters showed highly significant (P<0.01) positive correlation between Modified Ashworth Scale & Spasm Scale. All other correlations were non-significant (P>0.05) (Table 5)

Table 5
Correlation between various parameters

Parameters		Correlation (r)	P Value	Significance
MAS Score V/s PSFS Score	**Right**	+0.523	**<0.05**	**Significant**
	Left	+0.528	**<0.05**	**Significant**
MAS grade v/s Hmax/Mmax ratio	**Right**	+0.090	>0.05	NS
	Left	-0.151	>0.05	NS
Hmax/Mmax Ratio (%) v/s PSFS Scores	**Right**	-0.347	>0.05	NS
	Left	-0.351	>0.05	NS

IV. DISCUSSION

Spasticity is a major obstacle to rehabilitation of patients with spinal cord injury. It can cause discomfort, interfere with existing functions, or few additional complications. Many techniques - physical, chemical, and surgical - exist for modulation of spasticity. Prevention of nociception and establishment of an effective daily stretching program are the foundation on which all other managements are based.

In this present study, in Baclofen group none of the patient in this group complained of any side effect of the drug and drug was able to reduce spasm. It showed significant reduction in mean Hmax/Mmax ratio and PSFS. Gabapentin reduced spasticity but this group showed sedation as side effect of drug. Although Diazepam and Tizanidine also reduces spasticity but statistically it was not significant.

Present study also observed significant positive correlation (P<0.01) between Modified Ashworth Scale & Spasm Scale. All other correlation i.e. MAS with Hmax/Mmax ratio and PSFS with Hmax/Mmax ratio were non-significant (P>0.05)

Virginia Way etall[11] reported that stretch reflex activity was reduced after the administration of either tizanidine or baclofen. They observed that tizanidine had a stronger inhibitory effect on knee extensors and plantar flexors whereas baclofen had a stronger inhibitory effect on the knee flexors. So they concluded that antispastic drugs are effective in reducing stretch reflexes without substantially reducing volitional torque.

Eric Chang etall[12] concluded from their review that currently available treatment options of spasticity include oral medications and interventional procedures. Oral medications comprise centrally acting agents, such as baclofen, clonidine, and tizanidine, as well as anticonvulsants such as benzodiazepines and gabapentin and peripherally acting dantrolene. Interventional procedures include focal injections of botulinum toxin, phenol or alcohol, and an intrathecal baclofen pump

Delgado MR *et all*[13] concluded that generalized spasticity, diazepam is probably effective in reducing spasticity, Tizanidine is possibly effective.

Kheder A *et all*[14] concluded from their reviewed that management of spasticity involves identification and elimination of triggers; neurophysiotherapy; oral medications such as baclofen, tizanidine and dantrolene; focal injection of botulinum toxin, alcohol or phenol, or baclofen delivered intrathecally through a pump; and surgical resection of selected dorsal roots of the spinal cord. This article reviews the current understanding of pathophysiology, clinical features and management of spasticity.

A correlation between the scores of the MAS and the excitability of the α-motor neuron in subjects with untreated muscle spasticity. The validity of the MAS as a clinical tool for assessing muscle spasticity would be enhanced if such a correlation can be established. This is because increased α-motor neuron excitability is an important mechanism of muscle spasticity.[15] The excitability of the α-motor neuron was assessed in this study by measuring the H_{max}:M_{max} ratio and the H reflex latency. The sensitivity of these tests has been confirmed previously.[15]

Oral medications generally produce systemic side effects, so they are used in patients with diffuse spasticity. The most commonly used antispastic drugs are baclofen, benzodiazepine, Gabapentine, and tizanidine. These drugs could be used alone or in combination to obtain a desired effect and are administered orally or intrathecally.

Baclofen binds to and activates the presynaptic GABA-B receptor (i.e. acts as an agonist) on spinal cord neurons.[16] This alters potassium conductance resulting in net membrane hyper-polarization and a reduction in endogenous transmitter release.[17,18] Overall, baclofen reduces sensory and motor neuron activation.

Diazepam act as an agonist at the GABA-A receptor both presynaptically and postsynaptically and increases the opening frequency of the chloride channels thereby increasing the affinity of GABA for the receptor.[19] This decreases the polysynaptic reflexes and has muscle relaxant, sedation and antispastic effects.

Tizanidine is a central a-2 adrenergic agonist antispastic properties that shows good results in the treatment of patients with spasticity related to cerebral or spinal injury.[20] In clinical studies comparing its antispastic effects with diazepam and baclofen, tizanidine proved as effective as other antispastic drugs while offering a more favorable tolerability profile, especially in the case of debilitating muscle weakness.[21]

Although Gabapentin possesses multiple cellular mechanisms, it has been shown to inhibit presynaptic glutamate release.[22] When incorporated as an adjunct to standard pharmacological interventions, Gabapentin has the potential to help decrease the manifestations of spasticity in SCI individuals.[23]

The four drug groups i.e. Diazepam, Baclofen, Tizanidine and Gabapentin had five patients each. The number is too small to come up with any conclusion, but patients in Baclofen group had better symptomatic relief and also greater decrease in spasticity measures. Diazepam was least effective and four patients complained of sedation requiring discontinuation of drug. Gabapentin and Tizanidine were also able to give relief and were at par in effectiveness.

V. CONCLUSION

This present study concluded that Baclofen had better symptomatic relief and also greater decrease in spasticity measures. Diazepam was least effective and had sedation as side effect requiring discontinuation of drug. Gabapentin and Tizanidine were also able to give relief and were at par in effectiveness.

CONFLICT OF INTEREST

None declared till now.

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