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Adjunctive Oral Tacrolimus following fulguration in Hunner's lesion bladder pain syndrome/ Interstitial cystitis: A Pilot Study

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ABSTRACT

Introduction and Hypothesis: Hunner's lesion disease is increasingly recognised as a distinct phenotype of bladder pain syndrome/interstitial cystitis (BPS/IC). Given the immune-mediated pathways implicated in its pathogenesis, we hypothesised that adjunctive oral tacrolimus following fulguration may improve symptoms in patients with Hunner's lesion BPS/IC.

Methods: In this single-centre prospective pilot study, twelve patients with cystoscopically confirmed Hunner's lesions received oral tacrolimus (0.04 mg/kg/day) for 10 weeks following standard fulguration. Symptoms were assessed using the validated Apollo clinical scoring

system (ACS) at baseline and at 4, 8, and 12 weeks, and 6 months. Tacrolimus trough levels and biochemical safety parameters were monitored serially.

Results: The median baseline scores were 16/20 for pain, 8/10 for nocturia, 4/5 for urgency, 4/5 for frequency, 4/5 for psychosocial impact, and 37/50 for the overall ACS. Significant improvements in the median overall ACS and all symptom domains were observed at 4, 8, and 12 weeks compared with baseline ($p<0.001$). Improvements in the overall ACS and non-pain domains was sustained at 6 months, whereas pain scores no longer differed significantly from baseline ($p=0.067$). All patients demonstrated clinically meaningful reduction in ACS, with excellent clinical response (ACS reduction >30 points) observed in four patients at 4 weeks, and one patient at 6 months. Tacrolimus was generally well tolerated. Mild dyspepsia was the most common adverse event. One patient developed a urinary tract infection responsive to antibiotics, and no clinically significant biochemical toxicities were observed.

Conclusion: Adjunctive oral tacrolimus following fulguration demonstrated encouraging preliminary signals of clinical benefit with an acceptable safety profile in Hunner's lesion BPS/IC. Controlled studies are required to determine its incremental efficacy and long-term safety.

Keywords: Tacrolimus, Hunner's lesion, Interstitial cystitis, Bladder pain syndrome, pilot study

Brief summary

In this prospective pilot study, adjunctive oral tacrolimus demonstrated preliminary clinical benefit and acceptable short-term safety in Hunner's lesion type of BPS/IC**.**

Introduction

Bladder Pain Syndrome /Interstitial cystitis (BPS/IC) is a chronic disorder characterised by pain that worsens with bladder filling and is often accompanied by urinary urgency, frequency, nocturia in the absence of any identifiable causes such as infection, obstruction or neoplasia.[1] As per the Global Interstitial cystitis, Bladder pain Society (GIBS) defines BPS/IC as pain, pressure, or discomfort associated with the urinary bladder, often accompanied by urinary tract symptoms for more than 3 months after exclusion of other identifiable pathology.[2] BPS/IC comprises heterogeneous clinical phenotypes, among which Hunner lesion disease is increasingly recognised as a distinct entity.[4,5] Hunner lesions represent characteristic inflammatory mucosal lesions identified on cystoscopy and are associated with a bladder-centric disease process and intense transmural inflammation.[3,6] Histopathological studies have demonstrated epithelial denudation, pancystitis, clonal B-cell expansion, and lymphoplasmacytic infiltration in patients with Hunner lesions, suggesting that immune dysregulation contributes to disease pathogenesis.[7] In addition, abnormalities involving B-cell activation, cytokine expression, angiogenic pathways, and T-cell-mediated immune responses have been described in this phenotype of BPS/IC.[8–13] Collectively, these findings support the hypothesis that Hunner lesion disease may represent an immune-mediated inflammatory condition.

Systemic immunomodulation has therefore emerged as a potential therapeutic strategy in selected patients with Hunner lesion BPS/IC. Oral cyclosporine, a calcineurin inhibitor, has demonstrated clinical benefit, particularly in patients with Hunner lesions; however, concerns regarding its adverse effect profile and narrow therapeutic window have limited its widespread use in this benign condition.[8] Tacrolimus is a more potent calcineurin inhibitor that exerts its effects through inhibition of the calcineurin–nuclear factor of activated T cells (NFAT) pathway, resulting in suppression of interleukin-mediated T-cell activation and modulation of

downstream inflammatory responses.[14,15] Experimental evidence also suggests that calcineurin inhibition may attenuate angiogenic signalling through NFAT-dependent pathways.[16,17] Despite these mechanistic advantages, the use of tacrolimus in patients with Hunner lesion BPS/IC has not been evaluated.

We therefore undertook this prospective pilot study to evaluate the safety and preliminary clinical outcomes associated with adjunctive oral tacrolimus following fulguration in patients with Hunner lesion BPS/IC. We hypothesised that adjunctive tacrolimus therapy would be associated with improvement in symptom burden, as assessed by the Apollo Clinical Score, while demonstrating an acceptable short-term safety profile.

Materials and methods

This single-centre prospective interventional pilot study was conducted in the Department of Urology and Robotic Surgery, at Indraprastha Apollo hospitals, New Delhi, India. The study was approved by the Institutional Ethics Committee of Indraprastha Apollo hospitals, New Delhi (Institute Review Board No.-APP035IAHSep/23), and the Drug Controller General of India (DCGI) was duly notified of the study in accordance with applicable institutional requirements. This study was a 'pilot study' and not a 'clinical trial ', hence it wasn't registered in the central clinical trial registry All methods were performed in accordance with the relevant guidelines and regulations. This has been included in the manuscript

Study population

Between August 2023 to October 2024, 12 consecutive patients presenting with bladder pain syndrome/interstitial cystitis (BPS/IC) and fulfilling the Global Interstitial Cystitis/Bladder Pain Society (GIBS) diagnostic were enrolled. All patients underwent cystoscopic evaluation using a standardised institutional methodology. [18] Patients in whom Hunner lesions were identified underwent fulguration as part of routine lesion-directed management. Subsequently,

as per the institute's phenotyping protocol procedure [5], eligible patients were counselled regarding participation in this investigator-initiated pilot study evaluating adjunctive oral tacrolimus following fulguration. Written detailed informed consent as per standard guidelines was obtained from all participants prior to enrolment.

Intervention

All enrolled patients received oral tacrolimus at a dose of 0.04 mg/kg/day for 10 weeks. Prior to initiation of therapy, all patients were evaluated by a senior nephrologist to assess suitability for calcineurin inhibitor therapy and to guide safety monitoring. Concomitant standard symptomatic therapy for BPS/IC was permitted as per institutional practice.

Assessments and follow-up

Symptom severity was assessed using the validated Apollo Clinical Score (ACS), administered at baseline (pre-fulguration) and at 4, 8, and 12 weeks, and at 6 months after initiation of tacrolimus therapy. Safety monitoring included complete hemogram, renal and liver function tests, fasting blood glucose, lipid profile, and urine routine examination performed at baseline and at weeks 2, 6, and 10. Tacrolimus trough levels were measured at week 2 to guide dose adjustment, with a target range of 4–6 ng/mL. Glycosylated haemoglobin (HbA1c) was assessed at week 10.

Patients were excluded if they had pregnancy, lactation, known hypersensitivity to macrolides, chronic liver disease, chronic pulmonary disease, cardiomyopathy, malignancy, paediatric age group, recent unexplained viral illness, or concomitant use of cytochrome P450-modulating drugs. Treatment discontinuation criteria included acute kidney injury, acute liver injury, refractory hyperkalaemia, uncontrolled hyperglycaemia, or any life-threatening adverse event.

Statistical analysis

Continuous variables were summarised as median values. Changes in ACS over time were analysed using non-parametric repeated measures methods, with $p<0.05$ considered

statistically significant. Statistical analysis was performed using appropriate standard statistical software (details to be specified).

Results

Twelve patients with Hunner lesion bladder pain syndrome/interstitial cystitis were included in the analysis. The mean age was 46.2 years, and the female-to-male ratio was 3:1. Eight patients (66.7%) were from urban areas, while four (33.3%) were from rural areas. Of the rural patients, three (75%) were female and one (25%) was male. Similarly, among urban patients, six (75%) were female and two (25%) were male.

Baseline characteristics

The median baseline overall Apollo Clinical Score (ACS) was 37/50. Domain-wise baseline medians were 16 for pain, 8 for nocturia, and 4 for urgency, frequency, and psychosocial impact. Three patients were sexually active at baseline, with a median sexual function domain score of 4/5 in this subgroup, Only three patients were sexually active, the scores for this domain in all other patients was kept as zero. In three patients who were sexually active, the baseline score was 4/5.

Clinical outcomes

Improvement in median overall ACS and all symptom domains was observed at 4, 8, and 12 weeks compared with baseline (all $p<0.001$). At 6 months, improvement remained statistically significant for overall ACS and all domains except pain, which showed a non-significant change compared with baseline ($p=0.067$). The magnitude of improvement in individual patients is shown in Table 1.

Clinical response

All patients showed reduction in symptom burden during treatment, achieving a good clinical

response defined as drop in median ACS score less than 20 points. An excellent clinical response (ACS reduction >30 points) was observed in four patients at 4 weeks, two at 8 weeks, two at 12 weeks, and one patient at 6 months. One patient had a limited response at 6 months with a 15-point reduction in ACS. In the three sexually active patients, improvement in the sexual function domain was reported during treatment and follow-up

No patient discontinued due to adverse events during the study. The most common adverse event was mild dyspepsia (3/12 patients). One patient developed diarrhoea and one reported transient tremor, which did not require intervention. No clinically significant abnormalities were observed in glycaemic parameters, lipid profile, or renal and liver function tests during follow-up. The safety outcome in individual patients is shown in Table 2.

Discussion

The present pilot study evaluated the efficacy and safety of oral tacrolimus in patients diagnosed with Hunner lesion subtype of Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC), a chronic inflammatory bladder condition characterized by urothelial injury and mucosal lesions. Twelve patients were treated with oral tacrolimus for 10 weeks and followed for up to 6 months.

The study cohort demonstrated a female predominance (75%), consistent with the known epidemiology of BPS/IC. Baseline age distribution and symptom severity were comparable with previously reported series, supporting the clinical representativeness of the enrolled population.[20]

Clinically meaningful improvement was observed in all symptom domains, including pain, urgency, frequency, nocturia, and psychosocial impact, with significant reductions in the Apollo Clinical Score (ACS) at 4, 8, and 12 weeks, sustained up to 6 months. The magnitude

and consistency of improvement across multiple domains suggest a broad symptomatic benefit in this subgroup of patients with Hunner lesions.

Pain reduction was most prominent during the treatment phase and remained significant through 12 weeks; however, a partial attenuation of benefit in some patients by 6 months suggests that treatment duration or maintenance strategies may be relevant considerations in sustaining long-term response. This is further supported by the observation that the majority of patients (10/12) expressed willingness to continue therapy beyond the study period due to perceived clinical benefit, reflecting the burden and chronicity of this disease.[21]

Limited prior evidence exists regarding systemic immunomodulation in this phenotype. Notably, previous studies evaluating steroid-based approaches in refractory BPS/IC have suggested that systemic therapy may be required in addition to local treatment in selected patients, supporting the broader concept of immune-targeted therapy in this condition. [22]

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The observed clinical response may be biologically plausible given the immune-mediated inflammatory milieu described in Hunner lesion disease, including T-cell activation, cytokine upregulation, and angiogenic signalling. In past ,calcineurin inhibition through tacrolimus may modulate these pathways, thereby reducing inflammatory activity[23] Although intravesical tacrolimus has been used in this condition earlier[24], the present study utilises systemic use of this molecule . However, mechanistic inference cannot be confirmed in the present study.[27]

The cost and monitoring requirements associated with tacrolimus are relevant considerations; however, these must be weighed against the chronic symptom burden, repeated interventions, and impact on quality of life in refractory Hunner lesion disease. The safety of. Calneuron inhibitors has been widely studied and documented elsewhere [25-28]. During this study, oral tacrolimus was generally well tolerated. Adverse events were mild and included dyspepsia, diarrhoea, and isolated tremor, none of which required treatment discontinuation. Importantly,

no clinically significant nephrotoxicity, metabolic derangements, or haematological abnormalities were observed during the study period, although the small sample size and limited duration warrant cautious interpretation.

This study has several limitations, including small sample size, single-centre design, lack of control group, and reliance on a symptom-based scoring system. These factors limit generalisability and preclude definitive conclusions regarding efficacy. Nonetheless, the consistent improvement across multiple time points provides preliminary evidence supporting further evaluation in larger controlled studies.

Conclusion

In this pilot study, oral tacrolimus was associated with clinically meaningful improvement in symptoms of Hunner lesion BPS/IC with an acceptable short-term safety profile. These findings warrant confirmation in larger, controlled, multicentre studies with longer follow-up to define durability of response and optimal treatment duration.

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Tables

Table 1: **Individual Change in Apollo Clinical Score (ACS) from baseline during follow-up**.

Patient ID	**ΔACS (4 weeks)**	**ΔACS (8 weeks)**	**ΔACS (12 weeks)**	**ΔACS (6 months)**
P1	32	30	30	30
P2	25	25	25	15
P3	27	25	25	23
P4	23	22	22	22
P5	25	23	23	23
P6	31	29	24	22
P7	23	23	23	22
P8	30	27	26	21
P9	29	28	28	28
P10	28	28	28	28
P11	25	24	24	22
P12	32	31	31	28
Patients with excellent response (>30)	4	**2**	**2**	**1**

Note: Values represent reduction in ACS from baseline. Excellent response defined as reduction >30 points.

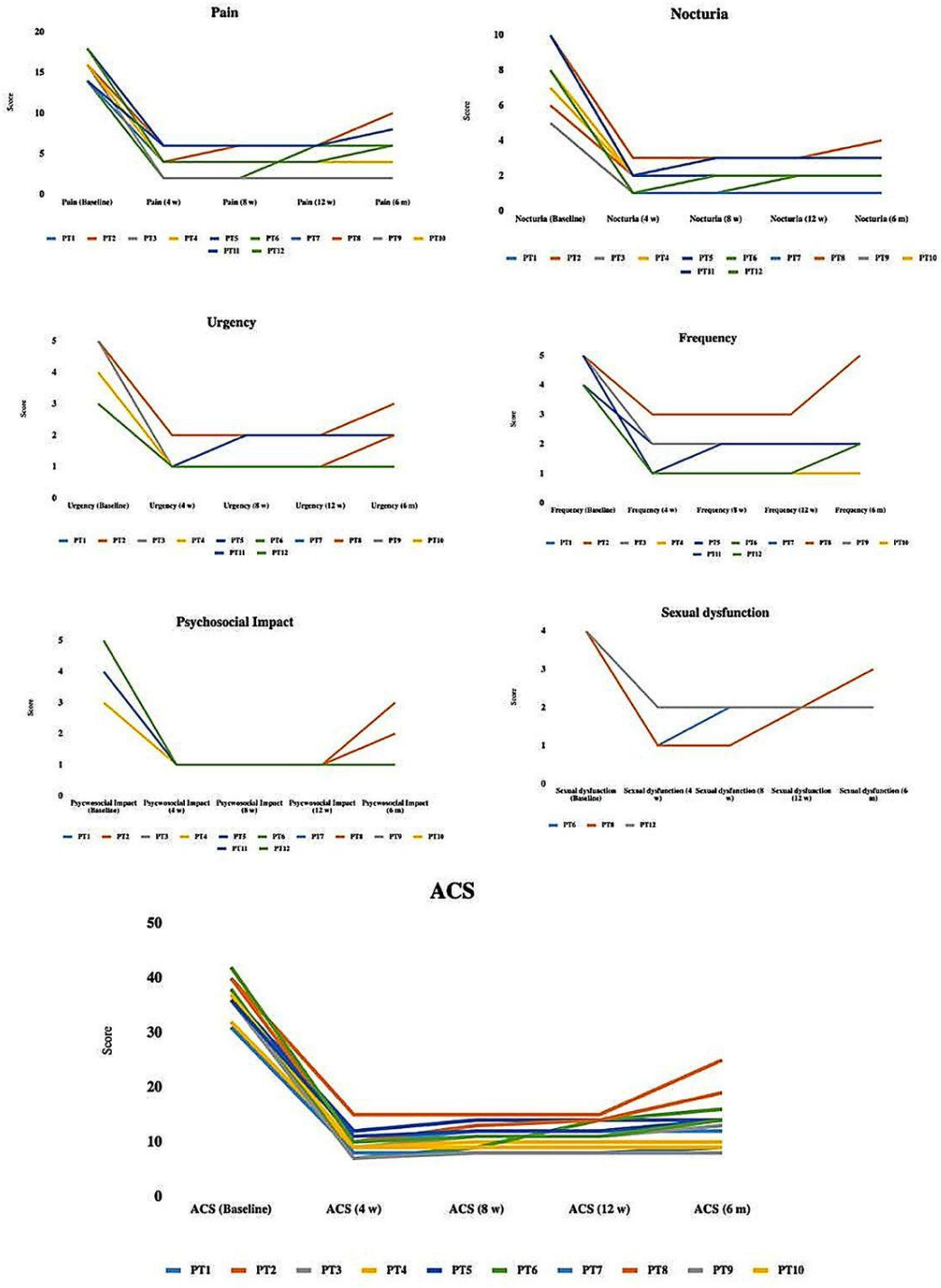
Table 2: Adverse events during tacrolimus therapy (Safety population, n=12)

Adverse event	n (%)
Mild dyspepsia	3 (25.0)
Diarrhoea	1 (8.3)
Tremor	1 (8.3)
Headache	0 (0)
Tingling/numbness	0 (0)
Insomnia	0 (0)
Dyslipidaemia	0 (0)
Elevated blood pressure	0 (0)
Hyperglycaemia	0 (0)
Oedema	0 (0)
Neurotoxicity/seizures	0 (0)
Nephrotoxicity	0 (0)
Note: All adverse events were mild in severity and self-limiting. No treatment discontinuations were required due to adverse events.	

347 **Figure 1 Depiction of. Domain wise plotting of Apollo clinical score in twelve patients**

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Figure 2 Median Apollo Clinical Score (ACS) Over Time.jpg

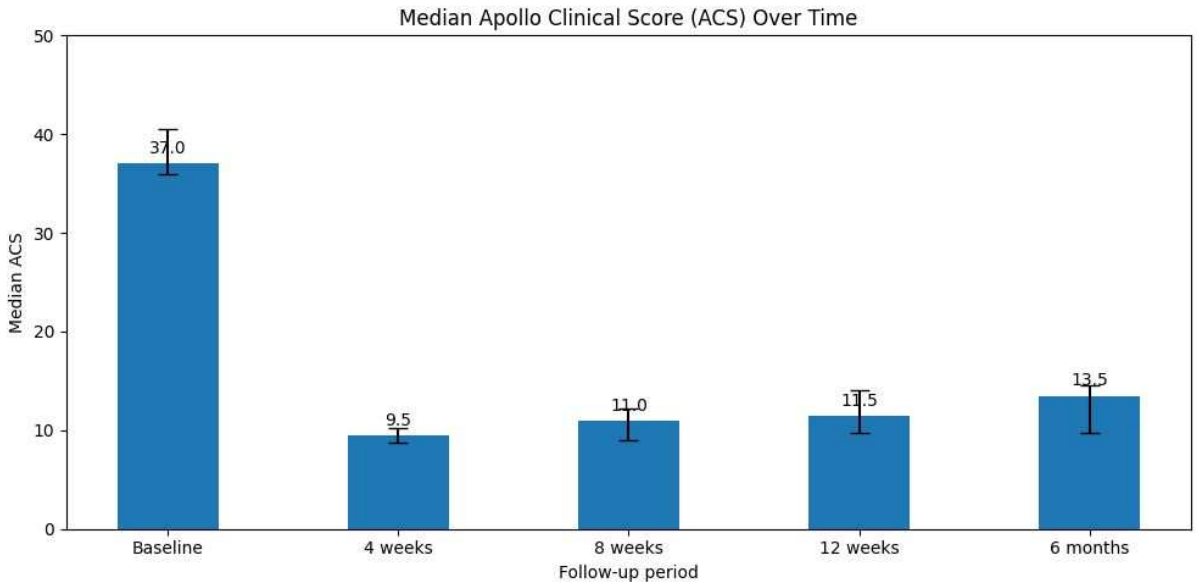


Figure 3 Change in ACS Over Time

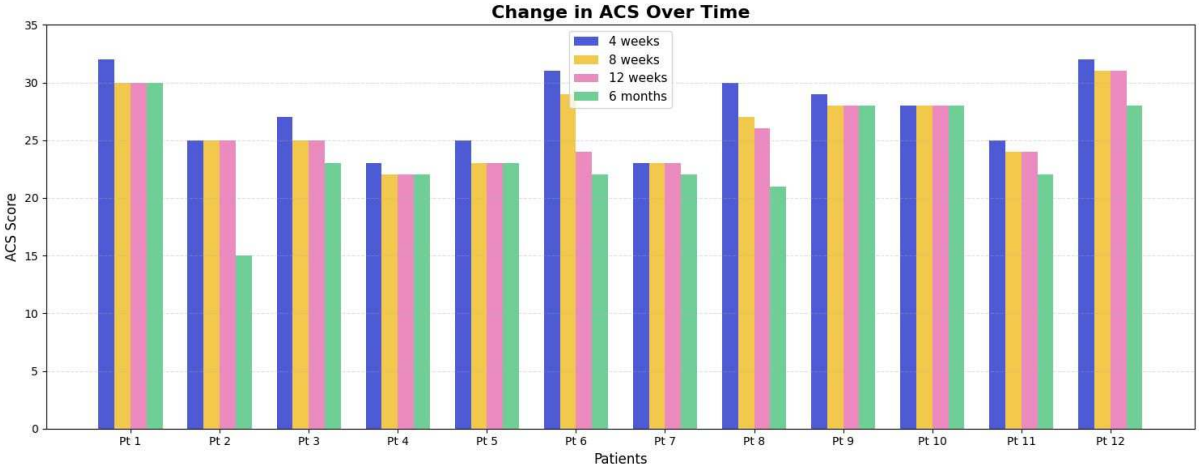
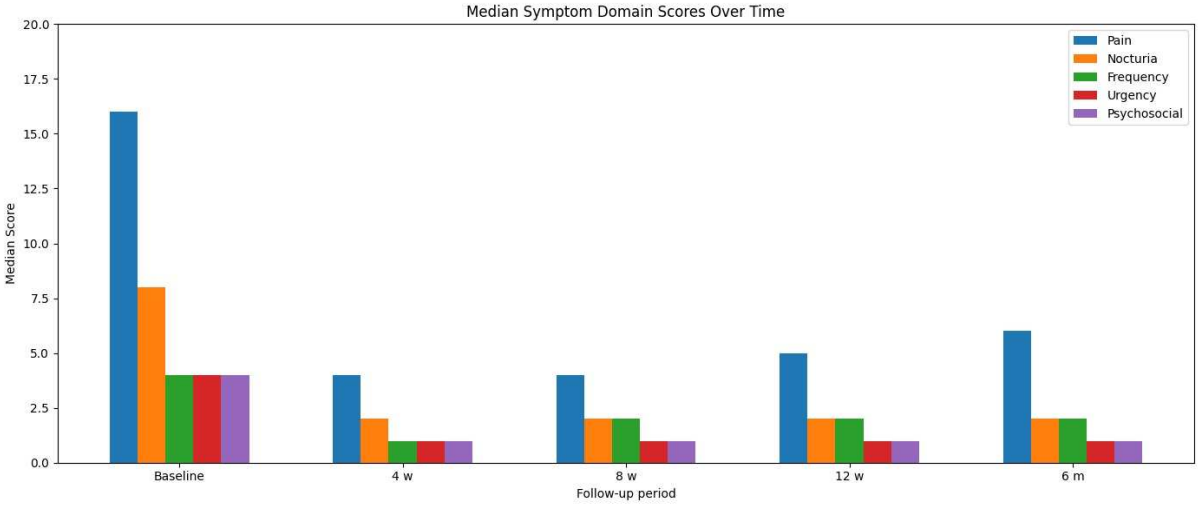


Figure 4 Median Symptom Domain Scores Over Time



Annexure1 Apollo clinical Scoring System for Interstitial Cystitis / Bladder Pain syndrome

1.Urgency (0-5)

How often have you felt the strong need to urinate with little or no warning?
0. Not at all
1. Less than l in 5 times
2. Less than half the time
3. About half the time
4. More than half the time
5. Almost always

2. Frequency (0-5)

How often have you had to urinate less than 2 hours after you finished urinating?
0. Not at all
1. Less than l time in 5
2. Less than half the time
3. About half the time
4. More than half the time
5. Almost always

3. Nocturia (0-10)

How often did you most typically get up at night to urinate?

0. Never
2. Once
4. 2 times

6. 3 times
8. 4 times
10. 5 times or more

4. Pain (0-20)

Have you felt Burning, pain, discomfort, or pressure in your bladder?

0. Not at all
4. Once a day
8. A few times a day
12. Fairly often
16. Almost always
20. Persistent pain that is not reduced after emptying bladder

5. Sexual dysfunction (0-5)

A Female

0. No problem in sexual activity
1. Can engage in sexual activity with minimal discomfort.
2. Non penetrative genital contact can be tolerated.
3. No genital contact can be tolerated.
4. Vulvodynia
5. Aversion to sexual thoughts

B Male

0. No problem in sexual activity
1. Post ejaculatory discomfort.
2. Moderate to severe pain post ejaculation
3. Pain at the time of erection
4. Complete loss of erection
5. Loss of libido with ED

6.Psychological impact (0-5)

How much have the symptoms bothered you mentally (score 0-5):

0. No problem
1. Very small problem
2. Small problem
3. Medium problem
4. Big problem
5. Suicidal tendency

Total Score …… /50