Use of BioGlue Surgical Adhesive in Hypospadias Repair
Stanislav Kocherov    Genady Lev    Boris Chertin
Department of Pediatric Urology, Shaare Zedek Medical Center, Faculty of Medical Science, Hebrew University, Jerusalem, Israel

Key Words
Hypospadias • BioGlue • Hypospadias repair • Urethrocutaneous fistula

Abstract
Purpose: To prospectively evaluate the efficacy of albumin glutaraldehyde tissue adhesive (BioGlue) in the surgical treatment of patients with hypospadias. Materials and Methods: Two groups of 20 patients each who underwent hypospadias repair were included in the study. In the first group we utilized BioGlue as an additional protective layer to the suture line of the neo-urethra, while patients in the second group were operated on utilizing a routine surgical technique. Results: There were no statistical differences between patients from the 2 groups in terms of surgical complications. Urethrocutaneous fistula was revealed in 4 (20%) patients after repair with BioGlue and in 3 (15%) patients from the control group (p = 0.686), suture line breakdown in 4 (20%) and in 1 (5%) patients (p = 0.478), meatal stenosis in 1 (5%) and in 1 (5%) patient (p = 1). Furthermore more patients in the BioGlue group (n = 12, 60%) demonstrated poor cosmetic results compared to the control group where most patients – 19 (95%) had acceptable cosmetic outcomes (p = 0.007). Conclusions: Our data showed no benefits of BioGlue use in hypospadias repair.

Introduction
Hypospadias is the most common congenital abnormality of the external genitalia in boys. The incidence of hypospadias in Western countries has tremendously risen and is approximately 1 in 150,300 male births [1].

The first description of urethral hypoplasia and hypospadias malformation goes back to Celsius and Galen, and dates as far back as the first and second centuries AD [2]. The renaissance of hypospadias surgery was established by Thiersch and Duplay during the second part of the 19th century [3, 4]. Since then, hundreds of techniques have evolved, mostly to answer the challenge of creating a functional neo-urethra. The complication rate varies with the complexity of the repair, technical modifications and the experience of the surgeon [5].

Some authors have demonstrated that covering the first suture line with single or double dartos flap or spongiosplasty may decrease the incidence of fistula development [5–9]. Others have demonstrated some benefits with the use of fibrin glue as a sealant for urethrocutaneous fistula prevention after hypospadias repair and for the closure of fistulas [10–12]. However fibrin sealants from a single-donor or multiple donors have some risks of HCV, HBV or HIV contamination, may sometimes lead to a sec-
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Materials and Methods

Following ethical committee approval, 40 patients were recruited into this study. All patients were randomly divided into 2 equal groups, each composed of 20 children. In Group I BioGlue surgical adhesive was applied as a thin layer on the second suture line of the neo-urethra. Patients in Group II were operated on utilizing the routine hypospadias repair technique. Demographic data and primary meatus location were similar in both groups (Table 1). The mean age of children was 32.1 ± 11 months in Group I and 26.7 ± 7.7 months in Group II (p = 0.69). In Group I the meatus was positioned in the distal penile shaft in 7 (35%), in the mid-shaft in 6 (30%), in the proximal shaft 1 (5%), and in the peno-scrotal area in 6 (30%) children. In Group II distal hypospadias was in 8 (40%), mid-shaft in 5 (25%), proximal in 1 (5%), and peno-scrotal in 6 (30%) children. Thirteen (65%) patients underwent primary hypospadias repair in Group I and 12 (60%) in Group II. A second repair was performed in 7 (35%) children in Group I and in 8 (40%) in Group II. In Group I, 12 (60%) patients underwent a tubularized incised plate (TIP), 4 (20%) Mathieu repair, 2 (10%) a TIP procedure as a second stage of staged hypospadias repair, 1 (5%) a prepuce tubularized flap as a covering, and 1 (5%) fistula closure. In Group II TIP hypospadias repair was performed in 14 (70%), Mathieu in 5 (25%), and fistula closure in 1 (5%) patients. Our regimen of the surgical treatment and follow-up after hypospadias patients was previously published [19]. All hypospadias repairs were performed during a 1-day surgery, utilizing loop magnification in all cases. The operations were performed by a single surgeon (B.C.). In all patients who underwent TIP hypospadias repair, a dartsos vascularized pedicled flap was utilized to cover the neo-urethra. The neo-urethra was created utilizing 2 suture lines. The first line of the 6.0 PDS interrupted suture followed by the second line of the running Vicryl 6.0. During the first stage, repair of penile chordee was performed including transsection of the urethral plate followed by transposition of the prepuce pedicled flap internal layer as a covering on the ventral part of the penis. The second stage was performed 6 months later. TIP procedure was performed in all study patients during the second stage.

A Silastic 6 or 8 Fr catheter was left for a period of 1 week in all study patients. As a part of the routine protocol in our department all hypospadias patients are advised to come back after 3 months following surgery, after 1 year, and at the age of 18 years. Mean follow-up in the study patients was 15 ± 2.3 months (mean ± SD). Cosmetic appearance and late complications: urethrocutaneous fistula, suture line breakdown and meatal stenosis were recorded.

Commercially available software Graph Pad Prism version 5.00 for Windows, (Graph Pad software, San Diego, CA, chi square and Fisher test) was used for statistical evaluation, with a p value of < 0.05 considered as statistically significant.

Results

There were no statistical differences between patients from the 2 groups in terms of surgical complications. Urethrocutaneous fistula was revealed in 4 (20%) patients after repair with BioGlue and 3 (15%) in Group II (p = 0.686) and 4 (20%) from the BioGlue group had suture line breakdown compared with 1 (5%) patient from Group II (p = 0.478). Meatal stenosis developed in 1 (5%) patient (p = 1) from each group. However, more patients in Group I (n = 12, 60%) demonstrated poor cosmetic results compared to Group II where most of the patients (n = 19, 95%) had acceptable cosmetic outcomes (p = 0.007).

Discussion

The proportion of patients who experience complications after undergoing hypospadias repair as infants is reported as 2 to 15% [6, 20, 21]. However, this rate varies depending on the degree of hypospadias and the surgical technique used. The most commonly reported complications in this population included fistula, stricture and wound breakdown [6].

The requirements for hypospadias techniques, particularly regarding cosmetic issues are very demanding.

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Table 1. Demographic data and meatus localization

<table>
<thead>
<tr>
<th></th>
<th>Group I (BioGlue)</th>
<th>Group II (Control)</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Age (months)</td>
<td>32.10 ± 11.00</td>
<td>26.70 ± 7.72</td>
</tr>
<tr>
<td>Distal shaft hypospadias</td>
<td>7 (35%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Mid-shaft hypospadias</td>
<td>6 (30%)</td>
<td>5 (25%)</td>
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<tr>
<td>Proximal shaft hypospadias</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Peno-scrotal hypospadias</td>
<td>6 (30%)</td>
<td>6 (30%)</td>
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</table>
and therefore the current policy of hypospadias repair has completely changed. The urethroplasty technique of ‘tubularized incised plate urethroplasty’ or TIP, is currently one of the most popular procedures in the surgical repair of hypospadias, and according to the last survey on the most popular hypospadias repairs, it was found to be utilized in 85% of all hypospadias cases [22]. This technique allows the creation of a slit-like meatus that addresses all esthetic demands, in contrast to the less satisfactory cosmetic results of other techniques, such as Mathieu’s flap [23, 24].

Although this technique has demonstrated superior cosmetic results, it is not without complications. Some authors reported 20–30% complications [25]. A lot of efforts were invested in order to reduce the number of complications. Use of a vascularized dartus flap or tunica vaginalis of the testis as a protective layer between the neo-urethra and skin, spongioplasty, and fine non-braided sutures were proposed in order to reduce the complication rate [5, 7–9, 26].

However the complication rate following TIP repair with regards to fistula rate and glans breakdown is still high in some cases [25]. In order to achieve a better sealing effect during formation of the neo-urethra, a number of tissue sealants agents were proposed to facilitate urologic surgery.

In the past, fibrin sealant was used to augment hypospadias repairs. Kinahan et al. [27] utilized Tisseel, a fibrin glue preparation, to augment hypospadias repairs in children. They showed a clear benefit of using Tisseel in patients undergoing hypospadias repair. In the group of patients where sealant agent was applied on the suture line, the fistula rate was significantly lower (9 vs. 28% in a control group). Furthermore, Hick et al. [28] concluded that fibrin sealant appears to promote early catheter removal and enhanced wound healing after pendulous urethral reconstruction. Barbagli et al. [29] published their experience with the use of fibrin glue in the buccal mucosa graft urethroplasty for bulbar urethral stricture. The authors clearly demonstrated a shortened overall operative time and a decreased occurrence of the early postoperative leakage. Others however have pointed out that the application of glue in hypospadias repair does not completely eliminate fistula formation, even though it seems that it may minimizes the incidence of fistula formation and flap dehiscence [11, 12].

The aforementioned publications regarding the use of fibrin sealant gel in repair of hypospadias, closure of urethrocuteaneous fistula and reconstruction of bulbar urethra have led us to investigate BioGlue’s efficacy in hypospadias repair in a prospective study. Since natural human fibrin tissue sealant may carry a potential risk of HIV, HBV or HCV contamination, BioGlue seems to be an ideal agent [13, 14]. BioGlue is a 2-component system consisting of purified bovine serum albumin and glutaraldehyde. Glutaraldehyde bridges the amine groups from the bovine serum albumin to extracellular matrix proteins of the target tissue forming a covalent bond between the tissue and adhesive. In spite of the technical characteristics and previously published encouraging data on use of fibrin sealing agents, our data failed to demonstrate BioGlue’s benefits regarding the decrease of fistula formation rate and reconstruction breakdowns. The patients from both group showed the same fistula formation and surgical breakdown. Although almost half of the patients in both groups had proximal type hypospadias, which is associated with a high rate of complications and often requires multiple repairs, the complication rate did not decrease with the use of BioGlue. Furthermore the patients from the BioGlue group were inferior to the control patients in cosmetic appearance with prominent severe fibrotic skin reaction in most cases. It has been published that BioGlue may lead to tissue toxicity, local inflammatory response and postoperative wound complications [30–32]. In spite of the fact that in all study patients an additional protective layer of dartus vascular flap was utilized between the sealant and penile skin, we are tempted to speculate that this complication may be explained by toxicity to glutaraldehyde.

This manuscript is not without limitations. We presented a relatively small cohort of patients, and therefore it is hard to demonstrate a noticeable difference between the groups. We included both distal and proximal hypospadias in one analysis, different repair techniques and a relatively high number of repair cases. However the aim of this pilot study was to evaluate whether the use of BioGlue sealant carries some benefits in hypospadias patients. Including heterogeneous patients allowed us to check out the benefits of the BioGlue in different clinical set-ups. A large group of more homogenous patients should be considering in further evaluation of biological tissue sealant in hypospadias repair.

Conclusions

The data clearly demonstrated that the use of BioGlue surgical adhesive in hypospadias repair in pediatric patients does not carry additional benefits to the existing surgical techniques.
References