ORIGINAL RESEARCH PAPER

Urology

ROLE OF ORAL PENTOSAN POLYSULFATE IN TREATMENT OF DOUBLE J STENT RELATED LOWER URINARY SYMPTOMS – A PILOT STUDY.

KEY WORDS:
Glycosaminoglycans, Pentosan Polysulfate , Questionnaires.

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ABSTRACT

Introduction – Double J stents affect the quality of life in up to 80% of cases, in this study we intended to evaluate the role of Pentosan Polysulfate (PPS) – an analogue of urinary bladder glycosaminoglycans in relieving Double J stent related symptoms.
Methods –82 patients were randomised into 4 groups, group A (N=21) received PPS 100 mg once daily for 2 weeks, group B (N=20)-PPS 100 mg thrice daily for 2 weeks, group C (N=19) -PPS 100 mg thrice daily for 1st week then placebo for 2nd week & group D (N=22) - placebo. Treatment was started at 1st week post surgery till removal of stent at 3rd week. All patients were evaluated with ureteral stent symptom questionnaire. Statistical tests were applied and level of significance was set at p value<0.05.
Results – Urinary symptoms, body pain and general health scores were significantly lower with PPS both after 1st and 2nd week of treatment as compared to placebo (p value < 0.05). Improvement in work performance and additional health problem scores was not significant and sexual health scores did not improve on PPS, 100 mg thrice daily dose had lower scores after 1st week of treatment in comparison to once daily dose but after 2 weeks the difference was not significant.
Conclusion: Pentosan Polysulfate (PPS) is a safe, well tolerated and effective drug in relieving DJ stent related symptoms. It can be started at 100 mg thrice daily dose and can be reduced to once daily dose after 1 week.

Introduction:

Ureteral stents are an integral part of urologic procedures since the time their first use was reported in 1967 by Zimskind[1] .Since its introduction there have been many advancements in the design and material of stents like the design of double J stent by Finney and Hepperlen[2] which has low migration rates. Despite the advancements more than 80% of patients experience bothersome stent related symptoms [3] such as lower urinary tract symptoms suprapubic pain, sexual dysfunction, hematuria, flank pain and reduced work capacity[4-6].

The pathophysiological basis of these symptoms is not yet fully understood [7]. Irritation of bladder mucosa, reflux of urine, smooth muscle spasm are all thought to contribute to the symptoms [8-9]. Liu et al [10] in 2015 reported that presence of stent causes friction in the bladder and causes loss of glycosaminoglycans (GAG's) in urine, thus exposing the bladder epithelium to urinary solutes and toxins which may contribute to stent related symptoms. GAGs are an important component of urothelium and their wide layer regulates basement membrane permeability [11]. Loss of GAG has been linked with diseases such as interstitial cystitis, recurrent urinary tract infections, chemical & radiation cystitis [12].

Pentosan Polysulfate (PPS) is an analogue of GAG's [13] and is a bladder mucosal protective agent and is primarily used for the treatment of interstitial cystitis[14]. Parsons et al [11] and Mulholland et al [15] in a guinea pig model showed that PPS can form a poly anionic layer of GAG over the bladder that resembles the natural mucosa of the uninjured bladder and protects the bladder mucosa from any insult.

Therefore, we designed this pilot study to investigate whether ureteral stent related symptoms are affected by treatment with PPS and to further analyze that injury of the GAG layer is causally linked to stent related symptoms.

Materials and Methods:

This prospective study was conducted in our department of urology. A total of 118 patients aged 18 to 50 years who underwent Double J (DJ) stenting following uneventful endourological procedures either percutaneous nephrolithotomy (PCNL) for stones size < 25 mm or ureteroscopic lithotripsy(URSL) for stone size <12 mm were evaluated for enrolment in the study. Patients with residual stone fragments post surgery, bilateral DJ stents , history of use of anticholinergic drugs, selective alpha 1 blockers, nitrate drugs in perioperative period, history of chronic use of analgesic drugs , known cases of neurogenic , overactive bladder , any prostate or uretheral pathology leading to irritative symptoms, history of lower urinary tract surgery in past, acute or chronic renal insufficiency, urinary tract infection , patients of interstitial cystitis , patients on anticoagulants , allergy to the study drugs, pregnant or lactating females were excluded from the study. Written informed consent was taken from all patients enrolled in the study after explaining them the nature of treatment.

At the time of surgery the decision for stent placement was taken by operating urologist, depending upon mucosal trauma, whether ureteral dilation was performed and large stone burden.

Polyurethane DJ stent of the same size (5Fr / 26cm) and from same manufacturer (Biorad Medisys) was used in all the cases. Postoperative X-ray kidney, ureter, bladder was done in all patients to rule out residual stone fragment and to confirm position of stent. Foleys catheter was removed on post operative day 1st in all the cases and nephrostomy tube on day 2nd after PCNL. All patients

were given analgesics (tablet diclofenac 50mg thrice daily) for 1st three days after surgery and were discharged on Tab. levofloxacin 500 mg once daily for 7 days as per our institute protocol. Patients were informed about stent related symptoms and a copy of Ureteral Stent Symptom Questionnaire (USSQ) was given to them on discharge and they were advised to report back on 7th day post surgery with filled questionnaire.

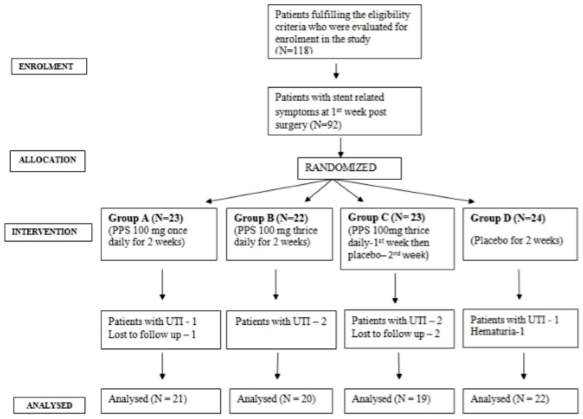
Out of 118 cases evaluated 92 (77.96%) reported bothersome stent related symptoms at 7th day post surgery and were then enrolled in study and randomised in 4 groups (A,B,C,D) by chit in box method. Group A was put on pentosan polysulfate (PPS) 100 mg once daily dose for 2 weeks, group B on PPS 100 mg thrice daily for 2 weeks, group C on PPS 100 mg thrice daily for 1st week then placebo for 2nd week and group D – placebo for 2 weeks. The drugs were started at 1st week after surgery till removal of DJ stent at 3rd week. All patients completed USSQ at 1st week post surgery (i.e. before starting drug) then at 2nd week and 3rd week post surgery.DJ stent was removed in all patients at 3 weeks post surgery. Urine Culture was repeated at 1st week and 2nd week after starting drug and any culture positive case was excluded from evaluation.

Patients were informed about side effects of drug without attention to the group number and were asked to immediately stop the drug and inform the study team if they experienced any side effect. Double blinding was followed to minimise bias.

Statistical Analysis:
Data so collected was tabulated in an excel sheet, under the guidance of statistician. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS), version 23 for Windows (SPSS inc. Chicago, IL, USA) and Primer for the generation of descriptive and inferential statistics. The Categorical data were presented as numbers (percentage) and were compared among groups using Chi Square test. The quantitative data were presented as mean and standard deviation and were compared using ANOVA Test and Post Hoc Test (Tukey Test) was applied to find out the most significant group among all the groups. Probability P value <0.05 was considered statistically significant.

Results:
92 patients with stent related symptoms and were started on treatment after randomization into 4 groups, during the course of study 3 patients were lost to follow up, 6 had positive urine culture so excluded from evaluation and 1 patient had gross hematuria, so the data of remaining 82 patients were analysed. The study design is presented in figure 1.

Figure legend :



PPS – Pentosan Polysulfate, UTI –urinary tract infection
None of the patients during the study period had side effects leading to discontinuation of treatment.

Table 1 shows the baseline characteristics of the patients in all the study groups, there was no statistically significant difference regarding male: female ratio, mean age and average height among the study groups.

Baseline characteristics of the patients in all the groups

Parameters	Group A (PPS 100 mg once daily for 2 weeks)	Group B (PPS 100 mg thrice daily for 2 weeks)	Group C (PPS 100mg thrice daily -1st week then placebo -2nd week)	Group D (Placebo for 2 weeks)	P value
No. of Patients (N = 82)	21	20	19	22	---
Male : Female	14 : 7	14 : 6	13 : 6	15 : 7	1.000[a]
Mean age ± SD (years)	33.62 ± 9.3	32.85 ± 7.6	35.05 ± 8.7	36.14 ± 8.8	0.67[b]
Average Height ± SD (cm)	165.38 ± 8.11	168.4 ± 7.22	167.21 ± 6.52	166.5 ± 8.08	0.62[b]

PPS – Pentosan polysulfate , SD – Standard deviation ,a-chi square test,b – ANOVA (analysis of variance)

Table 2 : Comparison of ureteral stent symptom questionnaire (USSQ) domain scores (mean ± standard deviation) among study groups – after one week of starting treatment.

USSQ Domains	Group A (N=21)	Group B (N=20)	Group C (N=19)	Group D (N=22)	P value			
					A v/s D[a]	B v/s D[a]	C v/s D[a]	A v/s B[a]
Urinary Symptoms	29.33±2.4	21.3±2.9	20.5±2.03	37.95±1.7	<0.001	<0.001	<0.001	<0.001
Body Pain	15.47±2.8	13.4±3.3	14.2±1.8	20.31±1.8	<0.001	<0.001	<0.001	.047
General Health	15.38±2.1	13.95±1.9	14.36±1.9	17.4±1.9	.006	<0.001	<0.001	.100
Work Performance	6.19±4.1	5.45±4.4	5.52±3.33	7.63±5.9	.749	.445	.489	.959
Sexual Health	5.57±3.9	5.5±3.9	5.84±4.19	5.45±4.03	.959	.959	.959	1.000
Additional Problems	9.6±2.008	9.55±1.9	9.21±1.43	9.68±1.8	1.000	.995	.841	.997

a-Post HOC test
USSQ - ureteral stent symptom questionnaire , PPS - Pentosan polysulfate
Group A- PPS 100 mg once daily for 2 weeks,
Group B - PPS 100 mg thrice daily for 2 weeks.
Group C - PPS 100mg thrice daily -1st week then placebo -2nd week.
Group D- Placebo for 2 weeks.

Table 3 : Comparison of ureteral stent symptom questionnaire (USSQ) domain scores (mean ± standard deviation) among study groups – after 2nd week of starting treatment.

USSQ Domains	Group A (N=21)	Group B (N=20)	Group C (N=19)	Group D (N=22)	P value			
					A v/s D[a]	B v/s D[a]	C v/s D[a]	A v/s B[a]
Urinary Symptoms	20.19±1.9	19.55±2.7	37.15±1.6	38.22±1.7	<0.001	<0.001	.344	.747
Body Pain	12.95±2.7	12.55±3.15	21.3±2	20.45±2.4	<0.001	<0.001	.715	.960
General Health	12.80±2.44	12.6±1.8	16.36±1.2	17.22±1.45	<0.001	<0.001	.417	.982
Work Performance	5.23±3.6	5.15±4.22	7±4.9	7.54±5.9	.389	.367	.983	1.000
Sexual Health	5.47±2.9	5.35±3.12	5.63±3.17	5.5±3.3	1.000	.999	.999	.999
Additional Problems	9.3±1.9	9.2±1.9	9.68±1.2	9.54±1.8	.990	.918	.994	.987

a-Post HOC test

USSQ - ureteral stent symptom questionnaire , PPS - Pentosan polysulfate

Group A- PPS 100 mg once daily for 2 weeks,
Group B - PPS 100 mg thrice daily for 2 weeks.

Group C - PPS 100mg thrice daily -1st week then placebo -2nd week.

Group D- Placebo for 2 weeks.

Patients on PPS had lower scores for urinary symptoms, body pain and general health domains of USSQ after 1 week of treatment and the difference was statistically significant as compared to placebo (table 2 - p value group A v/s D, B v/s D ,C v/s D < 0.05). Work performance and additional problem scores were also lower in treatment groups but the difference with placebo was not statistically significant (p value >0.05), sexual health domain scores did not improve and were comparable to placebo.

Symptoms were improved both at 100 mg once daily as well as thrice daily dose as compared to placebo after 1 week of treatment (table 2 - p value A v/s D , B v/s D <0.05) , but reduction in urinary symptom and body pain score was more with thrice daily dose (table 2 - p value group A v/s B < 0.05) but after 2 weeks of treatment the difference in the USSQ scores between the two different dose groups of PPS was not significant (Table 3 - p value A v/s B >0.05).

Further in group C after 1 week i.e. till the patient was receiving PPS, urinary symptoms, body pain & general health scores were significantly lower as compared to placebo (Table 2 - p value C v/s D < 0.05) but when the patient was put on placebo for the 2nd week of treatment, the scores were higher and were statistically not different from placebo group (Table 3 - p value C v/s D > 0.05). Side effects of the drug were minimal and none of the patients left the study because of side effects of treatment.

Discussion:

In the practise of urology Double J stents are an indispensable tool. They prevent upper urinary tract obstruction, dilate the ureter passively, divert the urine and allow for faster tissue healing but however, up to 80 % of patients report stent related symptoms following its use[3]. These symptoms include frequency, urgency, dysuria, hematuria, suprapubic pain, flank pain, and sexual dysfunction[4-6] and contribute to reduced work capacity.

The pathophysiologic basis for these stent related symptoms is not fully understood[7]. Irritation of the bladder mucosa and especially the trigone area by the distal portion of the stent, reflux of urine, smooth muscle spasm are all thought to contribute to such symptoms [8-9]. Liu S and colleagues [10] in 2015 reported that presence of stent causes friction in the bladder wall and causes loss of glycosaminoglycans (GAG's) layer of the bladder epithelium in urine, thus exposing the bladder epithelium to solutes and other chemicals present in the urine which may be responsible for the symptoms. Parsons [11] had shown that the GAG layer covering the bladder epithelium acts as a barrier and is a nonspecific defence mechanism of bladder against infections, urinary solutes, and toxins and they also reported that disruption of this GAG layer can increase trans epithelial flux of urine components[11]. Lilly JD and Parsons CL[16] also found that removal of bladder surface GAGs by instillation of protamine sulfate can initiate lower urinary tract symptoms as well as supra pubic pain.

With ongoing advancements in understanding of the pathophysiology behind stent related symptoms, the management of such symptoms is improving. Joshi et al in 2003 [3,5] developed and validated a questionnaire called the ureteral stent symptom questionnaire (USSQ) which is currently an invaluable tool to address clinical decision making related to stent symptoms. It consists of 38 items examining 6 sections: urinary symptoms, pain, work performance, sexual matters, overall general health and additional problems. It is a sensitive tool for comparing and evaluating efficacy of different treatment modalities for treatment of stent related symptoms [3].

Attempts to reduce stent related symptoms have mainly focussed on altering the design of stents and pharmacologically treating the symptoms. Ho et al [17] (2009) and Giannarini et al [18] (2011) highlighted the role of adequate stent length and concluded that an adequate stent length such that it does not cross the midline in bladder has low incidence of stent symptoms. Yakoubi R et al [19] (2011) in their meta analysis concluded that there is statistically significant reduction in total USSQ scores in patients on alpha blockers. Park et al [20] (2009) Zhou L et al [21](2015) and concluded that anticholinergics can significantly reduce irritative urinary tract symptoms and pain post stent placement. Ragab M et al[22] (2017) were the first to report that pregabalin which is a structural analogue of the neurotransmitter gamma amino butyric acid is also an effective agent in reducing stent symptoms and it acts mainly by inhibiting the C nerve fibres in the bladder. Among the pharmacological agents alpha blockers, anti cholinergic agents and their combinations have been extensively used to treat stent symptoms.

To the best of knowledge our study is the first to evaluate the role of pentosan polysulfate in relieving stent related symptoms. Pentosan polysulfate is a semi synthetic, sulphated polysaccharide and is chemically and structurally similar to heparin and glycosaminoglycans [13]. It binds to bladder epithelium and repairs the GAG layer in the damaged areas of the epithelium, thus reducing permeability in damaged parts of this layer and preventing solutes and other chemicals from the urine to irritate the urothelium [13].

PPS also stabilizes the mast cells of the host immune system and acts as an anti inflammatory agent [23]. The literature carries no data as regard application of PPS in management of stent symptoms but as Liu S et al [10] had hypothesized that presence of stent causes friction in the bladder and causes loss of GAG's in urine and so we further hypothesise that repair of the GAG layer with PPS and also the anti inflammatory actions of PPS could be the factor responsible for relief from stent related symptoms.

Our study showed that there was significant improvement in urinary symptoms, body pain and general health scores with PPS, improvement in work performance and additional health problem scores was not significant and sexual health scores did not improve on PPS, further 100 mg thrice daily dose had more improvement in

scores initially in comparison to once daily dose but after 2 weeks the difference in scores between the 2 different doses was not significant.

No major side effects were observed in the study groups except for 1 patient each in group c, d who had vomiting which was easily controlled with anti emetics.

The limitations of our study are its small sample size and that we did not compare the efficacy of PPS with other commonly used drugs for treating stent related symptoms like alpha blockers and anticholinergics.

Conclusions:

The present study showed that pentosan polysulfate (PPS) is an effective drug to relieve symptoms due to Double J stents and this study further supports the hypothesis that presence of stent in the bladder leads to loss of glycosaminoglycan layer of the bladder which may be a contributory factor of stent symptoms. It can be started at 100 mg thrice daily dose and then can be reduced to 100 mg once daily dose after 1 week of treatment. As this is a pilot study with a small sample size further research is needed to refine the results.

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