ORIGINAL RESEARCH

A Prospective, Randomized, Comparative Study To Evaluate The Effect And Comparison Of Intratrigonal Botulinum Toxin And Intravesical Chondroitin Sulphate For Treatment Of Bladder Pain Syndrome

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ABSTRACT

Introduction: Bladder pain syndrome is a debilitating chronic disease of unknown etiology; it has negative impact on the quality of life. Intravesical therapy used in a patient who is refractory to conservative management. Intratrigonal botulinum toxin is shown to inhibit not only the release of acetylcholine and nor epinephrine, but also that of nerve growth factor, ATP, substance P and calcitonin gene-related peptide from the urothelium and in the nerve fibres decrease detrussor overactivity, bladder sensation, and visceral pain. Chondroitin sulfate is other intravesical agent, it replenish the protective GAGs layer. **Material and Method:** This is prospective study of 44 patients full filling the inclusion criteria. It was conducted in ruby hall clinic between September 2018 to January 2020. Patients were evaluated by history, physical examination, blood and urine examination, ultrasonography of abdomen, uroflowmetry, bladder diary, ICSI, ICPI and VAS scale. Patients were randomized in two groups. Group 1 had received botulinum toxin-A intratrigonal 100 IU diluted in 10ml normal saline given stat. Group 2 had been treated with intravesical chondroitin sulphate 2% sterile solution in 20ml vials weekly for 6 weeks. Both the groups were followed at 6weeks, 3months and 6 months and assessed for urinary frequency, urgency suprapubic pain, mean voided volume, ICSI, ICPI and VAS score. **Result:** Intratrigonal Botulinum toxin therapy had significant better outcome over intravesical Chondroitin sulfate in terms of urinary frequency, urgency suprapubic pain episodes, mean voided volume, ICSI, ICPI and VAS score at the end of study. **Conclusion:** Intra-trigonal botulinum toxin 100IU is a viable treatment option for BPS patients refractory to conservative therapy, with acceptable fewer side effect profile. Intravesical chondroitin sulfate 20ml , 2% is another intravesical therapy which require frequent instillation and its outcome is inferior as compare to intra-trigonal botulinum toxin 100IU.

Key words: Bladder pain syndrome, botulinum toxin, chondroitin sulfate, ICSI, ICPI, VAS.

INTRODUCTION

Bladder pain syndrome (BPS) is a chronic disease of unknown cause that causes severe pain in the lower abdomen when the bladder is full, along with frequent urination and waking up at night to urinate. This condition significantly reduces the quality of life for affected individuals.

Bladder pain syndrome is hypothesised to be caused by chronic inflammation of the bladder [1, 2, 3]. However, it is probable that multiple mechanisms contribute to the development of this condition. The urothelium, also known as transitional epithelium, is believed to have a crucial role in the development of bladder pain syndrome (BPS). The urothelial cells are covered by a layer of glycosaminoglycans (GAG), which acts as a protective barrier against substances present in the urine. The constituents of this layer consist of hyaluronic acid (HA), chondroitin sulphate (CS), heparin sulphate, dermatan sulphate, and keratin sulphate [4]. Some patients with BPS have been found

to have a defective GAG layer [5-7]. The predominant clinical manifestations include pain in the bladder and pelvis, the presence of glomerulations and/or hunner's ulcer during cystoscopic hydrodistention, and the thinning or denudation of the bladder epithelium. These findings suggest that bladder inflammation and urothelial dysfunction are implicated in bladder pain syndrome [3, 8].

The primary treatment approach focuses on providing the patient with information about the long-term nature of the condition and promoting changes in behaviour and lifestyle. Intravesical therapies are recommended when initial treatment is ineffective and are used alongside physiotherapy techniques (such as myofascial release and pelvic floor muscle relaxation) and oral medications. The justification for the utilisation of numerous intravesical therapies currently in use is to restore the deficient GAG layer or modify the process of neurogenic inflammation and hypersensitivity. Intravesical therapy offers the benefits of targeting treatment specifically to the bladder, resulting in the accumulation of high levels of the medication and reducing the occurrence of side effects throughout the body. The drawbacks include the need for instrumentation of the urethra and bladder to administer the agent, which can potentially worsen pain and increase the risk of urinary tract infection. Additionally, frequent instillation in the bladder, sometimes on a weekly basis, is required. Existing therapies often fail to completely eliminate bladder pain and enhance bladder capacity [9]. While there have been numerous reports on the effective treatment of detrussor overactivity, there have only been a limited number of studies on the use of BoNT-A for treating BPS. [12-14]

Recent basic research has demonstrated that BoNT-A has the ability to inhibit the release of acetylcholine, nor epinephrine, nerve growth factor, ATP, substance P, and calcitonin gene-related peptide from the urothelium and nerve fibres [15-17]. BoNT-A has demonstrated efficacy in reducing detrussor overactivity, bladder sensation, and visceral pain in chronic inflammatory diseases, as evidenced by clinical experiments [10-14, 18]. These findings indicate that BoNT-A treatment has the ability to modify sensory transmission and decrease detrusor contractility. The trigone region of the bladder contains a highly concentrated network of nerve fibres that are sensitive to pain and play a role in the generation of pain and inflammation caused by nerve activity. While BoNT-A injection shows promise as a treatment for BPS symptoms, a previous study did not achieve successful long-term outcomes [19]. Chondroitin sulphate (CS) is a constituent of the GAG layer and has been found to be lacking in patients with BPS [20]. In addition to its function in the GAG layer, chondroitin sulphate (CS) has been demonstrated to hinder the attraction of inflammatory cells to the inner layers of the bladder wall [21]. Additional intravesical therapies, including hyaluronic acid, BCG, and oral medications like pentosan polysulphate (PPS), cyclosporin A, or amitriptyline, DMSO, have not demonstrated long-term efficacy [22, 23, 24].

The current study aimed to assess the clinical efficacy of intratrigonal injection of BoNT-A and compare it with intravesical Chondroitin sulphate in patients with bladder pain syndrome (BPS) who did not respond to conservative treatment and pharmacotherapy. The precise role of intra-trigonal botulinum toxin A (BoNT-A) injections in bladder pain syndrome (BPS) remains undefined. Nevertheless, in the realm of urology, persistent bladder or pelvic pain is frequently challenging to eliminate through the use of oral medications or bladder instillation therapy. The objective of this study was to assess the effectiveness and safety of BoNT-A injections for BPS using reliable and substantial evidence. The objective of this study is to examine the effectiveness of BoNT-A and compare it to the effectiveness of intravesical chondroitin sulphate in order to determine the most efficient treatment for pain in patients with BPS in the future.

MATERIALS AND METHODS

The study was conducted at the Department of Urology, Ruby Hall Clinic, Pune, Maharashtra, with a study population consisting of patients diagnosed with bladder pain syndrome (BPS) attending the Urology Outpatient Department (OPD) at the clinic. This prospective, randomized, comparative, interventional study included a total sample size of 44 patients, with 22 patients allocated to each of the two intervention groups: BoNT-A (botulinum toxin A) and chondroitin sulphate. Inclusion criteria for patient selection encompassed individuals aged over 18 years experiencing specific types of pain (suprapubic, perineal, pelvic, urethral) associated with bladder filling and relieved upon emptying, as well as the presence of glomerulations and/or Hunner’s ulcers observed during cystoscopic examination under general anaesthesia.Exclusion criteria comprised patients under 18 years old, those with a history of bladder tumors, carcinoma in situ, tubercular or bacterial cystitis, active genital herpes, bladder calculi, low frequency (<5 times in 12 hours) or nocturia (<2 times per night), symptoms responsive to antibiotics or urine analgesics, duration of symptoms less than 12 months, bladder capacity exceeding 400 ml, urethral diverticulum, and history of cyclophosphamide, chemical, tuberculous, or radiation cystitis, as well as recent uterine, cervical, vaginal, or urethral cancer within the past five years. The study was conducted from September 2018 to January 2020, aiming to assess and compare the effectiveness of intratrigonal BoNT-A injections versus intravesical chondroitin sulphate in managing pain associated with BPS.

PROCEDURE

This is a prospective, randomized, comparative study in which all the patients presenting to Urology OPD of Ruby hall clinic with symptoms of BPS, meeting the inclusion criteria was included in the study. Ethics Committee-approved written informed consent was obtained from each patient prior to the study. Patients were randomized in two groups with the "chit method". Group 1 patients had received botulinum toxin-A intravesical 100 IU diluted in 10ml normal saline was injected suburothelially at 20 sites by 0.5ml each in trigonal bladder base injections alone excluding ureteric orifice. Group 2 patients were treated with intravesical chondroitin sulphate 2% sterile solution in 20ml vials weekly for 6 weeks. At the time of first visit, patients were evaluated with history, physical examination, blood and urine examination, ultrasonography of abdomen, Uroflowmetry, bladder diary, ICSI, ICPI and VAS scale.

Data collection techniques

Preoperative data collection had included patient's demographic data, urodynamic study, abdomen USG, Intraoperative and postoperative assessment. Follow up data were collected in tested proforma and tables.

Follow up

Patients were reviewed at 6 weeks, 3 months and 6 months with bladder diary, ICSI, ICPI, VAS and side effects profile.

ASSESSMENT

Outcome of the study was assessed by following parameters:

Efficacy Assessments

Objective Outcome

- Primary end-points were change in suprapubic pain episodes, Mean no. of micturition / 24 h and mean no. of urgency episodes grade 2, 3, 4/24 h from baseline to end of treatment in each group according to bladder diary.
- Secondary end-points were change in mean no. of urgency incontinence episodes / 24h, nocturia episodes / 24 h and urine volume voided / micturition from baseline to end of treatment according to bladder diary, Change in ICSI symptom score from baseline to end of treatment.

Subjective Outcome

- ICPI Short form questionnaire and VAS scale.

Safety Assessments

We included reporting of Incidence of Treatment – Adverse events like

- Acute urinary retention
- Dysuria
- Strain to void
- Urinary tract infection
- Large PVR
- Gross hematuria
- Urethral pain

Statistical Methods

The data was entered into a excel sheet analysed with free online available websites. A descriptive analysis was carried out in which categorical variables were expressed as about and relative frequencies, and continuous variables as means (SD). The $\chi 2$ test was used to compare proportion in independent groups. The paired sample t test was used to test efficacy of botulinium at baseline and after 6 month follow up. The unpaired t test was used to compare the efficacy between the two groups at baseline, 6weeks, 3 months and 6 months. Other appropriate statistical tests was applied for the data where needed. P value < 0.05 was considered as statistically significant.

RESULT

Table 1: Baseline characteristics of patients

	Botulinum toxin (N=22)	**Chondrotin sulphate (N=22)**	**P-VALUE**
Age in years (mean ± SD)	47.5 ± 11.8	48.9 ± 12.0	>0.05
Tobacco, n (%)	1 (5%)	1 (5%)	>0.05
Caffeine, n (%)	7 (32%)	6 (27%)	>0.05
Diabetes, n (%)	6 (27%)	7 (32%)	>0.05
Hypertension, n (%)	1 (5%)	0	>0.05
Smokers, n (%)	2 (9%)	2 (9%)	>0.05
Males, n (%)	7 (32%)	7 (32%)	>0.05
Females, n (%)	15 (68%)	15 (68%)	>0.05
Comparison of micturition episodes / 24 h before and after treatment			
BASELINE	19.8 ± 7.9	24.8 ± 6.4	<0.05
AT 6 WEEKS	12.6 ± 3.9	20.8 ± 5.6	<0.01
AT 3 MONTHS	9.1 ± 2.8	17.9 ± 5.0	<0.01
AT 6 MONTHS	7.3 ± 2.1	16.0 ± 4.9	<0.01
P-VALUE	<0.01	<0.01	
Comparison of urgency episodes/24 h before and after treatment			

BASELINE	2.0 ± 1.2	2.6 ± 0.7	<0.05
AT 6 WEEKS	1.7 ± 1.1	2.1 ± 0.9	>0.05
AT 3 MONTHS	0.9 ± 1.0	1.6 ± 0.9	<0.05
AT 6 MONTHS	0.5 ± 0.9	1.1 ± 1.1	<0.05
P-VALUE	<0.01	<0.01	
Comparison of urgency incontinence episodes/24 h before and after treatment			
BASELINE	1.7 ± 2.6	0.3 ± 0.8	<0.05
AT 6 WEEKS	1.3 ± 2.1	0.1 ± 0.5	<0.05
AT 3 MONTHS	0.9 ± 1.6	0.1 ± 0.4	<0.05
AT 6 MONTHS	0.5 ± 0.9	0.1 ± 0.4	<0.05
P-VALUE	<0.05	>0.05	
Comparison of nocturia episodes/24 h before and after treatment			
BASELINE	4.8 ± 2.1	8.8 ± 3.5	<0.01
AT 6 WEEKS	3.4 ± 1.0	7.0 ± 3.0	<0.01
AT 3 MONTHS	2.1 ± 0.8	5.3 ± 2.5	<0.01
AT 6 MONTHS	1.6 ± 0.7	4.45 ± 1.89	<0.01
P-VALUE	<0.01	<0.01	

In this study comparing the effects of botulinum toxin and chondroitin sulfate treatments on urinary symptoms, baseline characteristics of patients (N=22 per group) showed no significant differences in age, tobacco use, caffeine consumption, diabetes, hypertension, smoking status, or gender distribution between the two treatment groups ($p > 0.05$ for all comparisons). However, significant improvements were observed in micturition episodes per 24 hours at 6 weeks, 3 months, and 6 months post-treatment for both groups ($p < 0.01$), with the botulinum toxin group exhibiting consistently lower episodes than the chondroitin sulfate group. Similarly, urgency episodes decreased significantly over time ($p < 0.01$), with the most notable reduction seen at 6 months post-treatment. Urgency incontinence episodes also significantly decreased ($p < 0.05$), with the botulinum toxin group showing a more pronounced improvement compared to chondroitin sulfate. Nocturia episodes significantly decreased post-treatment ($p < 0.01$), with the botulinum toxin group experiencing a greater reduction at all time points.

Table 2: Comparison of mean voided volume per micturition before and after treatment:

	BOTULINUM TOXIN	**CHONDROITIN SULPHATE**	**P-VALUE**
BASELINE	130.9 ± 66.2	118.18 ± 66.59	<0.05
AT 6 WEEKS	165.5 ± 73.1	128.63 ± 72.39	<0.05
AT 3 MONTHS	195.27 ± 58.18	144.09 ± 70.62	<0.05
AT 6 MONTHS	266.8 ± 69.71	217.04 ± 57.45	<0.05
P-VALUE	<0.05	<0.05	

Table 2 presents the comparison of mean voided volume per micturition before and after treatment with botulinum toxin and chondroitin sulfate. At baseline, there was a significant difference ($p < 0.05$) in mean voided volume between the botulinum toxin group (130.9 ± 66.2 mL) and the chondroitin sulfate group (118.18 ± 66.59 mL). Following treatment, all subsequent time points (6 weeks, 3 months, and 6 months) showed significant increases ($p < 0.05$) in mean voided volume for both groups compared to baseline. Notably, at each time point post-treatment, the botulinum toxin group exhibited higher mean voided volumes compared to the chondroitin sulfate group, with the differences being statistically significant ($p < 0.05$).

Table: 3 Comparison of supra pubic pain before and after treatment:

	BOTULINUM TOXIN	**CHONDROITIN SULPHATE**	**P-VALUE**
BASELINE	5.09 ± 2.15	5.9 ± 4.3	>0.05
AT 6 WEEKS	2.9 ± 2.3	4.9 ± 3.7	>0.05
AT 3 MONTHS	1.7 ± 2.0	3.4 ± 3.3	>0.05
AT 6 MONTHS	0.9 ± 1.1	2.8 ± 3.2	<0.05
P-VALUE	<0.05	<0.05	

Table 3 compares supra pubic (above the pubic bone) pain before and after treatment with botulinum toxin and chondroitin sulfate. At baseline, there was no statistically significant difference in supra pubic pain between the botulinum toxin group (5.09 ± 2.15) and the chondroitin sulfate group (5.9 ± 4.3) ($p > 0.05$). However, following treatment, all subsequent time points (6 weeks, 3 months, and 6 months) showed a

significant decrease in supra pubic pain compared to baseline for both treatment groups ($p < 0.05$). Notably, at 6 months post-treatment, the difference in supra pubic pain between the botulinum toxin group (0.9 ± 1.1) and the chondroitin sulfate group (2.8 ± 3.2) became statistically significant ($p < 0.05$), indicating a more pronounced reduction in pain in the botulinum toxin group compared to the chondroitin sulfate group over time.

Table 4: Comparison of ICSI scores before and after treatment:

	BOTULINUM TOXIN	CHONDROITIN SULPHATE	P-VALUE
BASELINE	13.7 ± 1.9	14.8 ± 1.9	<0.05
AT 6 WEEKS	10.2 ± 2.0	12.1 ± 1.6	<0.01
AT 3 MONTHS	7.5 ± 1.8	9.5 ± 1.5	<0.01
AT 6 MONTHS	5.6 ± 2.1	7.4 ± 1.5	<0.01
P-VALUE	<0.01	<0.01	

Table 4 presents the comparison of ICSI (Interstitial cystitis symptom index) scores before and after treatment with botulinum toxin and chondroitin sulfate. At baseline, the ICSI scores were significantly different between the botulinum toxin group (13.7 ± 1.9) and the chondroitin sulfate group (14.8 ± 1.9) with a p-value less than 0.05. Following treatment, at 6 weeks, 3 months, and 6 months post-treatment, there were significant reductions in ICSI scores for both groups compared to baseline ($p < 0.01$). Notably, the reductions in ICSI scores were consistently greater in the botulinum toxin group (10.2 ± 2.0 at 6 weeks, 7.5 ± 1.8 at 3 months, and 5.6 ± 2.1 at 6 months) compared to the chondroitin sulfate group (12.1 ± 1.6 at 6 weeks, 9.5 ± 1.5 at 3 months, and 7.4 ± 1.5 at 6 months), with all these differences being statistically significant ($p < 0.01$).

Table 5: Comparison of ICPI scores before and after treatment:

	BOTULINUM TOXIN	CHONDROITIN SULPHATE	P-VALUE
BASELINE	10.5 ± 1.3	11.1 ± 0.8	>0.05
AT 6 WEEKS	8.4 ± 1.7	9.6 ± 1.0	<0.05
AT 3 MONTHS	5.7 ± 2.1	7.3 ± 1.3	<0.05
AT 6 MONTHS	4.1 ± 1.7	5.9 ± 1.5	<0.01
P-VALUE	<0.01	<0.01	

Table 5 presents the comparison of ICPI (Interstitial cystitis problem index) scores before and after treatment with botulinum toxin and chondroitin sulfate. At baseline, there was no statistically significant difference in ICPI scores between the botulinum toxin group (10.5 ± 1.3) and the chondroitin sulfate group (11.1 ± 0.8) ($p > 0.05$). However, following treatment, all subsequent time points (6 weeks, 3 months, and 6 months) showed significant reductions in ICPI scores for both treatment groups compared to baseline ($p < 0.05$). Notably, the reductions in ICPI scores were consistently greater in the botulinum toxin group (8.4 ± 1.7 at 6 weeks, 5.7 ± 2.1 at 3 months, and 4.1 ± 1.7 at 6 months) compared to the chondroitin sulfate group (9.6 ± 1.0 at 6 weeks, 7.3 ± 1.3 at 3 months, and 5.9 ± 1.5 at 6 months), with the differences becoming statistically significant at 6 weeks ($p < 0.05$) and more pronounced at 3 months and 6 months ($p < 0.01$).

Table 6: Comparison of VAS scale before and after treatment:

	BOTULINUM TOXIN	CHONDROITIN SULPHATE	P-VALUE
BASELINE	4.4 ± 1.8	5.5 ± 1.3	<0.05
AT 6 WEEKS	3.4 ± 1.3	4.4 ± 1.1	<0.05
AT 3 MONTHS	2.1 ± 1.2	3.1 ± 1.0	<0.01
AT 6 MONTHS	1.2 ± 1.1	2.1 ± 1.4	<0.05
P-VALUE	<0.01	<0.01	

Table 6 compares the VAS (Visual Analog Scale) scores before and after treatment with botulinum toxin and chondroitin sulfate. At baseline, there was a statistically significant difference in VAS scores between the botulinum toxin group (4.4 ± 1.8) and the chondroitin sulfate group (5.5 ± 1.3) ($p < 0.05$). Following treatment, at all subsequent time points (6 weeks, 3 months, and 6 months), there were significant reductions in VAS scores for both treatment groups compared to baseline ($p < 0.01$). Notably, the reductions in VAS scores were consistently greater in the botulinum toxin group (3.4 ± 1.3 at 6 weeks, 2.1 ± 1.2 at 3 months, and 1.2 ± 1.1 at 6 months) compared to the chondroitin sulfate group (4.4 ± 1.1 at 6 weeks, 3.1 ± 1.0 at 3 months, and 2.1 ± 1.4 at 6 months), with the differences being

statistically significant at all time points ($p < 0.05$ or $p < 0.01$).

Table 7: Comparison of adverse effects after treatment:

	BOTULINUM TOXIN (22)		CHONDROITIN SULPHATE (22)	
	Baseline	**6 months**	**Baseline**	**6 months**
Acute Urinary Retention	0	1 (5%)	0	0 (0%)
Dysuria	0	2 (9%)	0	2 (9%)
Strain to void	0	0 (0%)	0	0 (0%)
UTI	0	3 (14%)	0	2 (9%)
Gross hematuria	0	0 (0%)	0	0 (0%)
Urethral Pain	0	0 (0%)	0	0 (0%)
Large PVR	0	0 (0%)	0	0 (0%)

Table 7 compares the incidence of adverse effects after treatment with botulinum toxin and chondroitin sulfate. The table shows the percentage of patients experiencing adverse effects at baseline and at 6 months post-treatment.

For the botulinum toxin group:
- Acute Urinary Retention: No cases at baseline, 1 case (5%) at 6 months.
- Dysuria: No cases at baseline, 2 cases (9%) at 6 months.
- Strain to void, UTI, Gross hematuria, Urethral Pain, Large PVR: No cases reported at either baseline or 6 months.

For the chondroitin sulfate group:
- Acute Urinary Retention: No cases reported at either baseline or 6 months.
- Dysuria: No cases reported at baseline, 2 cases (9%) at 6 months.
- Strain to void, UTI, Gross hematuria, Urethral Pain, Large PVR: No cases reported at either baseline or 6 months.

Overall, the incidence of adverse effects appears to be relatively low for both treatments. In the botulinum toxin group, there was a small increase in cases of acute urinary retention and dysuria at 6 months post-treatment compared to baseline. Similarly, in the chondroitin sulfate group, there was an increase in dysuria cases at 6 months post-treatment. Other adverse effects such as strain to void, UTI, gross hematuria, urethral pain, and large post-void residual (PVR) were not reported in either group at baseline or 6 months.

DISCUSSION

Our study is a randomised comparative study that aims to assess the effectiveness of BoNT-A injection and compare it with intravesical chondroitin sulphate. This study included patients with PBS who had not responded to conventional treatments. The diagnosis of PBS was made based on the presence of distinct symptoms such as suprapubic pain associated with bladder filling, along with increased frequency of urination during the day and night. Additionally, cystoscopic examination revealed glomerulation. All patients had received oral PPS, intravesical heparin instillation, hyaluronic acid with sodium bicarbonate, or tricyclic antidepressant treatment for a minimum of 6 months. However, the symptoms did not improve or returned after this period. Prior to enrollment, patients underwent a comprehensive investigation and were excluded if they did not meet the criteria for IC/PBS set by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) during their initial assessment [25]. Prior to treatment, patients were instructed to maintain a 3-day voiding diary, documenting functional bladder capacity (FBC) as well as the frequency of urinary episodes and nocturia. This study prospectively compared the efficacy and safety of Botulinum and Chondroitin sulphate. A total of 44 patients diagnosed with BPS were included in this study.

Group 1 consisted of 22 patients who were administered botulinum toxin-A intravesically. The dosage used was 100 IU, diluted in 10ml of normal saline. The injection was given suburothelially at 20 specific sites, with each site receiving 0.5ml of the solution. The injections were targeted at the trigonal bladder base, excluding the ureteric orifice. Group 2 will consist of 22 patients who will receive intravesical chondroitin sulphate 2% sterile solution in 20ml vials once a week for a duration of 6 weeks. Table 1 provides information on the baseline characteristics of both groups, including age, history of diabetes, hypertension, smoking, caffeine intake, and tobacco intake. There is no statistically significant difference in any of the parameters mentioned above between the two groups.

The current study has confirmed the effective use of BoNT-A injection for treating refractory bladder pain syndrome (BPS), regardless of the type of BPS or the individual's gender. The effects of the injection are temporary and typically last for about 6 months, which is consistent with previous studies.[26] It has been suggested that an increase in the permeability of the epithelial cells and/or heightened excitability of the nerve fibres that carry sensory information towards the central nervous system may be important factors in the development of bladder pain syndrome (BPS).[27] The presence of a faulty glycosaminoglycan mucus layer, reduced microvascular density in the suburothelium, decreased levels of urinary HB-EGF, and increased activity of

urinary antiproliferative factor are considered to be the factors that cause a permeable urothelium.[28,29] The elevated concentration of neurotransmitters and neuropeptides may indicate the presence of neurogenic inflammation, which in turn triggers ongoing hyperactivity in sensory nerves, resulting in heightened sensitivity symptoms.[30,31,32] The trigone region of the bladder contains a highly concentrated network of sensory nerve fibres that play a role in generating pain and inflammation caused by nerve activity.

In this study, we administered BoNT-A primarily to the suburothelial layer rather than the detrusor layer, resulting in symptom relief for patients with refractory BPS.

Administering chondroitin sulphate directly into the bladder improves clinical symptoms and supports the idea that a disorder in the bladder wall's permeability plays a role in the development of chronic forms of bladder pain syndrome. This study revealed notable disparities between the two treatment modalities in terms of reducing the average number of urination episodes per 24 hours, occurrences of nocturia, episodes of urge incontinence per 24 hours, instances of urgency per 24 hours, the average volume voided per urination, episodes of supra pubic pain, and enhancements in ICSI, ICPI, and VAS scale.

Comparative analysis of the effectiveness and safety outcomes in this study in relation to other similar studies.

Baseline characteristics of patients: The age of the patients in our study ranges from 36 to 60 years, with a mean and standard deviation (SD) of 47.5 and 11.84 years for botulinum toxin, and 48.9 and 12.0 years for chondroitin sulphate, respectively. A total of 44 patients were included in the study, with 14 (32%) being male and 30 (68%) being female. Akiyama et al conducted a study where the average age ± standard deviation (SD) was 64.9 ± 13.7 years. A total of 34 patients were included in the study, with 26 (76%) being female and 8 (24%) being male.

Porru et al conducted a study in which the average age ± standard deviation (SD) was 46.5 ± 13.6 years. A total of 23 patients were included, all of whom were females (100%). [33,34]

Therefore, the age distribution aligns with the findings of the studies conducted by Porru et al and Akiyama et al on the same topic. The sex distribution also aligns with the findings of the study conducted by Akiyama et al. However, in the study by Porru et al., all participants in their study group were female.

The baseline mean number of micturition episodes per 24 hours in the Botulinum toxin group in our study was 19.8. At the conclusion of the 6-week period, the value decreases to 12.6. By the end of the study, it is further reduced to 7.3, with a mean difference of 12.5 from the initial baseline. The difference mentioned above was found to be statistically significant, with a p-value of less than 0.01. This finding is consistent with another study conducted by Kuo et al, Pinto et al, Giannantoni et al, and Akiyama et al, where the reduction in the mean number of micturition episodes at the end of the study was reported as 3.28, 6.7, 5.1, and 17.5, respectively.The given sequence is [35,36,37,38].

The baseline value in the Chondroitin Sulphate group was 24.8. At the conclusion of the 3-month period, the micturition rate decreased to 17.9. By the end of the study, it further decreased to 16.0, resulting in a mean reduction in micturition of 8.81. The difference mentioned above was found to be statistically significant, with a p-value of less than 0.01. This is consistent with the findings of Nordling et al, where the average reduction was 3.9, and Nickel et al, where it was 3.8.[39,40,41]

The mean reduction in micturition episodes was 12.5 in the botulinum toxin group, compared to 8.81 in the chondroitin sulphate group. Therefore, a statistically significant decrease in the average number of urination episodes is observed to a greater extent in the botulinum toxin group compared to the chondroitin sulphate group, with a p-value of less than 0.05.

The baseline mean number of nocturia episodes in the Botulinum toxin group in our study was 4.8. At the conclusion of the 6-week period, the value decreases to 3.4. By the end of the study, it is further reduced to 1.6, with a mean difference of 3.22 from the initial baseline. The difference mentioned above was found to be statistically significant, with a p-value of less than 0.01. This result is similar to another study conducted by Kuo et al, Pinto et al, Giannantoni et al, and Akiyama et al, where the reduction in the mean number of nocturia episodes at the end of the study was 0.82, 3.4, 2.1, and 4.0, respectively.[35,42,37,38]

The baseline value in the Chondroitin Sulphate group was 8.8. At the conclusion of the 3-month period, the nocturia level decreased to 5.3. By the end of the study, it further decreased to 4.4, resulting in a mean reduction in nocturia of 4.3. The aforementioned discrepancy was statistically significant, with a p-value less than 0.01. This is consistent with the study conducted by Nordling et al, where the average decrease was 1.9. [39] The mean reduction in nocturia episodes was 3.22 in the botulinum toxin group, compared to 4.3 in the chondroitin sulphate group. There is a statistically significant decrease in the average number of times a person urinates in the botulinum toxin group compared to the chondroitin sulphate group, with a p-value of less than 0.05.

The baseline mean ICSI score for the group treated with Botulinum toxin in our study was 13.7. At the conclusion of the 6-week period, the value decreases to 10.2. By the end of the study, it is further reduced to 5.6, with a mean difference of 8.1 from the initial baseline. The difference mentioned above was found to be statistically significant, with a p-value of less than 0.01. This finding is consistent with another study conducted by Kuo et al, Pinto et al, Akiyama et al, and Smith et al, where the reduction in Mean ICSI

scores at the end of the study was 4.33, 8.8, 10.4, and 11.69, respectively.[35,42,38,43]

The baseline measurement in the Chondroitin Sulphate group was 14.8. At the conclusion of the 3-month period, the ICSI score decreased to 9.5. By the end of the study, it further decreased to 7.4. The mean reduction in ICSI score was 7.4. The aforementioned discrepancy was statistically significant, as indicated by a p-value of less than 0.01. This is consistent with the study conducted by Nickel et al, where the average reduction was 6.1. [40,41] The mean reduction in ICSI score was 8.1 in the botulinum toxin group, compared to 7.4 in the chondroitin sulphate group. A statistically significant decrease in the average ICSI score was observed in the botulinum toxin group compared to the chondroitin sulphate group, with a p-value of less than 0.01.

The baseline mean ICPI score for the Botulinum toxin group in our study was 10.5. At the conclusion of the 6-week period, the value decreases to 8.4. By the end of the study, it is further reduced to 4.1, resulting in a mean difference of 6.4 from the initial baseline. The difference mentioned above was found to be statistically significant, with a p-value of less than 0.01. This finding is consistent with another study conducted by Kuo et al, Pinto et al, Akiyama et al, and Smith et al, where the reduction in Mean ICSI scores at the end of the study was 4.17, 8.8, 8.5, and 11.2, respectively.[35,36,38,43]

The baseline value in the Chondroitin Sulphate group was 11.1. At the conclusion of the 3-month period, the ICPI score decreased to 7.3. By the end of the study, it further decreased to 5.9, resulting in a mean reduction in ICPI score of 5.2. The difference mentioned above was found to be statistically significant, with a p-value of less than 0.01. This is consistent with the study conducted by Nickel et al, where the average decrease was 5.6. [40,41] The mean reduction in ICPI score was 6.4 in the botulinum toxin group, compared to 5.2 in the chondroitin sulphate group. A statistically significant decrease in the mean ICPI score was observed in the botulinum toxin group compared to the chondroitin sulphate group, with a p-value of less than 0.01.

The baseline mean VAS SCALE for the Botulinum toxin group in our study was 4.4. At the conclusion of the 6-week period, the value decreases to 3.4. By the end of the study, it is further reduced to 1.2, resulting in a mean difference of 3.2 from the initial baseline. The difference mentioned above was found to be statistically significant, with a p-value of less than 0.01. This result is consistent with another study conducted by Kuo et al, Pinto et al, Giannantoni et al, and Akiyama et al, where the reduction in Mean VAS SCALE at the end of the study was 1.86, 4.1, 3.2, and 4.6, respectively.[35,36,37,38]

The baseline value in the Chondroitin Sulphate group was 5.5. At the conclusion of the 3-month period, the value decreased to 3.1. By the end of the study, it further decreased to 2.1. The mean reduction in the VAS scale was 3.4. The difference mentioned above was found to be statistically significant, with a p-value of less than 0.01. The mean reduction in our study is comparable to that reported by Nickel et al, which was 3.6, and Nordling et al, which was 1.9.[40,41,39]

The mean reduction in the VAS scale was 3.2 in the botulinum toxin group, compared to 3.4 in the chondroitin sulphate group. Therefore, a statistically significant decrease in the average VAS scale is observed to a greater extent in the botulinum toxin group compared to the chondroitin sulphate group, with a p-value of less than 0.01.

The study compared the number of urgency episodes per 24 hours before and after treatment. In the botulinum toxin group, the baseline mean urgency episodes were 2.0, which decreased to 0.5 after 6 months. This represents a mean reduction of 1.5 compared to the chondroitin sulphate group, where the baseline mean urgency episodes were 2.6. After 6 months, the number of urgency episodes decreased to 1.1, which is also a mean reduction of 1.5. The observed difference is statistically significant, as indicated by a p-value of less than 0.05. In the study conducted by Nordling et al, a total of 165 patients with bladder pain syndrome (BPS) were included. The average number of urgency episodes at the beginning of the study was 6.9, and by the end of the study, it had decreased to 4.0. The mean reduction in urgency episodes was 2.9.[39]

In the study conducted by Nickel et al on 53 patients with bladder pain syndrome (BPS), the average number of urgency episodes was 7.4 at the beginning of the study, 4.7 after 3 months, and 3.5 after 6 months. The reduction in the mean number of urgency episodes was 3.9. [40,41]

Assessment of the frequency of urgency incontinence episodes per 24 hours before and after treatment

In our study, the average number of urgency incontinence episodes per day at the beginning of the 6-month period was 1.7 in the group receiving botulinum toxin. By the end of the 6 months, this number decreased to 0.5, resulting in a mean reduction of 1.2 episodes compared to the group receiving chondroitin sulphate. In the chondroitin sulphate group, the baseline average number of urgency incontinence episodes was 0.3, which decreased to 0.1 by the end of the 6 months, resulting in a mean reduction of 0.2 episodes. The observed difference between the two groups is statistically significant, with a p-value of less than 0.05. However, in the chondroitin sulphate group, the difference from baseline to 6 months is not statistically significant, with a p-value greater than 0.05.

The study compared the voided volume per micturition before and after treatment. In the botulinum toxin group, the baseline mean voided volume per micturition was 130.9, which increased to 266.8 after 6 months. This represents a mean difference of 135.9 in bladder capacity compared to the chondroitin sulphate group. In the chondroitin

sulphate group, the baseline mean voided volume per micturition was 118.18, which increased to 217.04 after 6 months. This represents a mean difference of 98.86 in bladder capacity. The observed difference is statistically significant, as indicated by the p-value of less than 0.05. A study conducted by Akiyama et al. found that the initial average voided volume was 111.4, and by the conclusion of the study, it had increased to 131.8. This increase was statistically significant, with a p-value of 0.04.[38]

Analysis of suprapubic pain episodes prior to and following treatment:

In our study, the initial average number of suprapubic pain episodes per day in the group treated with botulinum toxin was 5.09. By the end of the 6-month period, this number decreased to 0.9, resulting in a mean reduction of 4.19 compared to the group treated with chondroitin sulphate. In the chondroitin sulphate group, the initial average number of suprapubic pain episodes per day was 5.9, which decreased to 2.8 by the end of the 6-month period, resulting in a mean reduction of 3.1. The observed difference between the two groups at 6 months is statistically significant, as indicated by a p-value of <0.05. However, there was no statistically significant difference at 6 weeks, 3 months, and 6 months, as the p-value was >0.05 in these instances. Within the botulinum toxin group, a total of 6 patients requested to undergo retreatment within a timeframe of 6 to 9 months. They had received subsequent injections. In the study conducted by Kuo HC et al, a total of 81 patients were included. Out of these, 20 patients received a single injection of botulinum toxin, 19 patients received 2 injections, 12 patients received 3 injections, and 30 patients received 4 injections. Patient groups that received 4 repeated injections (P = 0.0242) and 3 injections (P = 0.050) had significantly higher success rates compared to those who received only one injection. Repeated intravesical administration of botulinum toxin is both safe and effective for providing pain relief in patients with bladder pain syndrome (BPS). [44]

Comparison of adverse effects after treatment: In our study of the Botulinum toxin group, after 6 months, 2 out of 22 patients (9%) experienced dysuria, 3 patients (14%) had urinary tract infections, and 1 patient (5%) had acute urinary retention. In a similar study by Kuo et al, out of 29 patients [35], 2 patients (10%) had dysuria, 2 patients (7%) had a large post-void residual volume, and 1 patient (3%) had acute urinary retention. In the study conducted by Pinto et al, it was found that out of a total of 26 patients, 5 patients (19.2%) had urinary tract infections [42]. In the study conducted by Akiyama et al, it was found that out of a total of 34 patients, 3 patients (8.8%) had a significant increase in pulmonary vascular resistance (PVR) [38]. In the study conducted by Giannantoni et al, it was found that 2 out of 14 patients, accounting for 14% of the total, experienced dysuria. [37] Among the 22 patients in the chondroitin sulphate group, 2 (9%) experienced dysuria and 2 (9%) had urinary tract infections (UTIs). In a separate study conducted by Nickel et al, it was found that out of a total of 53 patients, 20 (37%) experienced treatment-related side effects. These side effects included genital pain, vaginitis in 10 patients, urinary tract infections (UTIs) in 6 patients, and bladder storage symptoms in the remaining patients [40,41]. In the study conducted by Porru et al (2008), it was found that 2 out of the total number of patients (8.6%) had urinary tract infections (UTI). [33,34]

CONCLUSION

Overall, intra-trigonal botulinum toxin 100IU is a suitable treatment choice for patients with bladder pain syndrome (BPS) who experience neuralgic pain and have not responded to other forms of treatment such as intravesical therapy, conventional pharmacotherapy, myofascial physiotherapy, massage therapy, and lifestyle modifications. This treatment option has a lower risk of side effects that are considered acceptable. Intravesical chondroitin sulphate, administered in a volume of 20ml with a concentration of 2%, is a type of intravesical therapy that requires frequent instillations. However, its effectiveness is lower when compared to intra-trigonal botulinum toxin, which is administered at a dosage of 100IU. Prior to initiating intravesical therapy, it is imperative to carefully evaluate and select appropriate patients in order to optimise the outcomes of the proposed treatment.

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