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Review

History and evolution of the use of oral mucosa for urethral reconstruction



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Abstract We report here the history and evolution of the use of oral mucosa in reconstructive urethral surgery since it was first used for urethroplasty in 1894. Since that time, many authors have contributed to develop, improve and popularize the use of oral mucosa as a substitute material. Paediatric urologists should be considered pioneers on the use of oral mucosa as they used it to repair primary and failed hypospadias. The use of oral mucosa to repair penile and bulbar urethral strictures was described, for the first time, in 1993. Important evolutions in the technique for harvesting oral mucosa from the cheek were reported in 1996. Today, oral mucosa is considered the gold standard material for any type of anterior urethroplasty in a one- or two-stage repair due to its biological and structural characteristics that make it a highly versatile that is adaptable to any environment required by the reconstructive urethral surgery. As the future approaches, tissue engineering techniques will provide patients with new materials originating from the oral epithelial mucosal cells, which are cultured and expanded into a scaffold. However, the path to reach this ambitious objective is still long and many difficulties must be overcome along the way.

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1. Introduction

The use of oral mucosa as a substitute material for urethral reconstruction greatly revolutionized the surgical techniques and the outcomes of anterior urethroplasty.

We describe here, step by step, the history of the use of oral mucosa for urethral reconstruction, emphasizing the evolution of the suggestions coming from the literature up to the current techniques and outcomes. In this paper we provide details on the use of oral mucosa for urethroplasty, from its pioneering experience to its future application using a tissue engineering materials. According to standard and accepted dental terminology the buccal mucosa refers to the oral mucosa overlying the inner cheek of the oral cavity, and we do not include on this review the use of lingual mucosa for urethroplasty [1].

2. History of oral mucosa

2.1. Oral mucosa in ophthalmology

The first use of oral mucosa as a substitute material in surgery dates back to 1873, when Stellwag von Carion, an ophthalmologist from Vienna, Austria, used lip mucosa to treat conjunctival defects [2]. In 1880 Van Milligen transplanted strips of oral mucosa to treat trichiasis, a congenital or acquired abnormal position of the eyelashes [2]. In the early 20th century, oral mucosa was suggested as a substitute material to treat many ophthalmic defects: symblepharon, a partial or complete adhesion of the palpebral conjunctiva of the eyelid to the bulbar conjunctiva of the eyeball; scarring after burns; conjunctivodacryocystorhinostomy (CDCR), a procedure by which a fistula is created between the medial commissural conjunctiva into the nasal cavity; orbital prostheses [2].

2.2. Oral mucosa in urology: the first pioneering experience

The first surgeon to use oral mucosa as urethral replacement was Kirill Sapezhko, a surgeon from Ukraine [3,4]. Kirill M. Sapezhko (1857–1928), before beginning to use oral mucosa in his patients, performed experimental studies on animals and described five sequential phases relating to changes in the transplanted oral mucosa: imbibition, inosculation, mucosa dimness, graft cleansing, and complete engraftment [4]. Sapezhko performed the first two-stage urethroplasty using lip mucosa as early as 1890. In the second case, in 1891, he performed a one-stage tubularized lip mucosa graft. The third case in 1893 consisted of a one-stage tubed urethroplasty for traumatic stricture and a fourth case was later carried out [4]. In 1902, the surgeon Thyrmos, who lived in Odessa and was a Kirill Sapezhko fellow and followed his technique using oral mucosa for urethroplasty, described a successful urethroplasty using oral mucosa [4].

These pioneering experiences coming from Eastern countries were not popularized and were kept out of the Western scientific community and literature until 2002 [3].

2.3. Oral mucosa in paediatric urology

In Europe, the use of oral mucosa for urethral reconstruction was initially reported by Graham Humby from the Hospital for Sick Children in London, UK [5]. Surely, Humby did not read the reports from Sapezhko and Thyrmos published in Russian scientific journals, which are not widespread in Western countries, but we can suppose that he had known of the use of lip mucosa in ophthalmology as he wrote: "...the graft had taken perfectly in the same way as an epithelial inlay from ectropion of the eyelid..." [5]. Humby successfully used the oral mucosa to repair a failed hypospadias in an 8-year-old boy, with a peno-scrotal fistula, but he was not fully convinced and reported: "With some misgivings, mucous membrane for the lower lip was taken for the implant" [5]. Humby's should be considered an anecdotal use of oral mucosa because no others reports, for many years, followed this experience.

Only 51 years later, in 1992 Bürger et al. [6] from the Department of Urology, in collaboration with the Division of Oral and Maxillofacial Surgery, in Mainz, Germany reported the first findings from animal experiments and the subsequent clinical application of oral mucosa in urologic paediatric cases. In the first dog, an 8 cm oral mucosal tube was crafted over a stent and placed in a subcutaneous pouch over the rectus abdominis muscle [6]. The tubed graft was examined 3 months later, showing a well vascularized, non scarred tube with no evident shrinkage and an intact mucosa. In the second dog, a 4 cm penile urethra was removed and replaced with an oral tube over an 8 Fr stent [6]. On postoperative day 10 the animal was sacrificed for severe infection and post-mortem examination showed the neo-urethra without pathologically significant findings [6]. After these animal experiments the authors used oral mucosa grafts in four patients with failed hypospadias repair (FHR), one with a short urethra and one with epispadias [6]. The oral graft was used to make a tube (4) or patch (2) in a one-stage (5) or two-stage (1) procedure [6]. Three urethral fistulas and one meatal stenosis occurred in three patients but the final outcome was considered cosmetically and functionally good in all patients [6]. The oral mucosa was harvested from the inner cheek, with a clear and detailed description of the harvesting technique, and the suture used at the harvesting site [6].

One month following the Bürger et al. [6] report, Desanti et al. [7] from the Children's Hospital in Brescia, Italy, fully reported the use of oral mucosa to repair primary hypospadias in 8 children. The oral mucosa was harvested from the inner surface of the upper and/or lower lip and was the only material used in three patients with penile hypospadias, while in five patients with posterior hypospadias it was used in combination with bladder mucosa: the results were excellent in all cases [7].

These two articles coming from paediatric urologists should be considered a milestone for the use of oral mucosa in urology. After these two publications appeared in rapid succession, a myriad of accounts on the clinical use of oral mucosa began to come out, mainly reporting small selected series of patients [8–12]. One year following these two reports from paediatric surgeons, the first series of adult

patients with urethral strictures treated using oral mucosa grafts appeared in the literature.

2.4. Oral mucosa in urethral surgery

In 1993, El-Kasaby et al. [13] from the Ain-Sin University in Cairo, Egypt, reported the first series of 20 adult patients with penile (12) or bulbar (8) urethral strictures treated by transplanting an oral mucosa graft. This is the first report on the use of oral mucosa for adult urethral stricture repair [13]. The oral mucosa was harvested from the mucosal membrane of the lower lip, the harvesting site was sutured, and the mucosa was applied to the penile or bulbar urethra as an onlay patch [13]. Out of 20 patients, 18 showed excellent results and two patients required revision surgery for recurrent strictures [13]. These authors reported that they started using this technique in 1975, many years before the Bürger and Dessanti articles, without suggesting why they decided to use the oral mucosa, but they had known and reported an article on the use of oral mucosa in ophthalmology [13]. We can suppose that this article was the first after Sapezhko's and Humby's reports on the use of oral mucosa in urology. However, it would be interesting to know why these authors started using this innovative surgery in 1975 and only described it in 1993, 18 years after their first application. Nevertheless, this report also represents a milestone in the history of the use of oral mucosa in urology.

3. Evolution of the use of oral mucosa for urethral reconstruction

3.1. Evolution of the harvesting technique

A great innovation in the use of oral mucosa for urethral reconstruction occurred in 1996 when Morey and McAninch [14] from San Francisco popularized a new approach to harvest oral mucosa from the cheek. These authors suggested the use of a two-team approach in which one team (usually an oral surgeon and urologist) harvests the graft from the mouth while the perineal team simultaneously exposes and calibrates the stricture. This two-team approach decreases operative time considerably [14]. Moreover, Morey and McAninch suggested the use of a Steinhäuser mucosa stretcher to stabilize the donor site, thus framing an area that is measured and marked for graft retrieval, usually 2.5 cm wide and 5–7 cm long [14]. This technique greatly simplified the harvesting of oral mucosa from the cheek, reducing the risk of oral complications and sequelae.

In 2007, Markiewicz et al. [1,15] reported the anatomic and biologic characteristics of the oral mucosa, suggesting these important steps in the harvesting technique:

1. To facilitate access to the oral cavity, nasal endotracheal intubation is the preferred method of airway control by the harvesting surgeon [1,15]. When oral endotracheal intubation is used, special precautions should be taken to maintain proper tube placement during the entire harvesting procedure, particularly

when the urethral defect requires a bilateral oral mucosa harvest [1,15].

2. Two separate sterile surgical instrument tables, instrument setups, prepping and drapings should be used to minimize cross-contamination of the oral and urethral wounds [1,15].
3. Using a simple lithotomy position, a two-team approach with separate and concurrent operating teams at the urethral and oral sites reduces lithotomy and general anaesthesia time [1,15].
4. Mouth retractors have proven useful in oral mucosa harvesting by adding the benefit of tongue and cheek retraction thereby increasing operator visibility and access to the harvesting site [1,15].
5. Primary closure of the harvesting site is suggested [1,15].

The technique described by Morey, McAninch and Markiewicz et al. was fully described and updated by Barbagli et al. [16], in a report of the results of 553 patients who received a detailed questionnaire regarding early and late postoperative oral complications.

In the pioneering experiences using oral mucosa for urethroplasty the preferred harvesting site was the lower lip [2], but the recent literatures report the cheek as the preferred harvesting site for primary or redo-urethroplasty [16–18].

3.2. Evolution of the techniques for urethral reconstruction using oral mucosa

In 1996, Morey and McAninch [19] described the use of oral mucosa as a non-tubularized onlay graft placed on the ventral surface of the bulbar urethra, closing the spongiosum tissue over the graft. In 1998, Barbagli et al. [20] popularized the use of oral mucosa as a non-tubularized onlay graft placed on the dorsal surface of the bulbar urethra. These two different techniques constitute fundamental evolutions and progress in reconstructive urethral surgery. Following these two publications, a myriad of reports also suggesting new approaches and procedures for the clinical use of oral mucosa began to appear [1].

In 2006, some authors reported that the placement of buccal mucosal grafts in the ventral, dorsal, or lateral surface of the bulbar urethra showed the same success rates (83%–85%) and the outcome was not affected by the surgical technique because stricture recurrence was uniformly distributed in all patients [21]. In 2006, some authors described that the use of glue may simplify the apposition of the graft and its adhesion to the corpora cavernosa [22,23]. In 2008, a new technique for the repair of bulbar urethral strictures that preserves the bulbospongiosum muscle and its perineal innervation was fully described [24]. In 2009, Kulkarni et al. [25] described a new one-sided anterior urethroplasty: a new dorsal onlay graft technique that, with the preservation of the vascular supply to the urethra and its entire muscular and neurogenic support, represented a significant step toward perfecting the technique of urethroplasty using a minimally invasive approach. In 2011, Andrich and Mundy [26], described a new bulbar anastomotic urethroplasty without transecting

the blood supply of the corpus spongiosum of the urethra, that represent and evolution of the vessel sparing anastomosis described by Jordan et al. in 2007 [27].

The use of oral mucosa greatly influenced not only the techniques for bulbar urethroplasty, but also the techniques currently suggested for penile urethral reconstruction. In 2001, Asopa et al. [28] described a new one-stage penile urethroplasty using an oral mucosa graft.

4. The use of tissue-engineered oral mucosa for urethral reconstruction

In 2004, Bhargava et al. [29] first reported the development of tissue-engineered buccal mucosa (TEBM) for future use in urethral reconstruction. In 2008, these authors reported the clinical outcomes using this material in urethral reconstructions in five patients with urethral strictures secondary to lichen sclerosus, using one-stage (2 cases) or two-stage (3 cases) techniques [30]. In 2015, Ram-Liebig et al. [31] published their experience on the use of tissue-engineered oral mucosa grafts in 21 patients with anterior urethral strictures. These two articles from Bhargava and Ram-Liebig are the only two reports available in the literature on the clinical application of tissue-engineered oral mucosa in humans [30,31].

5. Ideal guidelines for pioneering surgical work

5.1. Pre-operative selection, evaluation and preparation of patient

The following groups of patients are not ideal candidates for oral mucosa cheek harvesting:

- Patients who chew tobacco or consume areca nut products (betel quid, pan masala, gutka, mainpuri, mawa, kaini), as they are at risk for developing oral submucosa fibrosis, a disease characterized by a severe progressive fibrosis of the oral cavity resulting in dysphagia and a reduced ability to open the mouth [32].
- Patients who currently have an infectious disease affecting the mouth (candida, lichen, varicella-virus, herpes-virus and other).
- Patients who have had previous surgery in the mandibular arch prohibiting a wide opening of the mouth.

Moreover, patients who play wind instruments or work as speakers should be informed that the surgical harvesting of oral mucosa may negatively influence these activities in the early postoperative period.

Before planning to harvest the oral mucosa, patients should be fully evaluated to check the extension of the mouth opening, the size of available tissue on both cheeks and the presence of scars due to chronic cheek biting or previous surgeries. In patients who have undergone previous oral graft harvests, harvesting a new graft is possible though slightly more difficult due to the fibrosis and the fact that the graft need to be smaller than the previous one. The patient and the anaesthetist should be notified prior to surgery when bilateral oral graft harvesting is

planned. Three days prior to surgery, the patient should begin using chlorhexidine mouthwash for oral cleansing twice a day. The day before surgery the patient receives intravenous prophylactic antibiotics.

5.2. Instruments for oral mucosa graft harvesting

The following instruments are suggested for easier graft harvesting from the cheek:

- A Kilner-Doughty or Steinhäuser mouth retractor. These retractors, available in any oral surgery department, provide a wide and safe mouth opening. Using these retractors only one assistant is necessary to harvest the graft.
- A 10 mL syringe with 10 mL solution with bupivacaine HCl 2.5 mg/mL and epinephrine acid tartrate 0.0091 mg (0.005 mg epinephrine).
- Bipolar electrocautery.
- 5-0 absorbable sutures.

5.3. Preparation of patient for surgery

The patient is intubated through the nose, allowing the mouth to be completely free. Nasal intubation is not mandatory but presents the following advantages:

- The nasal tube is smaller and softer than the oro-tracheal tube and thus more comfortable for the patient.
- Nasal intubation is useful in patients with a small mouth or a limited mouth opening.
- Nasal intubation is useful in patients requiring double graft harvestings.
- Nasal intubation is useful at the beginning of our learning curve.

The patient is placed in a supine position for penile urethroplasty and in a simple lithotomy position for bulbar urethroplasty, with the calves placed in Allen stirrups with sequential inflatable compression sleeves and the lower extremities suspended by placement of the patient's feet within the stirrup boots. The patient is draped in two separated parts so that two surgical teams can work simultaneously. Each team has its own set of surgical instruments. One team harvests and prepares the oral graft, while the second team exposes the urethra.

5.4. Surgical technique of harvesting oral graft from the cheek

The external and inner mucosal surfaces of the cheek are prepared, disinfected and draped.

The Steinhäuser mouth retractor is put in place and three stay sutures are placed along the edge of the mouth to stretch the oral mucosa. Before starting the harvesting procedure it is mandatory to identify and mark the Stensen parotid duct near the second molar. If the Stensen duct cannot be clearly identified, applying some drops of lemon

juice to the tongue may stimulate secretion from the parotid gland.

The size and shape of the graft should be outlined by marked pen starting 1.5 cm from the Stensen duct and 1.5 cm from the external edge of the cheek. The shape, length and width of the graft vary according to the stricture characteristics and the type of planned urethroplasty (one-stage vs. two-stage). For a standard one-stage penile or bulbar urethroplasty the graft is designed in an ovoid shape, 4 cm long and 2.5 cm wide. A 4 cm long graft will stretch up to 6 cm due to the elasticity of the oral mucosa. Two 6 cm grafts (one from each cheek) are enough to repair the vast majority of anterior urethral strictures. In patients requiring a two-stage urethroplasty the graft is designed in a rectangular shape 4 cm long and 4 cm wide. A 10 mL solution with bupivacaine HCl 2.5 mg/mL and epinephrine acid tartrate 0.0091 mg (0.005 mg epinephrine) is injected along the edges of the graft to facilitate haemostasis and dissection. The graft is dissected in the plane between the mucosa and the muscle. The donor site is accurately examined and bleeding is controlled with bipolar electrocautery. The Stensen duct should be clearly visible. In patients who underwent an ovoidal graft harvest, the suture of the harvest site is simple and safe, helps prevent early and late postoperative complications and provides high patient satisfaction [16]. Two traction stitches are passed at the distal and proximal apex of the donor site, and when traction is applied to these stitches the two lateral margins of the donor site tend to approximate towards the midline, which makes primary closure easier and tension-free with running 5-0 absorbable sutures.

On the contrary, in patients who underwent a rectangular graft harvest, it is better to leave the harvest site open, because closing the large defect on the mucosal surface of the cheek with sutures under traction may cause early postoperative pain and a later scarred contraction of the cheek [16]. The graft is stabilized on a silicone board to remove the submucosal tissue and tailored according to the stricture characteristics. If necessary, another graft can be harvested from the contra-lateral cheek using the same technique.

5.5. Post-operative care and complications

An ice bag is applied to the cheek for 24 h to reduce pain and the risk of haematoma formation. The patient consumes a cold clear liquid diet on the first postoperative day before advancing to a regular diet the next day, ambulates on postoperative day 1 and is discharged from the hospital 3 days after surgery. The patient continues using a chlorhexidine mouthwash for oral cleansing twice a day for 3 days after surgery and is maintained on oral antibiotics until the catheter is removed. The closure of the Stensen duct may be caused by a surgical stitch or by a post-operative mucosal oedema, and may cause parotid enlargement and pain, requiring emergency consultation with the oral surgeon. In patients who underwent large graft harvest without closure of the harvest site, post-operative bleeding may occur.

In 2011 we reported the early and late complications of harvesting oral mucosa from the cheek a large series of 553

consecutive patients and univariable and multivariable analyses revealed that bilateral graft harvesting was the only significant predictor of patient dissatisfaction [16].

6. Conclusion

Since 1894 when Kirill Sapezhko from Ukraine, firstly described the use of oral mucosa for urethroplasty, a slow and progressive evolution of this technique has taken place [1,2,4]. From its primary use in paediatric surgery, the oral mucosa has become the most popular substitute material for urethral reconstruction using a wide range of surgical techniques [1]. This is due to the fact that oral mucosa possesses biological and structural characteristics that make this material highly versatile and adaptable to any different environment required by the reconstructive urethral surgery [15]. However, the popularity of oral mucosa is also related to the great evolution of the harvesting technique [14]. In paediatric experiences, the preferred harvesting site was the lower lip, but the cheek later became the most used harvesting site as it can provide larger grafts, conceals the scar and a low incidence of postoperative aesthetic sequelae [16,17]. The suggestions we have presented regarding harvesting oral mucosa from the cheek are based on our experience with the largest series of patients (553) reported in the literature to date [16,17].

The future of this field will involve the utilization of oral mucosa generated from tissue-engineered technology. This entails a small biopsy being taken from the mucosa of the cheek which is then cultured and expanded in a scaffold and used as the substitute material in urethral reconstruction. This technology may offer many advantages compared to the current technique because there should be no complications at the harvest site and we can obtain longer and wider grafts for the reparation of long and complex strictures.

Tissue engineering solutions have been suggested within the field of urology for many decades, but despite technical success in the laboratory, clinical application has been modest [33]. Unfortunately, at present there are only two reported experiences on the use of this procedure in human [30,31].

However, we strongly believe that the realization of this project represents a very difficult challenge and, honestly, we must take care to not deceive our patients into thinking that this "quiet revolution" in urethral reconstruction will be available soon for all urethral conditions (congenital or acquired, simple or complex) requiring surgery. The realization of this project also includes important and non-negligible legal and economical aspects [31,33]. There are two important questions regarding the future development and clinical use of tissue-engineered materials for urethral reconstruction. Will it be possible in the near future to develop tissue-engineered materials to be used on a large scale in any country? Will it be possible in the near future to develop tissue-engineered materials to be used on a large scale for any different urethral conditions (simple vs. complex)? Presently we are a long way from reaching these two objectives, because the realization of these two objectives requires an incredible financial and human

resources and each country has a different level of these resources to invest in such projects. Moreover, the development of an internationally marketable product to be used in any country, also requires an incredible amount of financial, laboratory (GMP laboratory) and human resources, and several years of development before a product can be registered with the Committee and Agency that regulates any given country the use of these products in humans [31,33]. To reach their full potential, developing technologies need to bring together not only science and engineering but also the commercial upscaling of production in a safe and regulated framework for clinical use [33].

In conclusion, urologists involved in reconstructive urethral surgery will still need to rely on oral mucosa harvested from the mouth from quite some time. Therefore, it is imperative that urologists know the history and the evolution of the use of oral mucosa for urethral reconstruction and understand the surgical tips and tricks that may help to avoid troubles and complications.

Conflicts of interest

The authors declare no conflict of interest.

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