Surgery in Motion

One-stage Penile Urethroplasty Using Oral Mucosal Graft and Glue

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Abstract

Background: Repair of penile urethral strictures is a challenging problem for which different techniques have been suggested.

Objective: To describe a new surgical technique for one-stage penile urethroplasty using an oral graft and glue, and to assess its safety and efficacy.

Design, setting, and participants: A retrospective review of medical records for patients who underwent one-stage penile urethroplasty using oral mucosa and glue from February 2013 to October 2014 was performed.

Surgical procedure: The penile urethra was opened and the urethral plate was incised to create a wide window within which the oral graft was pasted with glue. The urethra was sutured over the catheter.

Outcome measurements and statistical analysis: Clinical data were collected in a database. Intraoperative and postoperative complications and outcomes were assessed. A descriptive statistical analysis was performed.

Results and limitations: Fourteen patients were included in the study. Median operative time was 60 min. The median postoperative stay was 3 d. Three intraoperative and one postoperative complication occurred. In all patients, voiding cystourethography 2 wk after surgery failed to show urethral fistula or sacculaion. No patients complained of penile chordee or sexual dysfunction after surgery. Median follow-up was 16 mo. Among the 14 patients, 12 (85.7%) procedures were successful and two (14.3%) were failures. Study limitations include the small sample size and short follow-up.

Conclusions: An in vitro study and a one-stage reconstruction of penile urethral strictures with an oral mucosa graft and glue showed that the procedure is safe and effective, but further studies including larger series of patients and longer follow-up are required.

Patient summary: We report on the repair of penile urethral stricture using one-stage urethroplasty with oral mucosa and glue. This new technique was safe and effective, with limited complications and satisfactory outcomes. We plan to increase the use of this technique in the future.

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1. Introduction

The aetiology of penile urethral strictures includes many and various causes. In developing countries, postinfection strictures related to Neisseria gonorrhoea still account for the majority of anterior urethral strictures. However, while infective urethritis has shown a decreasing trend in these countries, there has been an increase in strictures related to instrumentation and catheters [1–3]. Conversely, in developed countries there has been a decrease in infective urethritis and an increase in strictures related to iatrogenic idiopathic causes, lichen sclerosus (LS), and failed hypospadias repair [4–6].

Penile urethral strictures may require a one or two-stage repair. Complete obliteration of the external urethral meatus, wood-hard fibrosis that extends into the penile tract, and the removal of complex strictures associated with fistulae, scarring, chordee, abnormal meatus, small glans, and deficiency of the dartos layer are better managed using a staged reconstruction [7–9]. In one-stage penile urethroplasty, use of a flap or graft is still the subject of debate [10]. In recent years, graft use for anterior urethroplasty has become the most popular option for any augmentation tissue repair [10]. However, the current literature is too limited to answer the question of whether a flap or graft is superior for one-stage penile urethroplasty. Published reports include only a collection of retrospective patient series and meta-analysis, with variable definitions for stricture recurrence and successful outcomes, and success rates reported for penile urethroplasty using a flap or graft are similar [10].


The aim of this study is to describe the technique for one-stage penile urethroplasty including new surgical innovations, and to assess outcomes in a preliminary series of patients at our high-volume centre.

2. Patients and methods

2.1. Study population

Data were retrospectively collected from the medical records for a consecutive series of 14 patients who underwent one-stage penile urethroplasty at our centre between February 2013 and October 2014. All patients were counselled about the risks, benefits, and alternative treatments before providing their informed consent. The last follow-up for each patient reflects the last point of contact with the office. Follow-up was calculated for each patient as the time elapsed between the date of surgery and the date of their last office follow-up. The institutional review board approved the study. Patients who had undergone one-stage penile urethroplasty using an oral graft and glue and who had minimum of 12 mo of follow-up met the inclusion criteria for the study. Patients with LS or incomplete clinical records at follow-up analysis were excluded from the study. The primary outcome of interest was postoperative failure-free survival in the overall population. The secondary outcome of interest was evaluation of laboratory findings.

Preoperative data collected included age, clinical history, urine culture, retrograde and voiding cystourethrography, urethral ultrasonography, and urethroscopy. Clinical data consisted of stricture aetiology (idiopathic, trauma, infection, catheter, instrumentation) and previous treatments (dilation, urethrotomy, or urethroplasty). Urethrography was used to assess the stricture length and site. Uroflowmetry and a urine culture were repeated every 6 mo in the first 2 yr and annually thereafter. When symptoms of decreased force of stream were present and the maximum urinary flow rate (Q_{max}) was <12 ml/s, urethrography, urethral ultrasound, and urethroscopy were repeated to fully document restrictre features. Patient demographic data and stricture characteristics at presentation are reported in Table 1.

The glue used on patients in this study was Glubran 2 (GEM, Viareggio, Italy), an N-butyl-2-cyanoacrylate combined with a monomer (methacryloxy sulfolane) with good adhesive and haemostatic properties. The glue combination is ready to use and, once in contact with blood, the liquid and tissues polymerise in an exothermic reaction of approximately 45 °C [15]. The longer radical chain has a lower polymerisation temperature than Histoacryl, which results in lower toxicity and fewer inflammatory reactions [16]. Glubran 2 has been used for many procedures including skin closure of abdominal wounds, suture reinforcement, arterial-venous embolisation, endoscopic treatment of bleeding gastroduodenal ulcers and varices, occlusion of external biliary fistulas refractory to endoscopic drainage, endoscopic closure of pancreatic fistulas and for the fixation of polypropylene mesh in open and laparoscopic hernia repair, oncology and oral and cardiovascular surgery [16–19].

2.2. Laboratory tests in vitro

Preliminary studies on oral mucosa cells from tissue-engineered cultures were used to ascertain the effects of the glue on cells and tissues. Biopsy tissues from the bulbar urethra and oral mucosa were obtained from patients during urethroplasty. Urethral and oral mucosa keratinocytes were cultured on a feeder layer of lethally irradiated 3T3-J2 cells as previously described [20]. Fibroblasts were isolated by explant and cultivated on plastic. Cytotoxicity was analysed by dropping cyanoacrylic-based surgical glue on confluent keratinocyte and fibroblast cultures. Cultures were photographed and digitally analysed immediately and at up to 47 d. Dead cells were quantified at 24 h and 7 d. The long-term effects of adhesive contact on fibroblasts and keratinocytes were assessed by secondary plating and colony-forming efficiency assays, respectively.
Table 1 – Demographic data and stricture characteristics*

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>BMI (kg/m²)</th>
<th>Smoker</th>
<th>Stricture</th>
<th>Previous treatment</th>
<th>Date of surgery</th>
<th>Outcome</th>
<th>Follow-up (mo)</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Aetiology</td>
<td>Length (cm)</td>
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<tr>
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<td>54</td>
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<td>No</td>
<td>Instrumentation</td>
<td>3–4</td>
<td>AT</td>
<td>Jun 2014</td>
</tr>
<tr>
<td>2</td>
<td>62</td>
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<td>4–5</td>
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<tr>
<td>3</td>
<td>41</td>
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<td>Idiopathic</td>
<td>3–4</td>
<td>AT</td>
<td>Jun 2013</td>
</tr>
<tr>
<td>4</td>
<td>73</td>
<td>21</td>
<td>Ex</td>
<td>Catheter</td>
<td>4–5</td>
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<td>Apr 2014</td>
</tr>
<tr>
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<td>26</td>
<td>No</td>
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<td>30</td>
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</tr>
<tr>
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<td>Success</td>
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<tr>
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<td>26</td>
<td>Yes</td>
<td>Instrumentation</td>
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<td>Urethroplasty Aug 2014</td>
<td>Success</td>
</tr>
<tr>
<td>11</td>
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<td>25</td>
<td>No</td>
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<td>4–5</td>
<td>AT</td>
<td>Jul 2014</td>
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<tr>
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<td>3–4</td>
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<td>Sep 2014</td>
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<tr>
<td>14</td>
<td>48</td>
<td>26</td>
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<td>FHR</td>
<td>3–4</td>
<td>Urethroplasty Jun 2014</td>
<td>Success</td>
</tr>
</tbody>
</table>

AT = associated treatment; FHR = failed hypospadias repair.

* None of the patients had diabetes.

2.3. Surgical technique

2.3.1. Preoperative preparation and instrumentation
Patient clinical data and the site and length of the stricture are carefully examined to define the characteristics required for an oral mucosa graft. Patients with oral mucosa diseases and patients who have undergone previous surgery of the mandibular arch and thus are not able to open their mouth wide are informed that genital or extragenital skin will be used for the urethroplasty. All patients receive intravenous broad-spectrum antibiotics the day before surgery, during the procedure, and for 3 days thereafter. The patient starts using chlorhexidine for oral cleansing 3 days before surgery and continues for 3 days after surgery. The patient is intubated through the nose, allowing the mouth to be completely free. The operation is performed by two surgical teams working simultaneously, each with its own set of surgical instruments. The oral mucosa graft is harvested from the cheek according to our standard technique used on more than 553 patients [21,22]. The graft is tailored according to the site, length, and characteristics of the stricture.

2.3.2. Patient positioning and stricture approach
The patient is placed in a supine position. For strictures involving the external urinary meatus and extending into the distal part of the penis, the penile urethra is approached with a circular subcoronal incision and penile degloving. For more proximal strictures the penile urethra is approached with a midline longitudinal incision of the penile skin or with a perineal approach.

2.3.3. Preparation and opening of the penile urethra
The distal end of the stricture is identified with a 16F Nelaton catheter through the meatus, and the midline skin incision is outlined (Fig. 1A). The urethra is identified and left adherent to the corpora cavernosa (Fig. 1B). The urethra is opened along its ventral surface to expose the stricture (Fig. 1C). The urethral opening extends 2 cm into the distal and proximal healthy urethra. The midline incision of the urethral plate is outlined (Fig. 1D).

2.3.4. Incision and preparation of the urethral plate
The urethral plate is distended by placing a few stitches under traction, and a deep longitudinal midline incision is made using an ophthalmic scalpel, taking care to avoid opening the underlying tunica albuginea (Fig. 2A). The incision extends beneath the lateral margins of the urethral mucosa to increase the space for the graft (Fig. 2B). The scar tissue should be carefully removed (Fig. 2C). Any opening of the tunica albuginea should be recognised and sutured. The midline urethral plate incision is transformed into a wide window (Fig. 2D).

2.3.5. Gluing and suturing of the oral graft
The oral graft is sutured to the distal opening of the incised urethral plate and distented using three stitches. A 2-ml aliquot of glue (Glubran 2) is injected onto the urethral plate (Fig. 3A). The graft is quickly placed over the glue bed and held in place for 45 s using two small swabs (Fig. 3B). The graft is secured with two 6/0 polyglactin stitches placed at the extremities of the urethral plate incision and around its lateral margins; no full quilled sutures are used on the graft (Fig. 3C).

2.3.6. Closure of the urethra and penile skin
A 12F silicone grooved Foley catheter is inserted (Fig. 4A). The urethra is closed in a single layer over the catheter using 5/0 polyglactin sutures (Fig. 4B). The dartos fascia is closed over the suture line. The penile skin is closed (Fig. 4C) and a soft dressing is applied (Fig. 4D).

2.4. Postoperative course
Ice bags are placed on the cheek and the genital area for 24 h to reduce pain and haematoma formation.
Fig. 1 – (A) The stricture site is identified and the penile skin incision is outlined. (B) The penile urethra is left adherent to the corpora cavernosa and to its lateral surrounding tissues. (C) The urethra is opened ventrally. (D) The incision of the urethral plate is outlined.

Fig. 2 – (A) Midline incision of the urethral plate using an ophthalmic scalpel. (B) The incisions are extended beneath the lateral margins of the urethral mucosa to create space for the graft. (C) The white scar tissue is removed. (D) The midline incision of the urethral plate is transformed into a wide window.
2.5. **Postoperative follow-up**

Patients are discharged from the hospital 3 d after surgery; voiding cystourethrography is performed 2 wk later. The clinical outcome was considered a failure when any postoperative instrumentation was needed, including dilation. Uroflowmetry and urine culture were repeated every 6 mo in the first year and annually thereafter. When symptoms of decreased force of stream were present and $Q_{\text{max}}$ at uroflowmetry was $<12$ ml/s, the urethrography, urethral ultrasound, and urethroscopy were repeated.

2.6. **Data analysis**

Demographic data, preoperative clinical information, and perioperative and follow-up variables were extracted from medical files and recorded in a dedicated database. Clinical outcome was considered a failure when any postoperative instrumentation was needed, including dilation.

Complications were classified according to the Clavien-Dindo classification [23]. Descriptive statistics were calculated out for the available variables.

3. **Results**

To test if Glubran 2 may jeopardize engraftment of the free oral mucosa epithelial graft, fibroblast cultures were exposed in vitro to cyanoacrylic-based surgical glue. Cell toxicity was observed in conjunction with the adhesive, leading to a halo devoid of cells. The halo diminished over time in both urethral and oral mucosa cultures, reaching the...
margins of the adhesive in 8 and 7 d, respectively. No halo was observed in cultures exposed to fibrin glue. The area of polymerised adhesive was reduced by up to 30% for urethral fibroblasts and 20% for oral mucosa in 47 d. The percentage and morphology of dead cells in both groups after 24 h and 7 d of adhesive contact was similar to the control. Moreover, the number of dead cells at 24 h and 4 and 8 d after secondary plating did not differ between conditions. Transient toxicity of cyanoacrylic-based surgical glue, but not fibrin glue, was observed in urethral and oral mucosa keratinocyte cultures. Colony-forming efficiency assays showed long-term recovery of the cytotoxic effect.

A total of 14 patients with a median age of 60 yr (range 40–82) comprised the study cohort (Table 1). The stricture aetiology was instrumentation in eight (57.1%) patients, and the stricture length was between 3 and 5 cm in all patients; 11 (78.6%) patients had undergone previous treatment (Table 1). The median operative time was 60 min (interquartile range [IQR] 45–75), including graft harvesting and closure of the skin incision. The median postoperative stay was 3 d (IQR 2–4). Three (21.4%) intraoperative complications occurred, all of which were tunica albuginea injuries that were immediately discovered and sutured with 5/0 polyglactin sutures. Postoperative complications included one (7.1%) urinary tract infection (grade 2) in a patient with bladder diverticula treated with intravenous antibiotics. In all patients, voiding cystourethrography 2 wk after surgery failed to show any urethral fistula or sacculation. No patients complained of penile chordee or sexual dysfunction after surgery.

The median follow-up was 16 mo (IQR 12–32). Among the 14 patients, 12 (85.7%) procedures were successful and two (14.3%) were failures. The two failures were treated using two-stage repair.

4. Discussion

Use of an oral mucosa graft and glue for penile urethroplasty in a limited series of patients with short follow-up had a success rate of 85.7%, with no significant intraoperative or postoperative morbidity. This type of penile urethroplasty can thus be considered simple, safe, and efficient.

The main question regarding this technique is related to whether the glue negatively influences engraftment, imbibition, and taking of the free graft. Our in vitro studies on cultured keratinocytes and fibroblasts isolated from bulbar urethral and oral mucosa demonstrated that Glubran 2 glue has only a transient toxic effect, supporting its safe application for urethral reconstruction in humans.

In our preliminary experience, use of glue decreased the operative time by approximately 0.5 h, as it is deemed unnecessary to place quilting sutures over the graft. Moreover, the graft is well distended onto its bed, a fact that likely facilitates taking and makes it easier to suture the graft to the margins of the urethral plate. Furthermore, the glue also has an intrinsic biochemical haemostatic property that helps to limit haematoma formation between the graft and the underlying tissue. In Italy the cost of glue for each surgery is approximately €55 (1 ampoule).

Another question is the success rate of penile urethroplasty using glue. In this preliminary study, the success rate of penile urethroplasty using oral mucosa grafts increased from 81.8% to 85.7%. On the basis of the results obtained for one-stage penile urethroplasty, we now also use this glue in one-stage bulbar dorsal urethroplasty and in two-stage penile urethroplasty, obtaining the same advantages. Although we had achieved satisfactory outcomes using fibrin glue in bulbar graft urethroplasty, owing to the high cost of this product we had no choice but to discontinue its use for this procedure [24].

Penile urethroplasty is still a challenging problem and whether it is best to use a flap or a graft in one-stage repair is a matter of debate [10]. In our experience, the success rate of one-stage penile urethroplasty increased with the evolution of the surgical technique: 66.7% success using a skin flap, 78.3% using a skin graft, 81.8% using an oral graft, and 85.7% using an oral mucosa graft and glue [14]. The current results, however, do not offer any evidence for graft versus flap, and we believe that the choice should be based on stricture characteristics, surgeon background, and preference [7–10,25]. Finally, we suggest that the urethra should not be completely elevated during surgery, as it is for the repair of bulbar strictures, to avoid damage to the vasculature.

Our study is not without limitations. First, we included a limited series of patients with short follow-up. More studies with larger series of patients and longer follow-up are needed to evaluate the incidence of recurrent strictures over time [26]. Furthermore, we used $Q_{\text{max}}$ for outcome assessment during follow-up. We realise that $Q_{\text{max}}$ itself is not a reliable indicator of obstruction, especially without knowing the voided volume and flow pattern. It may be argued that our population is not entirely homogeneous. However, in this case series we excluded patients with LS and included only one patient with failed hypospadias repair. The majority of our patients had the same stricture aetiology and length and previous treatment. Finally, the absence of quality-of-life questionnaires and patient-reported outcome measures is another limitation of our study, especially since the outcome of penile urethra reconstruction involves not only functional but also aesthetic and sexual aspects.

5. Conclusions

The combined use of oral mucosa and glue for one-stage penile urethroplasty is safe and efficient and could represent a surgical innovation in the management of urethral strictures. Studies confirming our results with larger series are required before the technique is made available in the daily armamentarium.

Author contributions: Massimo Lazzeri had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Barbagli, Pellegrini.
Acquisition of data: Sansalone, Montorsi, Butnaru.
Analysis and interpretation of data: Barbagli, Lazzeri, Montorsi, Pellegrini.
Drafting of the manuscript: Barbagli, Pellegrini.
Critical revision of the manuscript for important intellectual content: Montorsi, Lazzeri, Pellegrini.

Statistical analysis: Sansalone, Butnaru.

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Supervision: None.

Other: None.

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Appendix A. Supplementary data

The Surgery in Motion video accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.eururo.2016.04.025 and via www.europeanurology.com.

References