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THE IMPACT OF PLATELET-RICH PLASMA INJECTION ON POST INTERNAL URETHRECTOMY STRICTURE RECURRENCE OF BULBAR URETHRAL STRICTURE

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ABSTRACT

Introduction: Urethral stricture refers to a fixed anatomical narrowing of the urethra that the lumen will not accommodate instrumentation without disruption of the urethra mucosal lining. The aim of study is to evaluate the effects of PRP injection on post internal urethrectomy stricture recurrence rate. **Method:** An interventional study compares two treatment regime modalities carried out between February 2019 till November 2020. The patient was categorized into two groups, the experimental group (13 patients) with DVIU and PRP injection and the controlled group (17 patients) with DVIU alone, and postoperative outcomes compared between the two groups. **Result:** We observed that iatrogenic trauma used to be the most common etiology of urethral stricture %43.3 (experimental group %30.8 vs. comparison group %52.9 p-values 0.225). In the experimental group, 7 (%53), 5 (%38.5), 2 (%15.4) developed hematuria, penile Pain, UTI, respectively, and stricture recurrence after 12 months of follow-up was 4 (%30.8). While in controlled group 6 (35.3), 3 (17.6), 1 (5.9) developed hematuria, penile Pain, UT, respectively, and the recurrence rate after 12 months was %35.3. complications in the experimental group were higher, but the p-value was not significant > 0.001. **Conclusion**: Throughout the study, we concluded that PRP injection after DVIU is safe preparation that may decrease urethral stricture recurrence but need more scientific research to understand the long-term outcome.

KEYWORDS: The impact, platelet-rich plasma injection, post internal urethrectomy stricture, recurrence, bulbar urethral.

INTRODUCTION

Anterior urethra begins from the tip of the glans penis to the urogenital diaphragm and further divided into the penile urethra(pendulous) that pass through the pendulous portion of the penis and bulbous urethra that run from the root of the penis to the junction of corpora cavernosum.[1] Urethral stricture is a permanent anatomical constriction of the urethra that prevents instrumentation without damaging the mucosa. Urologist's oldest and most serious illness is urethral stricture. It's caused by fibrosis of corpus spongiosis around the urethral lumen, creating stenosis. Scarring reduces urethral lumen diameter.[2] Iatrogenic trauma by urological instrumentation (cystoscopy, ureteroscopy, TURP, TURBT, urethroscopy) causes 33% of urethral strictures.[3] Less diagnostic endoscopy for boys and smaller calibre diminish this part.[4] Straddle or piercing trauma, infection, and inflammation produce urethral stricture. Due to better care and antibiotics, urethritis seldom causes urethral stricture nowadays.[5] The patient is asymptomatic until voiding symptoms such intermittency, hesitation, weak urine flow, suprapubic discomfort, and recurrent UTIs develop. Advanced instances included severe urine retention, bilateral hydronephrosis, and renal insufficiency.[6] Treatments for urethral stricture include dilatation, cold knife or laser urethrotomy, and surgery. DVIU is the oldest and most popular first stricture treatment. DVIU can cure strictures smaller than 1.5cm without dense, thick spongiofibrosis with a 70% long-term success rate.[7] The long-term success rate following internal urethrotomy is about 20%, according to research.[8,9] Urethral stricture comes from increased collagen type 1 synthesis and reduced collagen type 3, leading to fibrosis, scar development, and stricture.[10,11] Many adjuvants have been suggested to minimise urethral stricture recurrence following

internal urethrotomy, such as steroid injections and plasma rich platelets to reverse the disease's pathogenesis.[12] PRP is defined as a proportion of autologous blood plasma with above-baseline platelet concentration (before centrifugation).[13] PRP has a high amount of platelets and clotting factors, which last at physiologic levels.[14] GFs, chemokines, cytokines, and other plasma proteins.[15] In 1970, PRP was initially utilised in haematology to treat patients with thrombocytopenia.[16] In maxillofacial surgery, PRP became PRF after a decade. Fibrin has hemostatic qualities, while PRP increases cell growth.[17] Later, PRP was employed in sports injuries. Its usage by pro athletes has gained notice.[18] Cardiac, paediatric, gynaecological, urological, plastic, and ophthalmologic surgery also employ PRP.[19] The aim of study is to evaluate the effects of PRP injection on post internal urethrotomy stricture recurrence rate.

METHOD

Rizgary teaching hospital and Zheen international hospital evaluated two regimens. From February 2019 to November 2020, 46 patients with bulbar urethral stricture diagnosed with retrograde urethrography were included. 12 patients were excluded from the study due to a stricture of more than 2 cm, multiple strictures, previous two urethrotomies, history of urethroplasty, stricture in other parts other than the anterior urethra, benign prostatic hyperplasia, chronic steroid use, active urinary tract infection, neurogenic bladder disorders, or patient not wanting to take part in our study. After obtaining patient permission, patients were randomised into two groups: the control group (17 patients) with internal urethrotomy alone, and the experimental group (13 patients) with internal urethrotomy with platelet-rich plasma injection. Two surgeons performed direct visible internal urethrotomy on both groups using a cold knife to make incisions at 3, 9, and 12 o'clock and inject 1 to 2 ml PRP using a size 18 silicon catheter for five days. Postoperatively, patients were evaluated for pain, urethral bleeding, catheter leakage, UTI, and potency. Followed after 3,6,9,12 months following internal urethrotomy and at each visit by history of voiding symptoms (IPPS score), urinalysis to identify infection and hematuria, Abdominal and pelvic US to measure post-voiding residual volume, voiding flowmeter, and retrograde urethrogram for obstructive voiding symptoms. Platelet-rich plasma was produced using 30 ml of blood and a citrate solution on the day of the surgery. Plasma was isolated from red blood cells and leukocytes after centrifuging blood. Second, we centrifuged and utilised 5 cc of plasma for our investigation. All patients were pre-operatively evaluated by history, physical exam, and lab tests (urinalysis, RFT, virology screening). To confirm the diagnosis and locate the stricture, all patients had a retrograde urethrogram. All patients had 30 ml of blood collected and PRP taken the day of surgery. All patients received intravenous fluoroquinolones 30 minutes before the operation. In lithotomy position check, urethroscopy was performed, and internal urethrotomy was done at 3,9,12 till 24 FR urethroscopy could pass the stricture site into the bladder. One to two cc PRP was injected into the stricture location, then FR 18 was left for five days. 48 hours were spent looking for hematuria, penile discomfort, and dysuria. The catheter was withdrawn after five days. Every three to 12 months. Each patient was examined using voiding symptom records, abdominal and pelvic ultrasonography to determine post-voiding residual volume, and a urine flowmeter (uroflowmetry). If symptomatic or patient has severe voiding symptoms (IPSS) above 20, retrograde urethrogram is done to establish stricture recurrence. Using SPSS, data were examined (SPSS, version 25). Comparing the two research groups' proportions utilised a Chi-square test. When more than 20% of table cells were predicted to be less than five, Fisher's exact test was utilised. Student's t-test was performed to compare two means. A paired t-test compared a patient's baseline readings with three, six, nine, and twelve-month readings following surgery. Statistical significance was 0.05.

RESULTS

Thirty patients with urethral stricture were included in the study. They were separated into two groups, the experimental group (13 patients), where platelet-rich plasma injection was given after internal urethrotomy, and the comparison group (17 patients). Internal urethrotomy was done without the mentioned injection. The mean age ± SD of the studied sample was 40.4 ± 14.75 years, ranging from 20 to 70. The median was 36 years. Table 1 shows that the largest proportion (36.7%) of the sample were aged 30-39 years, and 30% were aged ≥ 50 years, but there was no significant difference in the age distribution of the two groups ($p = 0.840$). The table also shows that 29.4% of the comparison group were diabetics, compared with 15.4% of the experimental group, but the difference was not significant ($p = 0.427$). More than half (53.3%) of the sample were smokers, but there was no significant difference between the two groups ($p= 0.491$). One-fifth of the whole sample had a history of previous one-time urethrotomy (15.4% and 23.5% in the experimental and comparison groups, respectively), but the difference was not significant ($p = 0.672$). It is evident in Table 2 that urethral instrumentation was the predisposing factor for the stricture in 43.3% of the sample ($p = 0.225$), and trauma was the cause of 36.7% of cases of urethral stricture, then comes the urethritis (13.3%), and 6.7% were idiopathic. All the differences were not significant between the two groups regarding etiology's proportions ($p > 0.05$). Table 3 shows that there were no significant differences between the two groups regarding the mean of the stricture's caliber ($p = 0.683$), stricture length ($p = 0.719$), baseline IPSS ($p = 0.877$), and baseline QMAX ($p = 0.501$). So, the first three tables showed no significant differences between the two groups regarding the studied variables, so they are more or less comparable. The most common complications were hematuria and urethral bleeding (43.3%), leak around the

catheter (26.7%), and penile pain (26.7%), in addition to other less common complications as presented in Table 4. No significant differences were detected between the two groups regarding the following complications: urinary tract infections (p = 0.565), urine leak (p = 0.242), penile pain (p = 0.242), pelvic pain (p > 0.999), and hematuria and urethral bleeding (p= 0.310). It is evident in Table 3-5 that more than one-third (36.7%) of the sample developed voiding symptoms 12 months after the operation (30.8% in the experimental group and 41.2% in the comparison group). Still, the difference was not significant (p > 0.999). The recurrence rate 12 months after the operation was 33.3% (30.8% in the experimental group and 35.3% in the comparison group). Again, the difference was not significant (p > 0.999). The IPSS severity scores were compared in Table 6 which shows no significant differences between the two groups at baseline (p = 0.961), after three months (p > 0.999), after six months (p > 0.999), after 9 months (p = 0.853), and after twelve months (p = 0.862). According to the voiding QMAX, half of the sample had obstruction at baseline, as presented in Table 7. This proportion decreased after the operation to 0%, 13.3%, 23.3%, and 30.0% three, six, nine, and twelve months respectively, after the procedure. No significant differences were detected between the two groups in the different study periods regarding the voiding QMAX categories.

Table 1: Basic characteristics of the studied sample.

	Experimental group		Comparison group		Total		
	No.	(%)	No.	(%)	No.	(%)	p
Age (years)							
20-29	3	(30.8)	3	(17.6)	7	(23.3)	
30-39	5	(38.5)	6	(35.3)	11	(36.7)	
40-49	1	(7.7)	2	(11.8)	3	(10.0)	
≥ 50	3	(23.1)	6	(35.3)	9	(30.0)	0.840*
Diabetes							
No	11	(84.6)	12	(70.6)	23	(76.7)	
Yes	2	(15.4)	5	(29.4)	7	(23.3)	0.427*
Smoking							
No	7	(53.8)	7	(41.2)	14	(46.7)	
Yes	6	(46.2)	10	(58.8)	16	(53.3)	0.491†
Previous one-time urethrotomy							
No	11	(84.6)	13	(76.5)	24	(80.0)	
Yes	2	(15.4)	4	(23.5)	6	(20.0)	0.672*
Total	13	(100.0)	17	(100.0)	30	(100.0)	

Table 2: The Etiology of the urethral stricture.

	Experimental group (n = 13)		Comparison group (n = 17)		Total		
	No.	(%)	No.	(%)	No.	(%)	p
Urethral instrumentation	4	(30.8)	9	(52.9)	13	(43.3)	0.225†
Trauma	6	(46.2)	5	(29.4)	11	(36.7)	0.454*
Urethritis	2	(15.4)	2	(11.8)	4	(13.3)	> 0.999*
Idiopathic	1	(7.7)	1	(5.9)	2	(6.7)	> 0.999*

Table 3: Means of the baseline parameters of the two study groups.

	Experimental group		Comparison group		
	Mean	(±SD)	Mean	(±SD)	P*
Bulbar Stricture's caliber (French)	8.00	(±3.06)	8.47	(±3.12)	0.683
Bulbar Stricture length (mm)	9.00	(±2.92)	9.35	(±2.40)	0.719
Baseline IPSS	20.54	(±6.36)	20.94	(±7.48)	0.877
Baseline QMAX (Ml/Sec.)	10.00	(±3.56)	9.12	(±3.48)	0.501

Table 4: Postoperative complications.

	Experimental group (n = 13)		Comparison group (n = 17)		Total		
	No.	(%)	No.	(%)	No.	(%)	p
UTI	2	(15.4)	1	(5.9)	3	(10.0)	0.565*
Leak around catheter	5	(38.5)	3	(17.6)	8	(26.7)	0.242*
Penile pain	5	(38.5)	3	(17.6)	8	(26.7)	0.242*

Pelvic pain	1	(7.7)	1	(5.9)	2	(6.7)	> 0.999*
Urethral bleeding (hematuria)	7	(53.8)	6	(35.3)	13	(43.3)	0.310†

Table 5: Voiding symptoms and recurrence in the two study groups.

	Experimental group (n = 13)		Comparison group (n = 17)		Total		
	No.	(%)	No.	(%)	No.	(%)	p
Voiding symptoms							
At three months	0	(0.0)	1	(5.9)	1	(3.3)	>0.999*
At six months	2	(15.4)	4	(23.5)	6	(20.0)	0.672*
At nine months	3	(23.1)	6	(35.3)	9	(30.0)	0.691*
At twelve months	4	(30.8)	7	(41.2)	11	(36.7)	>0.999†
Recurrence							
At three months	0	(0.0)	1	(5.9)	1	(3.3)	>0.999*
At six months	2	(15.4)	3	(17.6)	5	(16.7)	>0.999*
At nine months	2	(15.4)	4	(23.5)	6	(20.0)	0.672*
At twelve months	4	(30.8)	6	(35.3)	10	(33.3)	>0.999*

Table 6: Categories of IPSS of the two study groups.

	Experimental group		Comparison group		Total		
	No.	(%)	No.	(%)	No.	(%)	p
Baseline IPSS							
Moderate	7	(53.8)	9	(52.9)	16	(53.3)	
Severe	6	(46.2)	8	(47.1)	14	(46.7)	0.961†
IPSS at 3 Months							
Mild	13	(100.0)	16	(94.1)	29	(96.7)	
Moderate	0	(0.0)	1	(5.9)	1	(3.3)	>0.999*
IPSS at six months							
Mild	11	(84.6)	13	(76.5)	24	(80.0)	
Moderate	1	(7.7)	2	(11.8)	3	(10.0)	
severe	1	(7.7)	2	(11.8)	3	(10.0)	>0.999*
IPSS at nine months							
Mild	10	(76.9)	11	(64.7)	21	(70.0)	
Moderate	1	(7.7)	3	(17.6)	4	(13.3)	
severe	2	(15.4)	3	(17.6)	5	(16.7)	0.853*
IPSS at 12 months							
Mild	9	(69.2)	9	(52.9)	18	(60.0)	
Moderate	1	(7.7)	5	(29.9)	6	(20.0)	
severe	3	(23.3)	3	(7.7)	6	(20.0)	0.862*
Total	13	(100.0)	17	(100.0)	30	(100.0)	

Table 7: Categories of QMAX of the two study groups.

	Experimental group		Comparison group		Total		
	No.	(%)	No.	(%)	No.	(%)	p
QMAX (baseline)							
Obstructive	6	(46.2)	9	(52.9)	15	(50.0)	
Inconclusive	7	(53.8)	8	(47.1)	15	(50.0)	0.713†
QMAX (three months)							
Inconclusive	11	(84.6)	13	(76.5)	24	(80.0)	
Normal	2	(15.4)	4	(23.5)	6	(20.0)	0.672*
QMAX (six months)							
Obstructive	2	(15.4)	2	(11.8)	4	(13.3)	
Inconclusive	9	(69.2)	14	(82.4)	23	(76.7)	
Normal	2	(15.4)	1	(5.9)	3	(10.0)	0.693*
QMAX (nine months)							
Obstructive	2	(15.4)	5	(29.4)	7	(23.3)	

Inconclusive	8	(61.5)	9	(52.9)	17	(56.7)	
Normal	3	(23.1)	3	(17.6)	6	(20.0)	0.780*
QMAX (twelve months)							
Obstructive	3	(23.3)	6	(35.3)	9	(30.0)	
Inconclusive	10	(76.6)	10	(58.8)	20	(66.6)	
Normal	0	(0.0)	1	(5.9)	1	(3.3)	0.113*
Total	13	(100.0)	17	(100.0)	30	(100.0)	

DISCUSSION

Urethral stricture is a chronic debilitating urological disease that affects the quality of life and frequently recurs after surgical treatment. Once urethral stricture happens, the patient needs frequent and regular urethral dilatation, direct vision urethrotomy, and sometimes end by urethroplasty.[13] it may result from urethral instrumentation, trauma, urethritis, and when no reason is found, classified as idiopathic. Our study found that up to 43% (experimental group 30.8%, comparison group 52.9%) resulted from previous urethral instrumentation, and 36.7 % due to trauma, 13.3% caused by infection and inflammation, and only 6.7 without any known etiology. (Fenton et al. 2005) found that the most common reason for urethral stricture is due to preceding instrumentation (cystoscopy, urethroscopy, urethral catheterization, TURBT, TURP), and the mechanism may be due to injury, pressure necrosis, inflammation that leads to fibrosis and subsequently urethral stricture (Jorgensen et al. 1986).[3, 14] Till now, no scientifically proven medical therapy available for the therapy of the urethral stricture (US), most urologists provide urethral dilatation or DVIU as initial surgical treatment for urethral stricture less than 1.5 cm. (Rosen et al. 2001), and (Santucci et al.) both showed that long success rate after urethrotomy is 20% and (Pansdorro and Emilio) stated that recurrence rate of urethral stricture after urethrotomy is between 30-38% also (Holm Nelsen and college) reported recurrence rate 50-70% during two years follow up. In our study, the recurrence rate at the endpoint (12 months after urethrotomy) was 33.3% (experimental group 30.8%, comparison group 35.3%). The reason might also be due to the shorter duration of follow-up in our study.[7, 20] Direct vision internal urethrotomy is a technically demanding procedure and needs skill. Some known common problems consist of puncture site pain, urethral bleeding, hematoma, chronic pelvic pain syndrome, impotence, arterial dissection, contrast reaction, and ischemic urethral stricture. our study outcomes confirm that the most common complication was hematuria and urethral bleeding %43.3 (experimental group %53.8, comparison group %35.3), followed by penile pain %26.7, leak around catheter %26.7 and urinary tract infection %10. (Mehran et al. 2017) confirmed frequent complications that met post urethrotomy had been %23 hematuria, %70 penile pain, 50% leak around the catheter.[21] Platelet-rich plasma is an accepted modality used broadly in many clinical fields, including diabetic wound healing[22], interstitial cystitis application[23], osteoarthritis application[24], and dermatological fields[25], and urology recently used for hypospadias and urethral stricture treatment. These occasions depend on inflammatory cytokines and growth factors.[24] PRP contains many growth factors like endothelial growth factors, insulin-like growth factors, transforming growth factors, and fibroblast growth factors reducing fibrosis development. In our study, results showed that recurrence rate throughout follow up the percentage of recurrence was less in the experimental group related to the comparison group (at three months %0 vs. %5.9, at six months %15.4 vs. 17.6, at nine months 15.4 vs. 23.5, at 12 months 30.8 vs. 35.3) but with the insignificant p-value. (Mehran et al.) also, report a decrease rate of stricture recurrence among the experimental group who received PRP injection submucosally after urethrotomy in his study.[21] In limited size investigation, Scarcia et al. used PRP gel to enhance vascularization of buccal mucosa graft and reduce fibrosis in urethroplasty and reported no stricture and minor side effect.[26] Although in clearance with previous surveys, we found a continued increase in stricture recurrence rate over time. It seemed that in our population, the percentage of recurrence might continue to rise after 12 months' follow-up period. Submucosal PRP injection delayed the recurrence and slowed down the time-dependent increase of post-urethrotomy stricture recurrence rate.[27]

CONCLUSION

PRP injection post urethrotomy is a safe preparation that helps reduce urethral stricture's recurrence rate after urethrotomy, although it was statically not significant. However, there is a need for more definitive scientific and experimental studies about the long-term outcome.

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