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REVIEW ARTICLE

Efficacy of DVIU and intralesional injection of mitomycin C in the treatment of bulbar urethral stricture

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Abstract: **Background and aim:** To find if intra-operative local injection of Mitomycin-C after internal Urethrotomy in patients with urethral stricture can improve the outcome of surgery. **Materials and Methods:** Seventy patients were allocated in two groups randomly and data were analyzed. The case group (n=35) was treated by internal Urethrotomy with intra-operative local injection of Mitomycin-C. The control group (n=35) was underwent standard internal Urethrotomy. The patients were followed after removing catheter and for 6 months after surgery by USS PROM questionnaire and uroflowmetry. **Results:** A significant difference was observed in terms of urodynamic indices like Q-max (p-value=0.006) and urine flow pattern (p-value=0.025) after internal Urethrotomy in the local injection of Mitomycin-C group and control group, six months after surgery. In the case group, in the six months after operation, only 2.9% of patients had Q-max less than 15 and no one had obstructive pattern, while in the control group, 25.7% of patients had Q- max less than 15 and 17.1% had obstructive pattern. However, the patient's satisfaction history did not show any significant difference in post-internal Urethrotomy voiding status in the local injection of Mitomycin-C group and control group, either immediately after removal of the urethral catheter (p-value=1) and six months after surgery (p-value=0.198). Also, no significant difference was observed in terms of urodynamic indices like Q-max (p-value=0.771) and urine flow pattern (p-value=1) after internal Urethrotomy in the local injection of Mitomycin-C group and control group, immediately after removal of the urethral catheter. **Conclusions:** Intra-operative local injection of Mitomycin-C after internal Urethrotomy can be regarded as a safe and efficient technique which has several advantages including lower cost. Lower recurrence rate of urethral stricture is the main effect of local Mitomycin-C application that is more prominent after six months follow up.

Keywords: Urethral stricture; Internal Urethrotomy; Mitomycin-C (MMC)

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1. Introduction

Urethral stenosis is one of the oldest known urological disorders as well as an unpleasant condition. It can be the result of trauma, catheterization, prostate surgeries, or even a congenital occurrence (1-6). There are several ways to cure this condition based on the location, size and cause of the stenosis, in addition to the skilfulness of the surgeon. Dilatation, internal Urethrotomy, stent insertion, and Urethroplasty are some of the methods currently used throughout the medical world (14,13,12,11,7,6,4,1,26). Furthermore, in order to increase the effectiveness of the surgery and to decrease the potential recurrence rate of stenosis, CIC (Alternating Conductive Catheterization) and/or hydraulic dilators can be prescribed for patients to maximise post-surgery results (12,10,8,6,5,17). However, despite these efforts, a high number of patients would experience the return of this condition post-surgery. Due to this concern, the need for alternative procedures arises. As a result, the idea of using fibrinolytic materials to break down the scar or prevent it from developing has been put forward. Thus, this paper aims to

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investigate the effects of local mitomycin-C, prescribed after internal Urethrotomy, in the overall effectiveness of the operation and the improvement of the condition in patients with stenosis.

2. Material and methods

In this randomized double blind clinical trial, a total number of 70 patients diagnosed with urethral stenosis were studied at Shohadaye Tajrish Hospital from June 2015 to June 2017. The study included all those who are present and available to be tracked throughout the project. It also required the candidates to experience internal Urethrotomy (Urethral Stricture length<1.5 cm), judging from their medical history, physical examination, and radiographic as well as cryptoscopic findings. Patients with long stenosis, Penile Urethral stricture, and other conditions such as BXO and BPH were not be included. Patients underwent a comprehensive history check (outlining their age, gender, reason for stenosis, and previous occurrences of this condition), physical examination (identifying the location and length of stenosis as well as the type(s) of previous surgeries), and radiographic studies (in cases of anterior stenosis). Subsequently, they underwent cystoscopy, anaesthesia, and a dorsal lithotomy position under the internal star-like Urethrotomy. The patients then had divided into two groups. One group, consisting of half of the study population, will have sub-mucosal injection of 0.1mg / 2cc mitomycin-C with a 22-Gauge needle administered to them. Then both groups were re-examined to identify potential differences. After the surgery, the catheter was implanted for five days.

Thereafter, Patients were examined for symptoms and uroflowmetry (6 months after the removal of the catheter). In case of abnormal results (Q-Max<15 & Obstructive pattern) RUG-VCUG and, if needed, urethrocystoscopy were performed. Furthermore, the need for internal Urethrotomy and dilatation was reviewed and, if needed, re-incision and re-injection of mitomycin-C took place. For the purpose of this paper, recovery was defined as patients' ease in urination and recurrence was defined as failure to resolve this condition.

3. Results

The average age of participants was 37.49 years (±2.483) in the case group and 39.64 years (±2.448) in the control group. The average length of stenosis was 0.8371 cm (±0.07219) in the case group and 1.0886 cm (±0.12694) in the control group. In the case group, there were 3 (8.6%), 23 (65.7%) and 9 (25.7%) cases of distal, mid and proximal bulbar, respectively. While, in the control group, the number of distal, mid and proximal bulbar cases were 5 (14.3%), 20 (57.1%) and 10 (28.6%), respectively. This showed no significant difference between the two groups (p-value = 0.691) (Table 1).

19 cases (54.3%) in the case group and 23 cases (65.7%) in the control group had a positive history of previous surgery. In mentioning that, there was no statistically significant difference between the two groups (p-value = 0.227). Furthermore, the status of the specimens, in terms of indicators for symptom assessment and urofluorometry (Q-max and urine flow pattern) immediately after surgery as well as 6 months after the operation, were expressed as numbers and percentages in both groups. Fisher statistical test showed that there was no significant difference between the two groups in terms of immediate postoperative index (p-value = 1) and six months after the surgery index (p-value = 0.198) (Tables 3 and 4).

The two groups were investigated based on indicators for symptom assessment immediately and 6 months after the surgery. In the case group, 4 patients (3 with unknown reasons and 1 due to previous surgeries) immediately after the surgery and only 1 candidate (due to catheterization) 6 months after the operation, were unhappy with the results. This was while, in the control group, 4 candidates (1 person due to inflation, 1 person due to catheterization, 1 person due to congenital causes, and the other patient due to unknown reasons) immediately after the surgery and 5 patients (1 person due to inflation, 1 person due to catheterization, 1 person due to congenital causes, and 2 patients due to trauma) 6 months after the operation, were not satisfied with the results.

When performed, Fisher statistical test showed that the two groups did not exhibit any significant difference in their uroflowmetry Q-max indexes immediately after surgery (p-value = 0.771). While, there was a significant statistical difference between the uroflowmetry Q-max indexes of the two groups in six months after surgery (p-value = 0.006) (Tables 5 and 6). Fisher statistical test showed that there was no significant statistical difference between the two groups in terms of uroflowmetry pattern immediately after surgery (p-value = 1). However, there was a significant statistical difference between the two groups in terms of uroflowmetry index six months after surgery (p-value = 0.025).

Patients who were dissatisfied either due to their post-surgery symptoms or based on their uroflowmetric Q-max >15 indexes, or those who experienced obstruction patterns, were put to undergo RUG. Fisher statistical test showed that the two groups had a significant statistical difference in RUG index (p-value = 0.011). In saying that, the case group had no difficulties in RUG, while 7 patients (20.0%) in the control group experienced stenosis in the procedure. Of these 7, 2 had distal bulbar stenosis, 2 had mid-bulbar stenosis, and 3 had proximal bulbar stenosis.

Table 1: Location of Stenosis in both groups

Location of Stenosis	Case Group	Control Group	Total
Distal Bulbar	3(8/6%)	5(14/3%)	8(11/4%)
Mid Bulbar	23(65/7%)	20(57/1%)	43(61/4%)
Proximal Bulbar	9(25/7%)	10(28/6%)	19(27/1%)
Total	35(100%)	35(100%)	70(100%)

Table 2: Etiology of stricture in both groups

Reason of Stenosis	Case Group	Control Group	Total
Infection	0(0%)	5(14/3%)	5(7/1%)
Trauma	9(25/7%)	11(31/4%)	20(28/6%)
Previous Surgery	3(8/6%)	4(11/4%)	7(10%)
Congenital	1(9/2%)	3(6/8%)	4(7/5%)
Previous Catheterization	6(17/1%)	5(14/3%)	11(15/7%)
Unknown	16(45/7%)	7(20%)	23(32/9%)
Total	35(100%)	35(100%)	70(100%)

Table 3: Patients' Status Immediately After Surgery

Patients' Status Immediately After Surgery	Case Group	Control Group	Total
Satisfied	31(88/6%)	31(88/6%)	62(88/6%)
Not Satisfied	4(11/4%)	4(11/4%)	8(11/4%)
Total	35(100%)	35(100%)	70(100%)

Table 4: Patients' Status 6 Months After Surgery

Patients' Status Immediately After Surgery	Case Group	Control Group	Total
Satisfied	34(97/1%)	30(85/7%)	64(91/4%)
Not Satisfied	1(2/9%)	5(14/3%)	6(8/6%)
Total	35(100%)	35(100%)	70(100%)

Table 5: Q-max Immediately After Surgery

Q-max Immediately After Surgery	Case Group	Control Group	Total
≥ 15	27(77/1%)	28(80%)	55(78/6%)
< 15	8(22/9%)	7(20%)	15(21/4%)
Total	35(100%)	35(100%)	70(100%)

Table 6: Q-max 6 Months After Surgery

Q-max 6 Months After Surgery	Case Group	Control Group	Total
≥ 15	34(97/1%)	26(74/3%)	60(85/7%)
< 15	1(2/9%)	9(25/7%)	10(14/3%)
Total	35(100%)	35(100%)	70(100%)

4. Discussion

Urethral stenosis may be due to biopsies, conduit manipulation, catheterization, diathermy, external trauma, hypospadiasis surgery, radical prostatectomy, other prostate surgeries, congenital causes, or an unknown reason. (1,2,3,4,5,6) During healing of the affected part of the urethra, extravasation of the urinary sub-epithelium and the subsequent scar tissue enlargement occur in the lumen and spongiofibrosis (1,4,5,7,8,9,10). A variety of methods are used to treat stenosis. These can include ductal dilatation, inter-

nal Urethrotomy, laser, stent placement, and open surgery (1,4,6,7,11,12,13,14). The success rates of luminal dilatation, Urethrotomy, laser, stent placement and open surgery are 60%, 50%, 56%, 40%, 90%, respectively (1,4,11,15,16). It is important to note that open surgeries cannot be done at all centres as they require high levels of expertise. In addition, the most common method of treatment is internal Urethrotomy and dilatation (4,10,12). The success rate of internal Urethrotomy is directly dependent on the length and extent of spongiofibrosis. In saying that, Internal Urethrotomy is used for stenosis less than 1.5 cm in the bulbar ducts and the Penile. If dilatation has been done for more than a year, more success will be achieved (1). However, the low success rate and the high rate of recurrence of stenosis despite the treatment, and the need to maintain the Foley catheter, duct stent, and CIC suggests the need for new methods (5,6,8,10,12,17). Corticosteroids (such as triamcinolone), traditional herbal remedies, TGF-β, oligodioxy nucleotide, and recombinant adenovirus have been used to prevent scarring (4,10,18,19,20,21,22). The other method is the use of mitomycin (12). Mitomycin-C is an antibiotic of Streptomyces caspitus origin that was discovered in 1958 and has been clinically used since 1963 in pterygium surgery. It also inhibits fibroblast proliferation, collagen deposition, and scar formation (1,4,5,12). Due to its antiproliferative and anti-scar effect of mitomycin-C, it has been used in a wide range of medical fields and applications. Mitomycin-C is used in the treatments of stenosis and scar formation in glaucoma trabeculectomy, pterygium, nasolacrimal duct obstruction, otitis media myringotomy, upper airway stenosis (laryngeal and tracheal stenosis), vaginal, anal, and conduit stenosis (5,8,12).

A study carried out by Dr. Mehdi Shirazi et al., in the field of captopril gel injection after internal Urethrotomy, published in 2007, found that 56 patients were 39.5 years of age with a mean follow-up of 16 months. For follow-up, maximal urine flow and RUG were performed, and cystoscopy and VCUG were completed as needed. The recurrence rate in the group of patients receiving captopril gel was lower than that of placebo group (8).

In a study by Dr. Hamid Mazdak et al., in the field of submucosal triamcinolone injection for bulbar stenosis, published in 2010, it was reported that 55 patients were divided into two groups. They then received symptoms and RUG follow-ups and if needed, Urethroscopy for 13.7 months (±5.5). Consequently, 21.7% of the patients after the triamcinolone injection and 50% of the control group candidates did not experience stenosis recurrence (10).

A review study by Dey et al., in India on the causes and treatments of common anterior stenosis, published in 2014, the topic of sub-mucosal injection of mitomycin-C is put forward and further explored. In this paper, the results showed that the risk of restenosis was reduced to 10% after the injection of mitomycin-C. While in the internal Urethrotomy alone 50% recurrence was reported during the 6-month period of follow-ups (1). A study by Ali Ayyildiz et al., in Turkey, which investigated the effect of mitomycin-C injections on the treatment of rat stenosis fibrosis and its results were published in 2004, reports that despite its toxic nature at high doses, mitomycin-C exhibits antifibrotic effects at low doses (4).

In a study performed by Vanni et al., in Massachusetts, in the field of intrathecal injection of mitomycin-C after Urethrotomy, published in 2011, it has been reported that after 12 months of follow-up with uroflowmetry, PVR determination, and flexible cystoscopy, of the 18 patients with bladder stenosis, 72% did not develop urethral stenosis again after 1 injection of mitomycin-C and 89% after two injections (12).

A 2015 multicentre Redshaw study in the United States, published in the Journal of Urology, examined the efficacy of mitomycin-C injections after bladder neck incision in 66 patients with 3-month cystoscopic follow-ups. It was concluded that this effect is less than that suggested in the previous studies and side effects have been observed in 7% of the cases (23).

In Farrell's studies in 2015 and Ryan's in 2017, local injections of mitomycin-C were made after internal Urethrotomy and were followed by CIC, and patients underwent urodynamic and cystoscopic examinations at 1, 3, 6, and 12 months. The results indicated that local injection of mitomycin-C and subsequent CIC can be considered as a safe, effective and accessible method for short, recurrent, and complicated bulbomembranous and bulbar stenosis (24,25).

5. Conclusion

It can be concluded that the injection of mitomycin-C into the stenosis after internal Urethrotomy can be considered as an effective and safe method of reducing the recurrence of this condition. The results of this injection in reducing the recurrence of stenosis will appear 6 months after the operation.

6. Appendix

None.

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6.2. Authors Contributions

All authors have the same Contribution.

6.3. Funding Support

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6.4. Conflict of Interest

All authors declare that there is no conflict of interest in this study.

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