Gabapentin Add-On Therapy for Patients with Spinal Cord Injury Associated Neurogenic Overactive Detrusors That Are Unresponsive to Combined Anticholinergic and Beta-3 Adrenergic Therapy

Ozer Cakici[1], Coskun Kaya[2], ADEM SANCI[3], Onur Serdar Gencler[1], Orkhan Mammadkhanli[1], and Abdullah Cindas[1]

[1]Affiliation not available
[2]Eskisehir Sehir Hastanesi
[3]Ankara University

March 30, 2022

Abstract

Spinal cord injury is a major cause of lifelong morbidity. Functional micturition problems are common while the management choices are comparatively narrow. Some patients are refractory to the combination of the available therapeutics, namely the anticholinergics and a beta-adrenergic named mirabegron. In this paper we report our results of using gabapentin as an add-on treatment in the refractory overactive detrusor cases secondary to spinal cord injury. Material and Methods A total of 27 patients who had spinal cord injury between the levels of second thoracic and fourth lumbar vertebrae and had an overactive detrusor in urodynamic studies were included in this retrospective study. The patients were selected as they also had not responded to a combination of an anticholinergic and mirabegron and had neuropathic pain. Gabapentin treatment was added to the previous therapy. Demographics, previous treatments, chronic conditions, urodynamic findings, clinical and urodynamic responses are reported in this paper. Results We observed the response in the urodynamic studies of 11 patients (40.17%), in terms of decreased detrusor contractions, maximal detrusor pressure, and the number of the incontinence episodes. Sixteen patients did not respond to the gabapentin add-on therapy and were referred for Botulinum Toxin injections to the bladder. Conclusion Gabapentin add-on therapy can be considered as an option in neurogenic overactive detrusor patients who did not respond to the combination of anticholinergics and mirabegron. The approved usage of gabapentin for neurogenic pain justifies its usage in this area. In our selected patient group, who had not responded to the combination therapy, we observed a clinical benefit in one-third of the patients.

Gabapentin Add-On Therapy for Patients with Spinal Cord Injury Associated Neurogenic Overactive Detrusors That Are Unresponsive

to Combined Anticholinergic and Beta-3 Adrenergic Therapy

Running Title: Gabapentin in Refractory Overactive Detrusor

Ozer Ural Cakici [1], Coskun Kaya[2], Adem Sanci[3], Onur Serdar Gencler[4], Orkhan Mammadkhanli[5], Abdullah Cindas[6]

[1]: Department of Urology, Yuksek Ihtisas University affiliated Medical Park Ankara Hospital, Ankara, Turkey.

[2]: Department of Urology, Eskisehir City Hospital, Eskisehir, Turkey.

[3]: Department of Urology, Ankara University, Ankara, Turkey.

[4]: Department of Neurology, Yuksek Ihtisas University affiliated Medical Park Ankara Hospital, Ankara, Turkey.

[5]: Department of Neurosurgery, Yuksek Ihtisas University affiliated Medical Park Ankara Hospital, Ankara, Turkey.

[6]: Department of Physical Therapy and Rehabilitation, Yuksek Ihtisas University affiliated Medical Park Ankara Hospital, Ankara, Turkey.

Correspondence:

Coskun Kaya, MD

Eskisehir City Hospital Urology Department

E-mail: coskun_kaya2008@yahoo.com

Phone (mobile): +90 506 443 41 54

Acknowledgements: None

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Material and Methods

A total of 27 patients who had spinal cord injury between the levels of second thoracic and fourth lumbar vertebrae and had an overactive detrusor in urodynamic studies were included in this retrospective study. The patients were selected as they also had not responded to a combination of an anticholinergic and mirabegron and had neuropathic pain. Gabapentin treatment was added to the previous therapy. Demographics, previous treatments, chronic conditions, urodynamic findings, clinical and urodynamic responses are reported in this paper.

Results

We observed the response in the urodynamic studies of 11 patients (40.17%), in terms of decreased detrusor contractions, maximal detrusor pressure, and the number of the incontinence episodes. Sixteen patients did not respond to the gabapentin add-on therapy and were referred for Botulinum Toxin injections to the bladder.

Conclusion

Gabapentin add-on therapy can be considered as an option in neurogenic overactive detrusor patients who did not respond to the combination of anticholinergics and mirabegron. The approved usage of gabapentin for neurogenic pain justifies its usage in this area. In our selected patient group, who had not responded to the combination therapy, we observed a clinical benefit in one-third of the patients.

Keywords: Gabapentin, Spinal Cord Injury, Overactive Bladder

Introduction

Spinal cord injury (SCI) is a major cause of lifelong morbidity [1]. Current papers reported an incidence rate of 54 cases per one million, according to US data [2]. Although a declining incidence in the young population was prevalent, as well as some improvements in overall life quality, , the management of a neurogenic bladder

after an SCI is still a challenging and crucial issue [3-6]. After an SCI, neurogenic bladder dysfunction may be present as neurogenic detrusor overactivity (NDO) or sphincter detrusor dyssynergia (DSD), which are due to SCI in the suprasacral levels, or as detrusor hypoactivity or complete areflexia as a result of damage to the sacral spinal cord [7]. The management of an underactive detrusor has mainly relied on active usage of clean intermittent catheterization, which is lifesaving [8]. On the other hand, the management of a neurogenic overactive detrusor is based on medical therapeutics that act on the receptors of the detrusor muscle cells [9]. Blockers of the acetylcholine receptors, namely anticholinergics, and an agonist of the beta-3 adrenergic receptors, mirabegron, are usually used as an initial management choice, either in combination or as a single therapy. Due to the contemporary clinical guidelines, unresponsive patients are recommended to be considered for Botulinum Toxin-A injections to the bladder wall, which is more invasive than an oral treatment [11]. With the aim of providing an option to these patients, several molecules have been reported to be successful in an experimental fashion [12]. Among them, gabapentin, a sodium channel blocker, has also been found to be clinically beneficial in suppressing the detrusor contractions with an acceptable side effect profile in both adults and children, as well as in neurogenic overactive bladder as in overactive bladder syndrome [13-18]. In this paper we report the results of a single neuro-urology working group that comprises 27 adult patients who did not respond to the combination of an anticholinergic and mirabegron and were treated with add-on gabapentin therapy.

Materials and Methods

Between June 2016 and June 2020, a total of 27 patients who had a history of traumatic SCI were admitted to our working group that consisted of three urologists, a neurosurgeon, a neurologist, and a physical therapy and rehabilitation specialist. All interventions in the study were a matter of routine patient follow-up and compatible with the declaration by the World Medical Association on the Ethical Principles for Medical Research Involving Human Subjects.

All patients had a referral urodynamic study which was compatible with detrusor overactivity despite regular use of an anticholinergic and mirabegron. A Visual Analogue Score (VAS) was obtained to evaluate concurrent neuropathic pain. A bladder diary comprising three consecutive days was obtained from each patient during their initial admission. After obtaining the diary, gabapentin (Neurontin, Pfizer Turkey, Istanbul, Turkey) therapy was initiated with a dosage of 100 milligrams a day. The patients were scheduled with outpatient appointments every 15 days, and the patients, or their caregivers, were instructed to complete a new bladder diary for the three consecutive days after each visit. Gabapentin dosage was further tailored due to the response of the patient up to 800 milligrams a day. Patients who responded to the gabapentin treatment were scheduled in regular yearly urodynamic studies while unresponsive patients were evaluated with a new urodynamic study and considered for Botulinum Toxin injections to the bladder. Clinical data obtained from the urodynamic studies, the bladder diaries, and the symptom scores before and after the gabapentin treatment were collected and compared.

The Kolmogorov-Smirnov tests were performed to evaluate whether the interval data showed a parametric distribution. Therefore, interval data is presented as mean (Standard Deviation (SD) and nominal data are expressed as total numbers (n). Pre- and post-treatment findings were compared using a two-tailed t -tests, p values smaller than 0.05 were deemed as significant.

Results

The mean age was 32.03 (SD: 6.7) years, the mean time duration between the SCI and referral to our group was 8.8 (SD: 2.3) months. The SCI area was cervical, thoracal, and thoracolumbar in 13, 5, and 9 patients, respectively. Neuropathic pain was prevalent in lower extremities in 15 patients while in both upper and lower extremities in 12 patients. The cause of the SCI was motor vehicle accident in 12 patients, falls in 9 patients, recreational injuries in 3 patients, sport injuries in 2 patients, and a gunshot injury in one patient.

We observed significant amelioration in terms of patient-reported numbers of daily incontinence episodes as well as increased maximal bladder volumes and decreased maximal detrusor pressures in urodynamic studies in a total of 11 (40.17%) patients in our cohort. A significant decrease in the VAS scores for the neuropathic

pain was also observed in this group.

The unresponsive patient group comprised 16 patients who were also found to have benefit from the gabapentin add-on treatment in terms of the amelioration of the neuropathic pain, which was apparent in comparison between the pre- and post-treatment VAS scores. However, the urodynamic results and the number of the incontinence episodes did not show a significant difference in these patients. These patients were referred for Botulinum Toxin injection to the bladder wall.

The clinical data of the study group is summarized in Table 1.

Discussion

SCI is a major disabling condition which has an incidence between 14 to 54 cases per million of the population in different areas around the globe, with a significant dominance of the males [2, 19-21]. The most common etiological factors are traffic accidents and falls, according to the previous reports [20-22]. In our study, all patients were male, and our age group was respectively young with a mean age of 32.03 (SD: 6.7) years. The most common etiologies were also those of accidents and falls in our cohort that comprised 12 and 9 patients, respectively. Unfortunately, we cannot provide any incidence rate or demographic distribution data because of the selective nature of the patient group in our study. On the other hand, we can report that as a multidisciplinary neuro-urology working group, we are faced with 2 to 5 refractory NDO cases per year, which makes one case per physician per year for our group. To the best of the authors' knowledge, a comprehensive nationwide mapping of SCI cases in our country is not available in the literature and consider that such a thorough report is warranted. Fortunately, individuals who have suffered from SCI are usually managed in specialized institutions, thus, such a comprehensive study or prospective trials in selected patients seems possible in these institutions.

The clinical picture of a SCI patient depends on the extent, whether it is complete or partial, and the level of the injury. A complete cervical disruption presents with tetraplegia while a partial lower lumbar injury may only affect a single extremity. Urinary functions are also in the same vein with the overall motor and sensory functions. Injuries of the cervical, thoracic, or lumbar spinal cord usually represent with an NDO and DSD, while sacral injuries virtually always result in an underactive detrusor with a functional or flask external sphincter [11, 23]. Our study comprised only complete suprasacral SCI lesions with refractory NDO and neuropathic pain, which represented our selected subgroup. Medical management options for these patients are comparatively few, thus, several studies were undertaken to increase the therapeutic choices. In experimental fashion, inosine, resiniferatoxin, an E-series prostaglandin 1 receptor antagonist, kynurenine gene transfer via viruses, gamma-aminobutyric acid A and B receptor agonists muscimol and baclofen, a transient receptor potential 1 and a transient receptor potential vanilloid 1 receptor antagonists, an arginase inhibitor, a prostacyclin receptor antagonist, an endothelin-A receptor antagonist, and memantine have been shown to be beneficial [24-33]. Clinical studies have indicated that mirabegron, tetrahydrocannabinol-cannabidiol oral spray, anticholinergic preparations, and gabapentin are effective in the management of neurogenic overactive detrusor [13-18, 34-39]. However, there is still a group of patients who are unresponsive to the combination of an anticholinergic with the ß-adrenergic therapeutic. These patients are considered for Botulinum Toxin injections or surgical options if the injections fail [11, 40]. Additionally, neuropathic pain is also a common component of the treatment for an individual who has suffered an SCI [41]. The management of neuropathic pain justifies the usage of gabapentin in these patients, akin to our study group. In our study, we aimed to utilize gabapentin's role for the management of both neuropathic pain and the neurogenic overactive detrusor, and our results showed that it has a beneficial effect. Our results are compatible with the previous studies, but with better urodynamic findings, decreased VAS scores, as well as continence status. As a result, we believe that add-on gabapentin therapy can be considered as a salvage option between the combinations of an anticholinergic with ß-adrenergic and Botulinum Toxin injection, and it is also beneficial in the management of the neuropathic pain of these patients.

As an important caution, physicians should be aware of the addictive and abuse potential of gabapentin [42]. Interestingly, to the best of the authors' knowledge, previous papers that reported the success of gabapentin

in the management of overactive bladder did not indicate any cases of addiction or abuse. Considering the follow-up periods of the available papers, future follow-ups must give importance to this point. A total of 11 patients had benefit from gabapentin and continued the treatment. Among them, we also have not observed any signs of addiction or abuse. We believe that the abusive potential may also be related to the individual's personality or behavior. This is an area of future research and we consider that future follow-ups of the available studies that have used gabapentin may be a matter of interest.

Our study brings encouraging results in the management of an unresponsive NDO due to SCI; however, the study has some shortcomings. Firstly, the cohort is a selected patient group. Therefore, we cannot indicate any demographic information or endorse a common clinical strategy based on our selected patients. The patient follow-up data is also limited after the initial treatment. A review of the patient charts revealed that among a total of 11 patients, only four of them are still being followed-up by our working group. We cannot report any long-term compliance data for the 7 patients who dropped out of our follow-up. Furthermore, we cannot report the success of Botulinum Toxin injections in the unresponsive group in our cohort. Further follow-ups would show the compliance rates and long-term success of gabapentin add-on therapy. The condition of the unresponsive patients is also a matter of interest. Whether a correlation exists between the unresponsiveness of the patients with the clinical course should be evaluated by prospective observational studies. However, we believe that our results hold importance by bringing clinical and urodynamic evidence in favor of the safety and benefits of gabapentin as an option in the treatment of NDO secondary to SCI.

In conclusion; Gabapentin is an option for the treatment of NDO after SCI. The approved usage of the therapeutic for neuropathic pain may justify its usage for such patients outside of clinical trials. We believe that it can also be considered as a salvage option in refractory NDO cases as well as a primary option in patients who have NDO concurrent with neuropathic pain.

Conflict of interest : Authors declared no conflict of interest

Authors' contribution: OC contributed to data collection and analysis, manuscript writing, and revision. OG contributed to study design, manuscript writing, and revision. TK contributed to literature review, manuscript writing, and revision. CK and AS contributed to data collection and analysis. OM contributed to study design, data analysis, and literature review. All authors approved the final version of the article for submission.

Data avaibility statement: The data that support the findings of this study are openly available in Harvard Dataverse with https://doi.org/10.7910/DVN/PGNNIY.

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Table 1. Clinical data of the cohort [1].

Parameter	**Responsive Group**	**Unresponsive Group**
VAS		
Pre-treatment	5.45 (1.55)	6.18 (1.73)
Post-treatment	2.54 (0.98)	3.62 (1.11)
p value	< 0.001 *	< 0.001 *
Daily Incontinence Episodes		
Pre-treatment	6.54 (2.7)	8.37 (2.82)
Post-treatment	2.27 (1.54)	7.56 (2.12)
p value	< 0.001 *	0.09
Maximal Detrusor Pressure		
Pre-treatment	38.81 (15.17)	29.62 (10.7)
Post-treatment	21.72 (8.62)	30.18 (10.51)
p value	0.01 *	0.79
Maximal Bladder Volume		
Pre-treatment	239.63 (58.19)	219.62 (57.25)
Post-treatment	262.81 (48.01)	221.81 (54.73)
p value	0.01 *	0.57

[1]: Interval data is expressed as the mean (SD).

*: Statistically significant comparison between the pre- and post-treatment results.

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