ROLE OF DULOXETINE IN TREATMENT OF CENTRAL POST STROKE PAIN

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Abstract

Background: Pain is a common complaint following stroke, reported in 11- 55% of stroke survivors. Central Post Stroke Pain (CPSP) is a central neuropathic pain condition in which pain arises as a direct result of a cerebrovascular lesion in the central somatosensory nervous system. In this study efficacy of duloxetine in treatment of CPSP was evaluated and compared with pregabalin.

Materials and methods: This was a single center open-label clinical trial conducted in the Department of Neurology, Dhaka Medical College Hospital, from July 2012 to November 2012. Initially 193 participant were invited. Patients of CPSP were randomized to receive 60 mg/day duloxetine or 300 mg/day pregabalin. Pain score were recorded using Visual Analogue Scale (VAS) on day 0, 6th week and 12th week. Data was collected through predesigned questionnaire. Data was entered and analyzed using SPSS version 22..0.

Results: In duloxetine group, mean VAS score decreased from 6.8 ± 0.91 to 3.01± 1.12 with 12 weeks of therapy. In pregabalin group, the mean VAS score decreased from 6.99 ± 1.22 to 4.91 ± 0.82 with 12 weeks therapy . At 12 weeks, duloxetine showed statistically significant low VAS scores than pregabalin. Adverse events were reported in 17.9% of the participants. Lathergy/ somnolence (8.1%) and peripheral edema (3.4%) were commonly reported in the pregabalin group and constipation (6.9%) and orthostatic hypotension (4.6%) were commonly reported in duloxetine group.

Conclusion: In this study, duloxetine 60 mg is statistically more efficacious than pregabalin 300 mg in reducing central post stroke pain. Both duloxetine and pregabalin have a promising safety profile and well tolerated.

Key words : Central Post Stroke Pain (CPSP); Duloxetine; Pregabalin.

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Introduction

Pain is the common complaint following stroke, reported in 11-55% of stroke survivors.[1] Post stroke pain can arise from muscles, joints or viscera or from the peripheral or central nervous system.[2] The most common types of post stroke pain include hemiplegic shoulder pain, pain due to painful spasms or spasticity, post stroke headache and central post stroke pain. Patients may have several types of post stroke pain concomitantly.[3]

Central Post Stroke Pain (CPSP) is a central neuropathic pain condition in which pain arises as a direct result of a cerebrovascular lesion in the central somatosensory nervous system. Other common causes of central neuropathic pain include multiple sclerosis, spinal cord injury, syringomyelia and syringobulbia, tumors and abscesses in Central Nervous System (CNS) and other inflammatory CNS disease (e.g myelitis). Like other post stroke pain in general, CPSP has a negative effect on quality of life in stroke survivors.[4]

CPSP was first described by the French neurologist Dejerine and the Swiss- French neuropathologist Roussy in 1906 in their famous paper " Le syndrome thalamique".[5]

Treatment of CPSP is difficult owing to the limited efficacy of the available drugs and their dose-limiting side effects. Only a few double-blinded, placebo controlled trials have been published on CPSP.[6] In line with other neuropathic pain conditions, CPSP may respond to Pregabalin, amitriptyline and lamotrigine.[7] Duloxetine relieved dynamic mechanical and cold allodynia in patients with CPSP or spinal cord injury.[8] Duloxetine is a serotonin and norepinephrine reuptake inhibitor. Its mechanism of action is related to the potentiation of serotonergic and noradrenergic activity in the descending inhibitory pain pathways of the central nervous system.[9] Pregabalin belongs to the class of anticonvulsants. It reduces the release of excitatory neurotransmitters involved in pain perception by binding to presynaptic neuronal calcium channels.[10] Both Duloxetine and Pregabalin are commonly used to treat peripheral neuropathy[11]. Pregabalin shows some side effect such as vertigo and somnolence but duloxetine are relatively safe

drug.[12] Although both of these drugs are currently used in the management of CPSP in Bangladesh, to the best of our knowledge, there was no head to head comparison in between pregabalin and duloxetine in the treatment of CPSP. This study aimed to find out efficacy of duloxetine in the management of CPSP in a tertiary care hospital and compared it with pregabalin.

Materials and methods

This was a single center open-label clinical trial conducted in the Department of Neurology, Dhaka Medical College Hospital, from July 2012 to November 2012. The study was conducted in the outpatient stroke clinic after approval from Ethical review committee. Informed consent was attained from all participants.

CPSP was diagnosed by the expert neurologist through the criteria given by Klit et al.[13]

Patients of CPSP were randomized into two group. Group-A patients receive 60 mg/day duloxetine and Group-B participant receive 300 mg/day pregabalin. Pain score were recorded using Visual Analogue Scale (VAS) on day 0, 6th week and 12th week.

At the beginning of the study, 193 participant were invited. Twenty of these were not included either due to lack of consent or language barrier. The remaining 173 were randomized to Group A (n =87) and Group B (n=86). On week six, no patient was lost to follow up in group A and two were lost in group B. By the week 12 follow up, two patients had stopped taking the medication in group B due to adverse effect. Another three patients were lost follow up in group B by the week 12 and five in group A. Hence, 12 week study was completed by 161 patients- 82 in group A and 79 in group B.

Data was collected through predesigned questionnaire. Data was entered and analyzed using SPSS version 22. Appropriate statistical methods will be applied for data analysis and comparison with 95% confidence interval taking p value ≤0.05 as significant.

Inclusion criteria

- Patient with central post stroke pain diagnosed by neurologist in stroke clinic fulfilling the diagnostic criteria presented in given by Klit et al.[13]
- Patient presented minimum 6 months after the occurrence of stroke.
- Patient age in between 30 to 55 years.

Exclusion criteria

- Patient with other probable cause of hemi sensory pain e.g cervical spondylosis, Diabetes Mellitus and Hypothyroidism.
- Patient with Dementia (MMSE< 18).

Results

Table I : Mean scores of pain intensity on day 0, week 6 and week 12 in duloxetine and pregabalin group.

	VAS score change			
Group	Day 0 (Mean±SD)	Week 6 (Mean±SD)	Week 12 (Mean±SD)	Statistical analysis (p-value)
Duloxetine (n-82)	6.81 ± 0.91	5.60 ± 0.89	3.01 ± 1.12	(p <0.0001)^{s}
Pregabalin (n-79)	6.99 ± 1.12	6.01 ± 0.82	4.91 ± 0.82	

p-value < 0.05 was considered to be significant.
s =Significant.
p-value was reached from t-test.

Table I compare the intergroup pain score change in both duloxetine and pregabalin group. In duloxetine group, mean VAS score decreased from 6.8 ± 0.91 to 3.01± 1.12 with 12 weeks of therapy . In pregabalin group, the mean VAS score decreased from 6.99 ± 1.22 to 4.91 ± 0.82 with 12 weeks therapy. At 12 weeks, duloxetine showed statistically significant low VAS scores than pregabalin (p <0.0001).

Table II : Frequency of adverse events reported in both study groups.

Adverse events	Group A Duloxetine (n=87)	Group B Pregabalin (n=86)
Discontinuation due to Adverse event	none	2(2.3%)
Lethargy/Somnolence	1(1.1%)	7(8.1%)
Decreased appetite	2(2.2%)	2(2.3%)
Peripheral edema	none	3(3.4%)
Vomiting	3(3.4%)	none
Constipation	6(6.9%)	3(3.4%)
Sexual dysfunction	none	2(2.3%)
Blurred vision	1(1.1%)	none
Orthostatic hypotension	4(4.6%)	none

Table II showed adverse events were reported in 17.9% (31/173) of the participants. Lathergy/ somnolence (8.1%) and peripheral edema (3.4%) were commonly reported in the pregabalin group and constipation (6.9%) and orthostatic hypotension (4.6%) were commonly reported in duloxetine group.

Discussion

In this study, among 161 patients, there were 93% men and 68% women. The mean age was 63 ± 7 years (Range: 54-70 Yrs). Mean age of group A is 62 ± 4 years and mean age of group B is 65 ± 5 years. There are no statistically significant difference between two group in respect to age (p-value > 0.05). This sample size is in consistent with Tanenberg et al.[14]

In the duloxetine group, mean VAS score decreased from 6.8 ± 0.91 to 3.01 ± 1.12 with 12 weeks of therapy. In pregabalin group, the mean VAS score decreased from 6.99 ± 1.22 to 4.91 ± 0.82 with 12 weeks therapy. At 12 weeks, duloxetine showed statistically significant low VAS scores than pregabalin ($p<0.0001$). So, null hypothesis was rejected and our study hypothesis "Duloxetine is more efficient than pregabalin in reducing Central Post Stroke Pain" was established. Kim et al also found duloxetine significantly reduce CPSP.[15]

Adverse events were reported in 17.9% (31/173) of the participants. Two patients stopped taking pregbalin in group B due to adverse effect but none of this occur in duloxetine group. Lethargy/ somnolence (8.1%) and peripheral edema (3.4%) were commonly reported in the pregabalin group and constipation (6.9%) and orthostatic hypotension (4.6%) were commonly reported in duloxetine group. This findings are also in similarity with Klit et al where they also found both pregabalin and duloxetine are relatively safe drug.[11]

Limitation

- This study was conducted in a single center with small sample.
- This was an open – label clinical trial; both participant and researcher could be biased.

Conclusion

Duloxetine at a daily dose of 60 mg/day is more efficacious than pregabalin 300mg/day in reduction of Central Post Stroke Pain (CPSP). Both duloxetine and pregabalin have promising safety profile and well tolerated. Further multi center, longitudinal, double-blind trials are recommended to ensure robust evidence on the superiority of either drug in the management of CPSP.

Recommendation

- Further multicenter study with large sample is recommended.
- The clinical trial should be double-blind.

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Contribution of authors

NHM-Conception, design, data collection, drafting & final approval.

SA-Interpretation of data, critical revision & final approval.

AKMHK-Data analysis, critical revision & final approval.

MMR-Design, data collection, drafting & final approval.

Disclosure

All the authors declared no competing interest.

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