

EFFECTS OF COMBINATION OF BI-INJECT (TRIAMCINOLONE AND MITOMYCIN) AFTER DIRECT VISION INTERNAL URETHROTOMY FOR SHORT URETHRAL STRICTURES

ABSTRACT

BACKGROUND:

Urethral stricture disease has always been a challenge for urologists. Different treatment modalities that are used for treatment of urethral stricture disease, however recurrence has been a persistent problem. Agents such as triamcinolone and mitomycin-C offer hope but merit to be researched.

OBJECTIVE:

To test the combination of triamcinolone and mitomycin in direct vision internal urethrotomy (DVIU).

METHODS:

This quasi-experimental analysis was conducted upon a sample of 116 patients (selected using non-probability, consecutive sampling) in two groups (A: Experimental and B: Control) of 58 each. Data was recorded onto a structured questionnaire containing inquiries pertaining to basic biodata, sociodemographic details, disease history, operative notes and postoperative follow-up. The data obtained was analyzed using SPSS 21.0 and MS. Excel 365.

RESULTS:

The mean age of the sample stood at 47 (SD \pm 05) years, with the age ranging from 19 to 80 years. The etiology was idiopathic in most (55.2%) of the cases and the primary urethral strictures were the commonest (67.2%). Most strictures appeared between 6 to 9 months after the procedure and the incidence decreased with passage of time till no new cases were reported at 1 year. The outcome of the treatment in group A bi-inject given was regarded as success in 49 (84.5%) and in group B bi-inject not given was 32 (55.2%) of the cases. Among those that experienced a recurrence, majority (63%) of the patients experienced bulbar urethral stricture, while the remaining (37%) faced membranous urethral strictures. Few complications were seen in both groups, predominant among which was bleeding.

CONCLUSION:

After careful consideration, it is concluded administration of triamcinolone and mitomycin in direct vision internal urethrotomy (DVIU) yields a successful outcome significantly (<0.05) more frequently (84.5%) than the control group (52.5%).

KEYWORDS:

Triamcinolone, Mitomycin, Division Internal Urethrotomy, Urethral Stricture and Stricture Recurrence.

INTRODUCTION

The human body is a combination of different organ systems working together in synchrony to keep us alive. One important system amongst them is the renal system that removes waste products carried towards it by the blood. It comprises of two kidneys, two ureters, a urinary bladder and a urethra which contribute in producing, storing and excreting urine. ^[1]

The renal system is vulnerable to many pathologies which account for approximately 830,000 deaths and 18,467,000 disability-adjusted life years annually, thus making them the 12 most common causes of death (1.4 percent of all deaths) and 17th most common causes of disability (1.0 percent of all disability-adjusted life years). Pakistan ranks eight in renal disease causing 20,000 deaths every year. ^[2,3]

There are a number of vulnerable sites in the renal system that are prone to morbidities, which result in a considerable disease burden. The sites include the kidney (chronic kidney disease, glomerulonephritis, polycystic kidney disease and renal calculi) and the urethra (urinary tract infections, urethral cancers, calculi and strictures). ^[4,5]

Urethral stricture is defined as disruption of urethral epithelium leading to scarring and fibrosis composed of thick collagen and fibroblasts, which usually extends into the surrounding corpus spongiosal tissue causing spongiosal fibrosis. These urethral constrictions

obstruct the flow of urine and causing proximal urethral dilation and dilation of prostatic ducts and hypertrophied urinary bladder. [6]

Urethral stricture could be a sequel of inflammation, infection, ischemia, trauma, or etiology of unknown origin. Urethral stricture is a relatively common disease with a prevalence of 229-627 per 100000 males, or 0.6% of the risk population, who are typically older males. [7, 8]

Treating urethral stricture disease always poses as a challenge. The different options available for the management of urethral stricture disease include urethral dilation, optical internal urethrotomy, stenting and urethroplasty. Each treatment modality has different medical indication. Direct vision internal urethrotomy (DVIU) is a worthwhile treatment modality for urethral strictures less than 1 cm, untreated and flimsy. The main issue with OIU is high recurrence rate, up to 68%. [7, 9 - 11]

Optical internal urethrotomy does not help in providing the epithelial approximation but rather helps in differentiating scarred epithelium allowing healing to occur by secondary intention where scar contraction with fibrosis leads to recurrence of urethral stricture. Therefore, any therapeutic agent which decreases fibrosis and healing process can decrease urethral stricture recurrence rate. Mitomycin C impairs healing by restricting the multiplication of fibroblast, epithelial cells and preventing collagen production. In addition to that it is expected to slow down contraction of wound. [12]

Similarly, triamcinolone (local corticosteroid) decreases formation of scar by decreasing the synthesis collagen and glycosaminoglycan and expression of inflammatory mediators.

S. Kumar in his study showed that the combined use of Triamcinolone, Mitomycin C and

Hyaluronidase, decrease stricture recurrence rate to 19.4% after the first procedure and 5.8% after the second Optical internal urethrotomy. In another study, triamcinolone injection following internal urethrotomy have decrease the recurrence rate of 35%. [8, 10, 13]

In other study the use of mitomycin c alone effectively declines the recurrence rate of urethral stricture up to 14% after DVIU. However, there is insufficient data regarding the combined effect of triamcinolone and mitomycin C in reducing the rate of urethral stricture and is still in experimental stages. Moreover, there is no study from our region highlighting the effect of Triamcinolone and Mitomycin c in reducing the rate of urethral stricture after DVIU. [6]

Therefore, this study was designed to evaluate the efficacy of Triamcinolone and Mitomycin c in reducing the rate of urethral stricture after DVIU in population of Pakistan. This combination of drugs is chosen because efficacy of these two agents is well proven in different studies and they are safe, cost effective and easily available. [6]

OBJECTIVE

To test the combination of triamcinolone and mitomycin in direct vision internal urethrotomy (DVIU).

METHODOLOGY

This quasi-experimental analysis was conducted upon a sample of 116 patients (selected using non-probability, consecutive sampling) in two groups (A: Experimental and B: Control) of 58 each. Data was recorded onto a structured questionnaire containing inquiries pertaining to basic biodata, sociodemographic details, disease history, operative notes and postoperative follow-up. The data obtained was analyzed using SPSS 21.0 and MS. Excel 365.

Inclusion criteria

- All patients with diagnosis of urethral stricture who complete the tenure of the study.
- Patients with urethral strictures of 1.cm or less at bulbar or membranous urethra.
- Patients of age between minimum 10 year to maximum 80 years of age.
- Patients whose uroflowmetry (UFM) shows a maximal flow rate (MFR) 10ml.

Exclusion criteria

- Patients with completely obliterated urethral stricture will not include in this study.
- Patient age <10 years and >80years.

- Patients with strictures greater than 1.cm.
- Patients having several urethral strictures, blind ending urethral stricture, urethrocutaneous fistula and history of urethroplasty.

Those patients who were presenting initially to us with no prior treatment will be refer as primary, whereas patients who have had previous procedure done for the management of urethral stricture were referred as secondary. Patients diagnosis depended on the clinical history, uroflowmetry, and retrograde urethrogram. The choice of anaesthesia was either general or regional. Preoperative antibiotic prophylaxis was given to all patients. Routine manner of optical internal urethrotomy was performed using a cold knife at the stricture site. Bi-inject was prepared by diluting triamcinolone 40 mg and mitomycin c 2 mg. Patients were assigned into 2 groups. In one, intralesional combination of drug was injected by using William endoscopic needle at the site of urethrotomy and about 1-2ml bi-inject was injected at every lesion. While simple Direct vision internal urethrotomy (DVIU) was performed to another group. An 18fr silicon catheter was placed for free passage of cystoscope into the bladder, the catheter was left in place for 2 days. Prophylactic antibiotics were started pre-operatively will be continued for 5 days. Patient were followed 2 weeks after DVIU.

After which patient were followed at regular interval of 3 months for the period of 1 year. On follow up, history of lower urinary tract symptoms (LUTS), examination for palpable bladder, uroflowmetry (UFM) were recorded. If the patient did not have any LUTS, normal examination, and max flow rate of >10ml/s on uroflowmetry, were followed 3 month with same protocol. If the patient complains of LUTS or UFM <10ml/s were further evaluated by ascending and descending urethrogram, to check for recurrence of stricture. Patient who remains asymptomatic and maintains the flow of urine >10ml on UFM were labelled as successful, where as those patients in whom urethrogram showed recurrence of stricture were labelled as failure.

To avoid “losing the patients” during one year follow-up the telephone/mobile no and address were recorded, and they were contacted periodically in order to remind or call them for follow-up. By adhering strictly to the inclusion and exclusion criteria, biasness and confounding variable were controlled.

RESULTS

This quasi-experimental analysis was conducted on a sample of 116 patients (selected using non-probability, consecutive sampling) in two groups of 58 each (A: Experimental and B: Control). Data was recorded onto a structured questionnaire including basic biodata,

sociodemographic details, disease history, operative notes, and post-operative follow-up. The data (obtained via a 3-monthly follow-up for 1 year) was then analysed using SPSS 21.0.

In this study, success (after DVIU) is defined as “no stricture” after 1 year of follow-up, while failure (after DVIU) refers to the recurrence of the stricture within 1 year of follow-up. Recurrence is defined as appearance of urethral stricture on x-ray urethrogram (which is advised if the patient develops obstructive urinary symptoms and peak flow of 10ml/s or less than 10ml/s, on uroflowmetry).

As shown in table 1 and 2 both groups were statistically comparable in terms of age, etiology, site of the urethral stricture, size of urethral stricture.

As shown in table 1 the mean age of the sample stood at 47 (SD ± 05) years, with the age ranging from 19 to 80 years. The aetiology was idiopathic in most (55.2%) and known in (44%) of the cases. According to the presentation, patients were divided into two types primary (no history of surgical intervention for urethral strictures), secondary (previously treated for urethral stricture i.e. OIU). Primary urethral stricture was more common (67.2%) and secondary stricture (32.8%). The commonest site of the urethral stricture on presentation was bulbar urethral stricture (63%) and the membranous urethral stricture (37%). Average size of stricture on X-Ray urethrogram on presentation in group A was (0.61cm) and in group B was (0.63cm).

The outcome of the treatment in group a (bi-inject given) was regarded as a success in 49 (84.5%) patients and group b (bi-inject not given) in 32(55.2%) patients. Among those that experienced a recurrence (labelled as failure), a majority (73.7%) of the patients experienced bulbar urethral stricture, while the remaining (26.3%) faced membranous urethral strictures. Most strictures appeared between 6 to 9 months after the procedure and the incidence decreased with passage of time till no new cases were reported at 1 year.

A summary of the descriptive statistics is tabulated below.

TABLE 1
Descriptive Statistics Summary (n = 116)

Variable		Statistic – n (%)
Age (Years)	<i>Mean</i>	47 (SD ± 05)
	<i>Range</i>	19 to 80
Etiology	<i>Known</i>	52 (44.8%)
	<i>Idiopathic</i>	64 (55.2%)
Site of Urethral Stricture On presentation	<i>Bulbar</i>	73 (63%)
	<i>Membranous</i>	43 (37%)
Type of urethral	<i>Primary</i>	78(67.2%)

strictures on presentation	<i>Secondary</i>	38 (32.8%)
Recurrence after treatment	<i>Bulbar</i>	25 (73.7%)
	<i>Membranous</i>	13 (26.3%)
Outcome	<i>Success</i>	81 (69.8%)
	<i>Failure</i>	35 (30.2%)

TABLE 2 (n = 116)
Comparative analysis – Group A (OIU+bi-inject) v/s Group B (Simple OIU)

Variable		Statistic – n (%)		P Value
		Group A (n=58)	Group B (n=58)	
Age (Years)	<i>Mean</i>	45 (SD ± 04)	47 (SD ± 09)	0.078 ^b
	<i>Range</i>	19 to 80	19 to 80	
Etiology	<i>Known</i>	33 (43.1%)	19 (32.8%)	0.015 ^a
	<i>Idiopathic</i>	25 (56.9%)	39 (67.2%)	
Site of Urethral Stricture On presentation	<i>Bulbar</i>	34 (63%)	39 (67.2%)	0.442 ^a
	<i>Membranous</i>	24 (37%)	19 (32.8%)	
Size of Urethral Stricture (cm)	<i>Mean</i>	0.61 (SD ±0.20)	0.63 (SD ±0.22)	0.003 ^b
	<i>Range</i>	0.2 to 1	0.3 to 1	
Type of Urethral Stricture	<i>Primary</i>	40 (34.5%)	38 (32.8%)	0.843 ^a
	<i>Secondary</i>	18 (15.5%)	20 (17.2%)	
Outcome	<i>Success</i>	49 (84.5%)	32 (55.2%)	0.001 ^a
	<i>Failure</i>	09 (15.5%)	26 (44.8%)	

^aFisher's Exact Test

^bStudent T-Test

DISCUSSION

Urethral stricture is disruption of urethral epithelium leading to scarring and fibrosis involving spongiosal tissue. It may be due to inflammation, infection, ischemia, trauma or unknown etiology. It is believed that “urethral stricture is a relatively common disease with a prevalence of 229-627 per 100000 males, or 0.6% of the risk population, who are typically older males”.^[14] Furthermore, evidence exists to support the claim that “among the wide variety of options available for the treatment of urethral stricture disease are included,

urethral dilation, optical internal urethrotomy, stenting and urethroplasty. Direct vision internal urethrotomy (DVIU) is considered ideal for urethral strictures less than 1 cm, untreated and flimsy, however, recurrence rate is up to 68% with DVIU".^[15]

Any therapeutic agent which decreases fibrosis and healing process can decrease urethral stricture recurrence rate. Mitomycin C impairs healing by restricting the multiplication of fibroblast and epithelial cells while also preventing collagen production, thus slowing down wound contraction as well.^[16] Similarly, triamcinolone (local corticosteroid) decreases formation of scar by decreasing the synthesis collagen and glycosaminoglycan and expression of inflammatory mediators. S. Kumar in his study showed that the combined use of Triamcinolone, Mitomycin C and Hyaluronidase, decrease stricture recurrence rate to 19.4% after the first procedure and 5.8% after the second Optical internal urethrotomy. In another study, triamcinolone injection following internal urethrotomy have decrease the recurrence rate of 35%.^[6, 16]

To date there is no study from our region highlighting the effect of Triamcinolone and Mitomycin c in reducing the rate of urethral stricture after DVIU. Hence this study included the population of Pakistan only. This combination of drugs is chosen because the efficacy of these two agents is well proven in different studies and they are safe, cost effective and easily available. This study was a quasi-experimental study, conducted at the urology department in Ziauddin university hospital Karachi. The sample size was calculated as 116 Patients (with 58 patients per group), keeping a 5% error of margin by using the Open Epi software (version 3.01) and a confidence interval of 95%. The **sampling technique** used was non-probability consecutive sampling and the patients divided into two groups, Group A-Bi-inject given and Group B- Bi-inject not given. A Successful case was defined as "No stricture" in the 1-year follow -up and "Failure" was defined as recurrence of the stricture within the 1 year follow-up.

Recurrence is defined as appearance of urethral stricture on x-ray urethrogram which is advised if the patient develops obstructive urinary symptoms and peak flow of less than 10ml/s, on uroflowmetry (U.F.M). The mean age of the sample stood at 47 (SD \pm 05) years, with the age ranging from 19 to 80 years. This is synonymous with the finding of Santucci et al, about urethral stricture disease being more common in the elderly population especially around the ages of 45 - 55 years. Additionally, the study also had similar findings compared

to that of Islam et al. and Khan et al., both of whom noted that urethral stricture was more common in patients older than 40 years. [17 - 19]

Most strictures appeared between 6 to 9 months after the procedure and the incidence decreased with passage of time till no new cases were reported at the 1 year follow up. The same was reflected by Naude and Heyns who reported recurrence was mostly within 3 to 12 months. [20]

Success of the treatment in group A –BI- INJECT given was 84.5% whereas in Group B –bi inject not given is was 55%. Total outcome of the treatment was regarded as a success in 81 cases (69.8%). Among those that experienced a recurrence, a majority (63%) of them were bulbar urethral stricture, while the remaining (37%) had membranous urethral strictures. Few complications were seen in both groups, predominant among which was recurrence, which was confirmed on X-ray -urethrogram.

CONCLUSION

After careful consideration, it is concluded administration of triamcinolone and mitomycin in optical internal urethrotomy (OIU) yields a successful outcome significantly more frequently (84.5%) than the control group (52.5%).

ETHICAL APPROVAL:

Ethical approval was obtained from the Ethical Review Committee of Ziauddin University before commencing the study.

PATIENTS' CONSENT:

Informed consent was signed by every patient before enrollment in the study.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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