Curr Urol Rep (2013) 14:366–372
DOI 10.1007/s11934-013-0334-9

PEDIATRIC UROLOGY (M CASTELLAN AND R GOSALBEZ, SECTION EDITORS)

Use of Buccal Mucosa in Hypospadias Repair

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Published online: 19 May 2013

Abstract Hypospadias is an embryological disorder that results in an abnormal ventral positioning of the urethral meatus. Among multiple surgical techniques described to correct this anomaly, the use of buccal mucosa grafts has gained popularity among pediatric urologists, pediatric surgeons and plastic surgeons. Buccal mucosa grafts have shown favorable histological changes that result in an excellent scaffold for urethral reconstructive surgery. This review describes the evolution of the use of buccal mucosa grafts in hypospadias repair.

Keywords Buccal mucosa · Graft · Hypospadias · Urethroplasty · Urethra

Abbreviations

BMG	buccal mucosa graft
SIS	small intestinal submucosa
BXO	balanitis xerotica obliterans

Introduction

Hypospadias is a developmental anomaly of the urethra. It is a spectrum disorder that ranges from a minimal ventral abnormal positioning of the urethral meatus to more severe forms, associated with incomplete ventral foreskin and penile curvature or chordee. Currently hypospadias is the second most common congenital anomaly (after cryptorchidism) affecting boys, with a reported prevalence of 1 in 200 to 1 in 300 live births [1, 2]. In the United States, the incidence of hypospadias increased from 20.2 to 39.7 per 10,000 boys born in the 1970–1993 period [3]. Studies have shown that this increased incidence could be related to many factors including, prematurity, small-for-gestational age infants, low birth weight and maternal age of 35 years or older [4–6]. Environmental factors have also been implicated. Recent investigations have questioned this increasing trend and subsequently showed a stable, if not decreasing, incidence of hypospadias [7, 8].

Currently, there are multiple surgical techniques employed worldwide for hypospadias repair. The goal is to have a functional penis without chordee, good cosmesis and a urethral meatus located in the glans, allowing the patient to void standing with a laminar flow. The generally agreed upon proper timing of genital reconstruction is age 6 months to 1 year. Manley and Epstein reported markedly improved emotionally and psychological results in patients when surgery was done at an early age [9]. The initial hypospadias surgical repair may be single or staged, depending on many factors, such as severity of ventral chordee, location of urethral meatus, deficiency of genital tissues and, surgeon preference. The use of buccal mucosa graft (BMG) is usually indicated for urethral reconstruction in cases of prior failed surgical attempts. In this article, we describe the evolution and currently applications of buccal mucosa graft techniques in hypospadias repair.

Histological Properties

Histological examination of buccal mucosa grafts have shown that the lamina propria is thinner than full thickness skin grafts, thus improving chances for revascularization [10]. Filipas et al. later described similar findings, comparing the histological differences between skin, bladder and buccal mucosa grafts after exposure to urine [11]. Buccal

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mucosa graft showed a greater stability in urine and enhanced early neovascularization in comparison with skin and bladder mucosa grafts. Histological results showed once again a thinner submucosal layer and a thicker epithelial layer in BMG.

Mokhless et al. described the histological changes of buccal mucosa grafts in 31 patients (14 adults and 17 children) with hypospadias [12••]. Buccal mucosa graft showed excellent uptake within 5 days in all cases. After 6 months from surgery, the buccal mucosa was well vascularized and pliable. Histological analysis of buccal mucosa tissues was done before and after graft harvesting and at 6 months after surgery. The analysis revealed epithelial hyperplasia with mild and focal keratinization. Lamina propria was slightly edematous and minimally infiltrated by mononuclear inflammatory cells. Buccal mucosal graft showed good vascularization similar to that of the normal urothelium. These superior characteristics, plus the ease of harvest, minimal contractility, and absence of hair, make the buccal mucosa graft an invaluable tool for hypospadias repair.

Historical Background

The use of buccal mucosa graft for hypospadias repair was first reported in 1941 by Humby, when he used a lower lip mucosal graft in a patient with multiple hypospadias repair who presented with a fibrotic urethra and a penoscrotal fistula [13]. After this initial report, buccal mucosa graft did not gain popularity, whilst bladder mucosa grafts gained popularity among reconstructive surgeons for urethral repair and substitution. However, bladder mucosa grafts were associated with meatal complications such as mucosal prolapse and meatal stenosis [14, 15]; furthermore, there was the added morbidity of the lower abdominal incision required to access the harvest site. Bladder mucosal graft resulted in poor aesthetic outcomes and delayed wound healing [16]. In 1992, Bürger et al. described their experience using autologous buccal mucosa graft in six patients, including three patients with prior failed hypospadias repair and limited genital skin [17]. Complications were high in this series, where three patients developed urethral fistulae and one patient had a meatal stenosis. Dessanti et al., reported excellent results with buccal mucosa graft for complex hypospadias repair [18]. They used BMG alone or in combination with bladder mucosa graft in eight patients with hypospadias. With a short follow-up (6 to 18 months), only one patient in whom reconstruction was done using BMG alone developed an urethrocutaneous fistula.

In 1995, Duckett et al. reported the use of BMG to reconstruct the urethra of 18 pediatric patients [10]. Buccal mucosa grafts were used in the surgical treatment of complex hypospadias (12), epispadias (4) and urethral strictures (2). In most patients (16), the buccal graft was tubularized and in two patients the graft was used as an onlay. High number of patients had complications with tubularized BM grafts. Three patients (17 %) required further surgical inteventions and five patients (28 %) developed meatal stenosis. Urethrocutaneous fistula was noticed in one patient (6 %) and was repaired uneventfully. Since the 1990s, the use of BMG has been reported more frequently, with good results in patients with complex hypospadias [19–21].

Two-Stage Urethroplasty

In 1995, Bracka brought up his concern about the poor aesthetic result from one-stage hypospadias repair [22••]. He described a two-stage approach as an alternative for hypospadias repair, where a natural glans and meatus may be achieved more consistently. In the first stage, the glans is split in the midline, ventral chordee tissue is removed and a proximal meatotomy is performed. The ventral defect is covered with a graft of buccal mucosa, preputial skin, or post-auricular skin, which is sutured and covered by "a firm 'tie-over' dressing". After at least 6 months, patients are brought back to the operating room to complete genital reconstruction. The second stage includes correction of any remaining penile curvature, tubularization of the graft or neourethra, and the use of a Dartos flap to cover the suture lines and prevent urethral fistulae. Bracka used this method in 600 patients (1984–1994), initially as a salvage surgical approach in adults with prior failed surgeries, but later he also applied this technique to pediatric patients as a primary repair. These patients were divided as follows: 457 children (369 patients had primary repair and 88 patients had secondary or salvage repair) and, 143 adults (22 primary, 121 secondary). Follow-up of these 600 cases ranged from 6 months to 10 years. Thirty-four patients (5.7 %) had urethrocutaneous fistulae, the majority occurring in the group of patients requiring more challenging salvage therapy. Forty-one patients (7 %) developed urethral strictures and 28 patients developed late onset strictures (2 to 5 years after surgery), mostly because of lichen sclerosus (BXO). The author emphasized the high recurrence of strictures when urethral reconstruction is done with local skin in patients with lichen sclerosus, although this may not be apparent for several years. The use of buccal or bladder mucosal grafts, or a combination greatly reduces the risk of urethral stricture recurrence in patients with lichen sclerosus.

Others authors have described their experience with a two-stage hypospadias repair in the pediatric population. Snodgrass et al. described their initial experience with buccal mucosa grafts in staged hypospadias reoperations [23]. In their series, 25 patients had an average of 4.4 prior failed

hyspopadias surgeries before undergoing staged repair with buccal mucosal graft. The graft was harvested from the cheek in 15 cases, and from both the cheek and lower lip in ten cases. The cheek donor site was sutured in 17 patients and left open in two, and the lower lip was left open in five patients. Fibrin glue was used to seal the donor site defect on the cheek and lower lip in five patients. The graft took successfully in 22 patients (88 %) without evidence of scars or contracture. The other three patients required partial excision and re-grafting prior second stage neourethral tubularization. Of these patients, 20 underwent complete urethroplasty (2nd stage surgery). The barrier layer placed over the neourethra was small intestinal submucosa (SIS) (Biodesign 4-layer tissue graft, Cook Medical Inc, Bloomington, IN) in two patients and flaps of dartos and/or tunica vaginalis in 18 patients. Follow-up ranged from 6 weeks to 14 months. Complications occurred in seven patients (35 %) who required further surgical repair. Urethrocutaneous fistulas occurred in the two patients in whom SIS was used as the barrier layer and, in only one patient (5 %) in whom dartos/tunica vaginalis flaps were used to cover the neourethra. Partial or complete glans dehiscence occurred in four patients and a distal reoperative glansplasty was successful in all four patients.

Recently, Leslie et al. described their experience with staged buccal mucosa graft urethroplasty in patients with prior failed hypospadias repair [24]. In a 5-year period, they performed 32 urethroplasties in 30 patients, with a mean age of first stage surgery of 7 years (range 1 to 17 years) and a mean interval between first and second stages of 9.3 months. Meatal position before the initial surgery was distal in 16 % of patients, mid-shaft in 39 %, and proximal in 44 %. Buccal mucosa grafts were harvested from the cheek in 25 patients, from the lower lip in two patients, and from both in four patients. Four patients (13 %) needed re-grafting prior second stage surgery due to initial graft fibrosis or contracture. Mean follow-up after complete urethroplasty was 25 months. Complications after second stage surgery occurred in 11 of the 32 surgeries (34 %), urethral stenosis in five repairs (16 %), glandular dehiscence in three repairs (9 %), and urethrocutaneous fistula in three repairs (9 %). In this series complications occurred in 82 % of patients with unfavorable graft take compared to 19 % of patients with favorable graft take defined as the grafts having no fibrotic or indurated areas ($p<0.001$).

Onlay/Inlay Buccal Mucosa Graft

Morey and McAninch described their experience with onlay patch graft of buccal mucosa in 13 patients with complex bulbar strictures [25]. They combined this technique with other reconstructive procedures such as stricture excision and fasciocutaneous penile flaps. With a median follow up of 18 months, none of the patients required further instrumentation, showing the adequacy of buccal mucosa graft for repair of long and dense urethral disease. The use of onlay buccal mucosa graft was later described in 17 of 22 pediatric patients with previously failed hypospadias repair (tubularized grafts were done in five patients) [26]. In this series, complications were reported in three patients, fistula (2) and urethral stricture (1); showing that onlay BMG is a very good procedure for complex hypospadias repair.

In 1996, Barbagli described dorsal grafts in the reconstruction of bulbar urethral strictures [27]. In this technique, the urethra is opened along it dorsal aspect, exposing the tunica albuginea of the corpora cavernosa. A graft is harvested and sutured to the corpora and the urethra. The regeneration of the urethral mucosa is enhanced by the graft, which works as a scaffold, reducing significantly the time for urethral healing. The Barbagli technique had been extensively used, mostly for bulbar urethral stricture repairs, and several modifications had been described, such as the use of fibrin glue and nerve-sparing techniques. Initially, it showed a success rate of 92 %, which decreased to 85 % with an extended follow-up due to expected substitution urethroplasty deterioration [28]. Similarly, long-term outcome of ventral buccal graft have showed success rate of 85–90 % [29, 30]. Ventral onlay grafts showed to be a stable option for urethral repair, with most complications occurring in the first 12 postoperative months [31]. Long-term follow-up revealed similar success outcomes in both techniques.

Recently, the combination of both dorsal and ventral double BMG has been described in urethral reconstruction of adults with bulbar strictures. In one series of 48 cases, 43 repairs (89.6 %) were successful and five (10.4 %) failed with stricture recurrence; four were treated with direct vision internal urethrotomy and one with a temporary perineal urethrostomy [32]. With this combined technique, the authors reported excellent urinary and sexual post-operative outcomes in adult patients [33].

Asopa et al. described the use of dorsal buccal mucosa grafts to treat urethral strictures via a ventral sagittal urethrotomy approach without mobilizing the urethra [34]. Twelve adult patients with long or multiple strictures of the anterior urethra were treated by a dorsal free full-thickness preputial or buccal mucosa graft. After a follow-up of 8 to 40 months, one recurrence developed and required dilation. They concluded that ventral sagittal urethrotomy approach for dorsal free graft urethroplasty is not only feasible and successful, but is easy to perform.

The concept of dorsal inlay graft in hypospadias repair was introduced by Hayes et al. [35•]. This technique combines the excellent cosmetic and functional outcomes of the tubularized incised plate urethroplasty repair [36], with the use of buccal mucosa graft. In this technique, the urethral

plate is dissected from surrounding glanular and penile skin tissue and then the plate is incised longitudinally in the midline and its edges drawn apart. The diamond-shaped defect is covered by a graft harvested from the lower lip preferentially, although it may also be obtained from the inner preputial skin if present [37]. The graft is sutured in place around its edges, and quilting sutures may be applied in the middle of the graft to secure it into the neourethral groove. The neourethra is then tubularized around an indwelling urethral catheter and the skin is in the same stage. This technique is useful in patients with prior failed hypospadias repair in whom the urethral plate is not scarred, and when there is no significant residual chordee. It is not applicable to patients with liquen sclerosum (BXO) where all diseased tissue needs to be resected and the entire urethral plate replaced with a buccal mucosa graft. In such cases, a staged repair is necessary.

In 2011, Macedo et al. described the 3-in-1 one-stage complex hypospadias repair, where patients had ventral chordee repair with urethral plate sectioning [38]. Buccal mucosa graft is harvested to cover the ventral defect and function as a scaffold for the neourethra. After tubularization, the neourethra is covered by a transverse preputial flap. Then a tunica vaginalis flap is obtained from the contralateral side. He used this technique in 35 patients with proximal hypospadias and 31.5 % needed a second intervention due to fistulae and urethral diverticula [39].

Snodgrass et al. described an algorithm for the approach to patients with prior failed hypospadias repair [40••]. The author's preference was to perform a one-stage inlay graft to patients who had prior surgery over the urethral plate without scarring, and a staged buccal mucosa graft in patients with severely scarred urethral plate/skin strip or with a ventral curvature greater than 30 degrees.

Our Experience

At our institution between 1994 and 2011, we used buccal mucosa graft for urethral reconstruction in 107 patients with history of hypospadias. Age ranged from 6 months to 55 years old (mean 9.6 years), where 85 % of the patients were under 21 years of age. The buccal mucosa graft size ranged from 2 to 9 cm in length (mean 5.4 cm). We used BMG in 31 patients with primary proximal hypospadias, nine patients with midshaft/distal hypospadias and small urethral plate, and 67 patients with a prior history of hypospadias repair. In this last group, patients had between two and 13 previous failed hypospadias surgeries. With a follow-up between 1 to 18 years (mean 9.6 years), 86 patient (80.3 %) had excellent cosmetic and functional outcomes. 21 patients (19.7 %) developed complications: eight patients (7.5 %) had urethrocutaneous fistulas, five patients (4.7 %) developed meatal stricture, four patients (3.7 %) showed anterior urethral diverticulum, three patients (2.8 %) had glans dehiscence, one patient (0.9 %) had a short urethral stricture and another patient (0.09 %) developed a complete neourethral stricture.

Our preference is to perform these cases in a simultaneous two-team surgical approach, with one surgeon harvesting the buccal mucosa graft and the other surgeon working on the penile shaft and completing the graft transfer. In this way, operative time and chances of cross-contamination are decreased. General endotracheal anesthesia is administered either with a nasotracheal or orotracheal tube. Our initial site of choice for graft harvesting is the lower lip, but if the patient has a large defect to be covered, then the graft is harvested from the cheek, sometimes from both. If the harvesting is from the cheek, we pay special attention to avoid donor site Stensen's duct. We first infiltrate the buccal mucosa graft with lidocaine 0.5 % with epinephreine (1:200,000); this helps to create the plane between the muscular tissue and the graft. Initial incisions are done with a #15 blade around the graft margins. The rest of the dissection is done with a fine Metzenbaum scissors (Fig. 1 a–c).

Once the graft is obtained, we proceed to defat it and it is placed in a container with normal saline solution to keep it hydrated (Fig. 1 d, e). Once the recipient site is fully prepared, we fix the graft in place (Fig. 2 a–d) and fix it to the penile skin laterally, to the glands distally, and to the urethral meatus proximally with 7–0 absorbable suture (Fig. 2 e, f). We perform small incisions with a #11 blade along the graft to help drain any blood or serous fluid from beneath the graft, therefore minimizing the chances of hematoma or seroma formation, which could result in graft take failure. In addition, the graft is attached to the corporal bodies with quilting 6–0 absorbable suture. Donor site hemostasis is obtained with minimal bipolar electrocautery, and we leave the defect open placing a Surgicel strip (Polyanhydroglucuronic acid, Ethicon Inc., Somerville, New Jersey) over it. At the end of surgery, before endotracheal tube removal, we do a last evaluation of the donor site and keep the Surgicel in place. An indwelling catheter is placed through the meatus to keep urine diverted from the graft. We use a dressing similar to that described by Bracka (16), with two films of Tegaderm (Acrylic dressing, 3 M, Maplewood, Minessota) and sterile gauzes kept in place with Monocryl 5–0 (Poliglecaprone, Ethicon Inc., Somerville, New Jersey).

In our experience the donor site defect heals quickly, in about 2 to 3 weeks after surgery. We do not close the cheek or labial defects after graft harvesting. Rourke et al. described the effect of wound closure on buccal mucosa graft donor sites with a randomized prospective trial [41]. In this series, 50 patients were randomized to either closure (26 patients) or not (24 patients) of the harvesting site. Patients in whom the defect was left open showed less early postoperative pain, earlier return to regular diet and less bothersome periorbital numbness

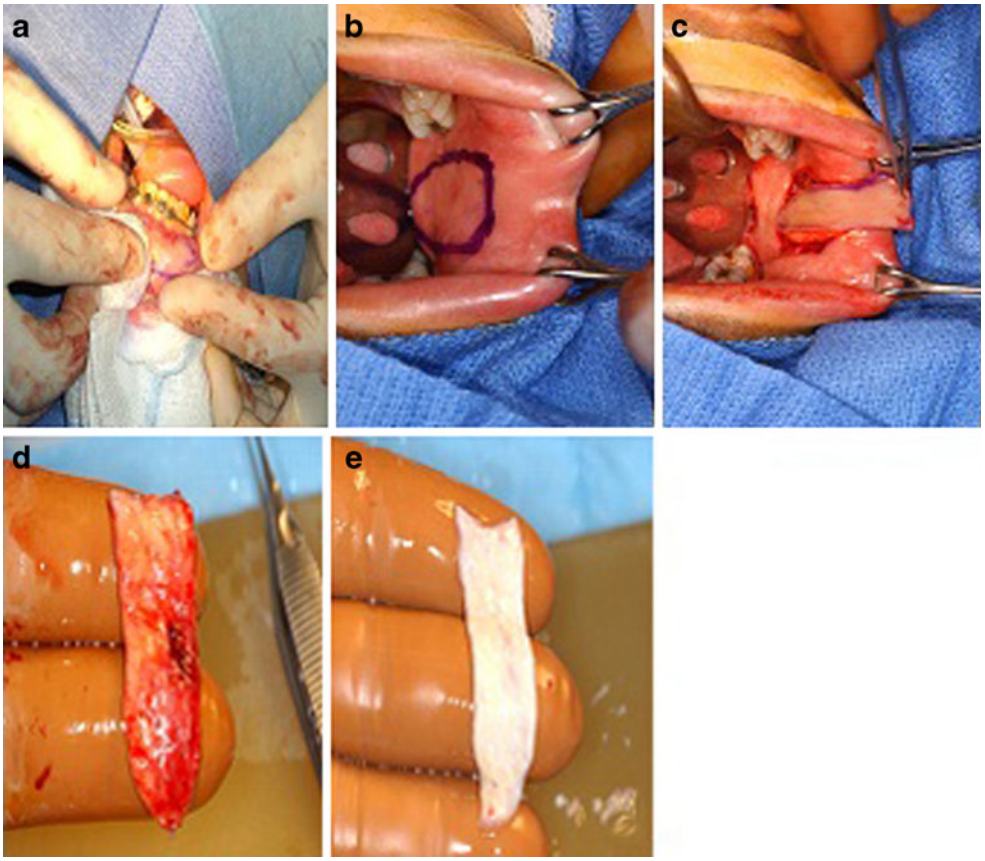

Fig. 1 Buccal mucosa graft retrieval. (**a**, **b**) Area of the graft to be harvest is marked on the lower lip (also can be obtained from the cheek with special attention to avoid Stensen's duct). (**c**) After hydrodistention is done with lidocaine 0.5 % with epinephreine (1:200,000), the graft is carefully removed from donor site. (**d**) Visualization of buccal mucosal graft after removal from donor site. (**e**) Graft is defatted as much as possible to assure imbibition and improve inosculation

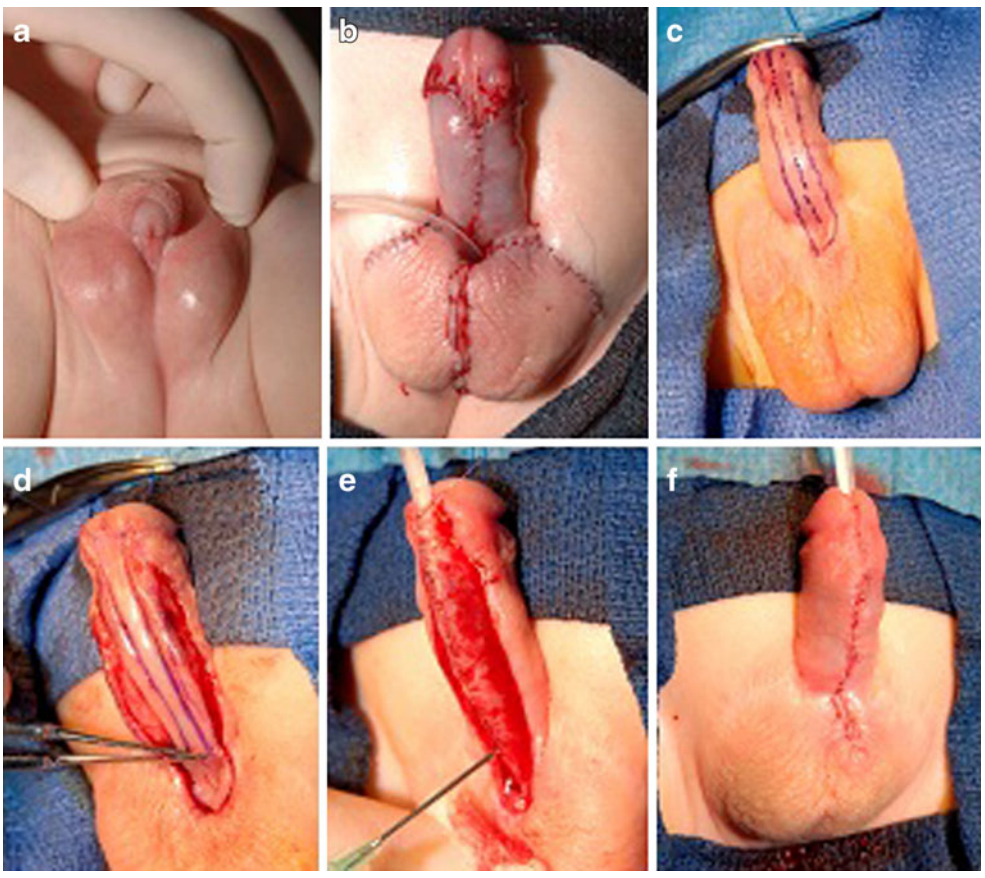

Fig. 2 Inlay muccal mucosa graft: staged hypospadias repair with an inlay buccal mucosa graft. (**a**) This is a 10-month-old boy with a severe proximal hypospadias and ventral curvature. (**b**) Patient underwent first stage hypospadias and chordee repair as well as scrotal transposition repair. (**c**) For the second stage hypospadias repair, neourethra is demarcated, including midline incision for an inlay buccal mucosa graft placement (**d**) BMG is placed in the midline of the neourethra. (**e**) Tubularization of the neourethra is done with 7–0 absorvable suture. (**f**) Final result of repair with an orthotopic meatus

at 6 months postoperatively. Even though patients are uncomfortable during the first postoperative days, most of them tolerate regular diet. For those few that cannot manage regular diet, a blenderized diet is recommended, which can be advanced as tolerated in the next 2 to 3 days.

Promising Techniques

Recently, the use of lingual mucosal grafts, first described by Simonato et al. [42], have been gaining acceptance among reconstructive surgeons involved in hypospadias repair. Maarouf et al. compared the buccal and lingual mucosal graft in complex hypospadias after failed hypospadias repair [43]. Forty-four patients were prospectively randomized into two groups: 23 patients underwent reconstruction with BMG and 21 patients with lingual mucosa graft. Lingual mucosa graft harvesting time was significantly shorter than BMG (19 min vs. 24 min). With a mean follow up of 20.8 months, successful outcome in BMG cases was 78.2 % vs. 76.1 % in those with lingual mucosal grafts. Donor site pain was reported in both groups, although patients with lingual mucosal graft seem to have an earlier recovery. Peri-oral numbness, mouth tightness and oral discomfort were reported mostly in patient with buccal mucosa grafts. On the other hand, patients with lingual mucosa grafts experience slurred speech and difficult tongue protrusion. Complication rates were similar in both groups, with 21.7 % in patients with buccal mucosa graft and 23.8 % in patient with lingual mucosa graft requiring further procedures.

A novel technique is currently in development by using autologous cell culture grafts in urethral repair. Palminteri et al. recently described their initial results with the use of autologous cell cultures of buccal mucosa for urethroplasties in five patients with urethral stenosis [44]. Buccal mucosa biopsies were obtained and keratinocytes and fibroblast were isolated in cell culture dishes. Once the tissues were ready, they were transplanted to the patients. As it is commonly done in staged repairs, 6 months later, the neourethra were tubularized. Two patients (40 %) had successful outcomes, while the other three patients (60 %) had complications, including one patient for whom the graft did not take successfully, and two others that developed urethral stenosis after tubularization. Although the grafts obtained were far from adequate in terms of tissue extension and thickness, the use of biotechnology may provide a useful scaffold for complex urethroplasties cases in the future.

Conclusion

For more than 20 years, buccal mucosa grafts have been routinely employed in complex hypospadias and urethral stricture repairs. Its unique histological characteristics, such as thin lamina propria and thick epithelium, facilitate inosculation and enhance its vascular supply in comparison to other urethral substitution materials. Furthermore, the ease of harvest, minimal contractility and absence of hair make it the preferred tool for such challenging cases. Buccal mucosa grafts had been used for urethral reconstruction in patients with hypospadias in a ventral or dorsal position with similar reported outcomes. The surgeon should individualize the decision as to whether do a single vs. staged repair after considering multiple variables, including severity of hypospadias, condition of the urethral plate, skin deficiency, chordee and surgeon preferences [45].

More recently, use of lingual mucosal graft has been gaining adepts amongst reconstructive surgeons, due to its ease of harvest, faster recovery and less perioral numbness and difficulties tolerating oral intake. In the near future, biotechnology may provide a useful graft to be used for complex urethral surgeries, without the morbidities and discomfort associated with buccal mucosal graft harvesting.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Omar Cruz-Diaz reported no potential conflicts of interest relevant to this article.

Dr. Miguel Castellan is a section editor for *Current Urology Reports*.

Dr. Rafael Gosalbez is a section editor for *Current Urology Reports*.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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