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Original Article

Looking beyond the dartos fascia and tunica vaginalis: reviewing the stance of common adjuvant covering biomaterials in hypospadiology

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Abstract: Hypospadias, one of the commonest congenital anomalies in boys, can have a spectrum of clinical presentation based on the location of the meatus and the presence of chordee. The surgical repair of hypospadias involves great precision, especially in proximal varieties and redo/complex cases of hypospadias. Hypospadiologists have put in tremendous efforts to improve the outcomes of these children. The utilization of adjuvant biomaterials is one such effort that has gained significant attention over the recent years. Biomaterials are used to cover the urethral suture line in instances where the ideal covering agents (dartos fascia and tunica vaginalis) are unavailable. We reviewed the mechanism of action, current stance, and advantages/disadvantages of three commonly used adjuvant agents, i.e. autologous platelet concentrates, tissue glues, and acellular dermal matrixes. Although individual studies have highlighted the therapeutic benefits of these adjuvants, the available literature has a limited level of evidence. Moreover, it is believed that the application procedure of these covering agents needs to be scrutinized in future studies. In addition, it is suggested that the application of any covering agent right up to the meatus is non-anatomical and redundant. Well-designed randomized controlled trials with a uniform application procedure and comparing different covering agents need to be conducted in the future before any definite conclusion is drawn.

Keywords: Hypospadias, adjuvant biomaterials, covering agents, tissue sealants, platelet-rich plasma, acellular dermal matrix

Introduction

Hypospadias is one of the commonest congenital anomalies seen in boys with an approximate incidence of 1 in 250 male live births [1]. It can have a spectrum of clinical presentations based mainly upon the location of the meatus and the degree of chordee [2]. The surgical management of hypospadias involves great precision. More than 300 different types of surgical procedures described just for the milder form (distal hypospadias) are a testament to the fact that no two cases of hypospadias are completely alike [3].

The surgical treatment of hypospadias is offered by pediatric urologists, pediatric surgeons, adult urologists, and plastic surgeons. Despite this, most of these surgeons would agree on the usefulness of a covering layer during the operative repair of hypospadias. A covering layer over the urethral suture line significantly reduces the incidence of postoperative complications [4]. Out of all the available coverage tissues and agents, the dartos fascia is considered the most physiologic and efficacious [5]. However, in scenarios of multiple redo-surgeries and hypospadias cripples, the ideal tissue coverings like dartos fascia and tunica vaginalis have already been utilized in previous surgeries and are not available. In fact, tunica vaginalis from both the testes have been used in majority of these cases. Therefore, there is a paucity of good quality covering tissue to provide adequate coverage and anchorage to the urethral suture line. In addition, the grafts from buccal mucosa, bladder mucosa, and small intestinal mucosa might have been

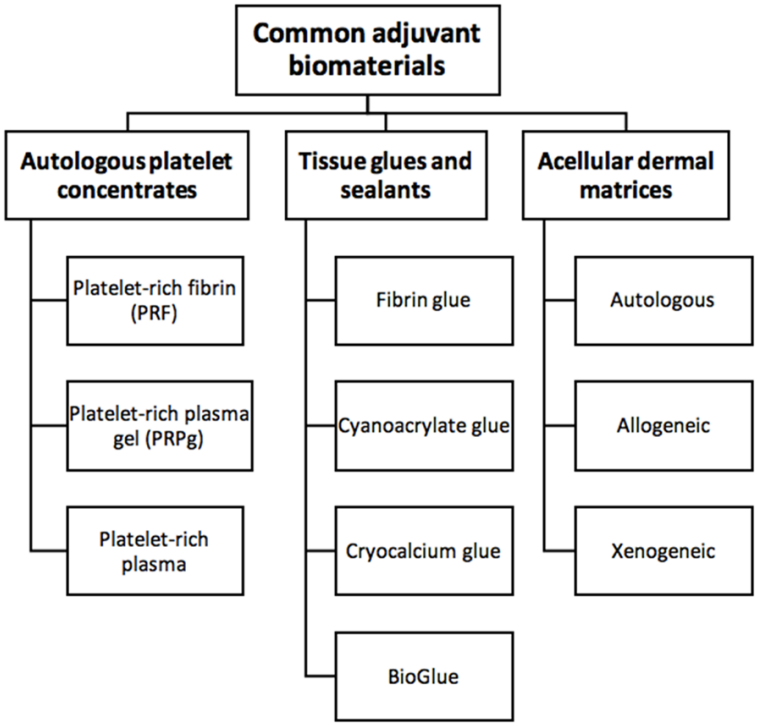

Figure 1. Commonly used adjuvant biomaterials in hypospadiology. The commonly used adjuvant biomaterials include autologous platelet concentrates, tissue glues or sealants, and acellular dermal matrices. The subtypes of each adjuvant agent are depicted in the figure.

already tried in these cases or might not provide an optimal covering layer.

Adjuvant covering agents and biomaterials are useful in these instances. Recent studies have demonstrated a multitude of options as adjuvant covering agents. The common adjuvant agents (**Figure 1**) include autologous platelet concentrates, tissue glues, and acellular dermal matrixes [4, 6, 7]. The present review aims to summarize the current literature regarding the mechanism of action, application procedure, results from previously published studies, advantages and disadvantages of these three common covering agents. It is expected that this review will provide valuable insights for further research on adjuvant covering agents.

Autologous platelet concentrates

Platelet-rich products or platelet concentrates include materials such as platelet-rich fibrin (PRF), platelet-rich plasma gel (PRPg), and liquid platelet-rich plasma (PRP) [8-10]. These are a source of growth factors and promote collagen synthesis, thus, supporting the process of wound healing [11]. The first report on the application of autologous platelet concentrates was published in 2013 by Soyer et al. [8]. The authors had described the successful closure of a recurrent UCF (developed after urethroplasty for coronal hypospadias) in a child following PRF utilization. Subsequently, various studies have demonstrated the beneficial effects of these products in hypospadiology.

Mechanism of action and preparation

Platelet concentrates act as a source of growth factors including platelet-derived growth factor, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), etc. [8, 11]. Since there is a paucity of an anticoagulant in these concentrates, unimpeded activation of the platelets promotes fibrous tissue formation and neovascularization [11].

The liquid PRP can be produced by centrifuging a pre-donated blood sample (with added anticoagulant) for 5-6 minutes [9]. Platelet-rich plasma can be used as such or in the form of a gel (PRPg) after adding an activator, e.g. calcium gluconate [9]. Alternatively, PRF can be used for this purpose [8, 11]. Generation of PRF involves centrifuging the freshly collected patient's blood for 10 minutes. It yields three layers: the topmost layer of plasma, the middle layer of PRF, and the lowermost layer of red blood concentrate. The middle layer is isolated and used in the surgery. The process of PRF generation can be performed in the operation room [11].

Advantages and disadvantages

The application of platelet concentrates not only serves the purpose of a coverage agent but hastens the wound healing process. It has several advantages over the sealants and glues, i.e. it is cheaper, simpler to obtain and

use, and not associated with the risk of infection transmission (**Table 3**). As it utilizes the patient's blood, the risk of allergic reactions and anaphylaxis is minimal [8].

The major drawback with the usage of this surgical adjuvant is the lack of sufficient literature supporting its role in hypospadiology. The present single-center studies have a limited sample size and focus on a selected subset of hypospadias patients.

Findings from the previous studies

Four studies have demonstrated the usage of platelet concentrates in hypospadiology. All four had used PRF (**Table 1**). Guinot et al. [7] explored the efficacy of PRF coverage over the urethroplasty suture line in distal hypospadias. The authors compared the incidence of complications in 33 patients (only PRF without any tissue cover) versus 72 controls (dartos flap cover only). The occurrence of UCF showed no significant difference among the two patient groups. No other complications were reported in either group. A similar study in distal penile hypospadias was conducted by Mahmoud et al. [10]. Ninety patients received PRF coverage (Group A) and an equal number was subjected to dartos flap coverage (Group B) as a second layer after urethroplasty. The incidences of overall complications and superficial wound infection were significantly low among the children belonging to group A. However, the occurrence of other complications showed no difference among the two patient groups.

Recently, Eryilmaz et al. [11] conducted a prospective study in children with mid-penile hypospadias. The postoperative outcomes of twenty patients (PRF between dartos flap and skin) and twenty controls (dartos flap coverage only) were compared. Compared to the controls, the wound infection rates were significantly low among the patients. However, there were no differences in the incidences of other complications. Although the results of these studies are promising, it is noteworthy that these concentrates have only been tested in a very selected subset of patients, i.e. distal and mid-penile hypospadias. Further studies must focus on its application in more complex cases of hypospadias (proximal hypospadias, hypospadias cripples, etc.) before a definite conclusion in terms of their therapeutic benefit is drawn.

Tissue glues and sealants

Tissue glues and sealants are common bioadhesives described initially for wound closure, tissue repair, and fixation of stents or implants [12]. Their application in hypospadiology was first highlighted by Tsur et al. in 1979 [13]. A significant reduction in urethrocutaneous fistula (UCF) incidence following urethroplasty was demonstrated in children where butyl-cyanoacrylate was used to reinforce the suture line. Since then, different types of glues (**Table 2**) have been explored for usage in hypospadias surgery [14, 15]. The commonly used tissue glues are composed of fibrin and cyanoacrylate. Recently, the application of cryocalcium glue, an autologous preparation from the patient's blood, was described by Hosseinpour et al. [16].

Application procedure and mechanism of action

The majority of the published studies have depicted the application of a tissue glue layer over the suture lines, either on skin only or both skin and dartos [6, 16]. In addition, few studies have also demonstrated the practice of sealant application beneath the tissue flaps to be beneficial in minimizing postoperative tissue edema [14]. Only a few milliliters of these sealants are sufficient to produce the desired effects [15, 16].

These agents bind to the tissue surfaces following their application and form a strong waterproof bond. However, the exact mechanism of action and the pathways activated by the various types of sealants differ considerably. Cyanoacrylate glue creates a strong film by exothermic polymerization upon binding to the target tissues [12, 17]. The mechanism of action of fibrin glue involves the activation of the last steps of the coagulation cascade [12, 15]. Although cryocalcium glue also activates the coagulation cascade, it utilizes the patient's own blood as the origin of thrombin [16]. BioGlue also has a peculiar mechanism of action. Glutaraldehyde, a key component in BioGlue, stimulates a network formation between albumin, extracellular matrix, and cells [18].

Table 1. Summary of findings from studies utilizing autologous platelet concentrates

SN	Author	Study design	Type of platelet concentrate	Patients	Main findings
1	Eryilmaz et al., 2020 [11]	Pro	PRF	20/20*	The occurrence of UCF, wound infection and urethral stricture were higher in the control group. However, significant difference was noticed only in terms of wound infection.
2	Mahmoud et al., 2019 [10]	Pro	PRF	90/90*	Overall complications and superficial wound infections were significantly low among patients versus controls. Rest of the complications showed no difference.
3	Guinot et al., 2014 [7]	Pro	PRF	33/72	PRF coverage over the urethral suture line provided no significant benefit in terms of the incidence of UCF in patients versus controls.
4	Soyer et al., 2013 [8]	Case report	PRF	1	Successful closure of recurrent UCF following application.

*Randomization done. Abbreviations: Pro, Prospective study; PRF, Platelet rich fibrin; UCF, Urethrocutaneous fistula.

Table 2. Summary of findings from the studies utilizing Tissue glues and sealants

SN	Author	Study design	Sealant type	Patients/ Controls	Main findings
1	Shenoy et al., 2021 [23]	Pro	Fibrin glue	20/20	Benefit of sealants in terms of overall complications, early postoperative ooze, torsion and flap-related complications.
2	Singh et al., 2021 [22]	SR	Fibrin glue, BioGlue, Cryocalcium glue	410/236	No difference in the incidence of overall complications. A significantly low rate of UCF, wound-related and neo-urethral complications in patients vs controls.
3	Hosseinpour et al., 2019 [16]	Pro	Cryocalcium glue	300/100	Beneficial effect of sealants in terms of lower incidence of UCF and postoperative edema.
4	Ambriz-González et al., 2014# [17]	RCT	2-OCA	21/21	No difference in the recurrence of UCF.
5	Kocherov et al., 2013 [18]	RCT	BioGlue	20/20	No difference in the complication rates. However, significantly more number of patients had an acceptable cosmesis.
6	Hosseini et al., 2011 [19]	Case series	Cyano-acrylate	2/0	Skin necrosis in both the cases.
7	Kajbafzadeh et al., 2011# [20]	Pro	Fibrin glue	8/0	One patient with partial skin dehiscence. No fistula recurrences in long term.
8	Gopal et al., 2008 [6]	RCT	Fibrin glue	60/60	Incidences of UCF and overall complications were significantly lower among the patients vs controls.
9	Ambriz-González et al., 2007 [15]	Pro	Fibrin glue	30/56	Incidences of UCF and flap-related complications were significantly lower among the patients vs controls.
10	M Castañón García-Alix et al., 2003 [21]	**	2-OCA	8/0	Only one child had UCF. The aesthetic results are good.
11	Kinahan et al., 1992# [14]	Retro	Fibrin glue	78/97*	Significantly lower fistula rate when sealant was applied. No difference in postoperative edema.
12	Tsur et al., 1979 [13]	Retro	BCA	115/69	No difference in the incidence of postoperative UCF.

Abbreviations: SR, Systematic review and meta-analysis; Pro, Prospective study; RCT, Randomized controlled trial; Retro, Retrospective study; UCF, Urethrocutaneous fistula; BCA, Butyl cyanoacrylate; 2-OCA, 2-octyl cyanoacrylate. *Subgroup division of patients not mentioned. However, the number of procedures per group is depicted; #Studies focusing on sealant usage for fistula closure. Kinahan et al. also included cases of urethroplasty; **Details about study design not mentioned.

Table 3. Advantages and disadvantages of different types of adjuvant biomaterials

Type of adjuvant	Advantages	Disadvantages
Autologous platelet concentrates	-Promotes wound healing -Low cost -Easy to obtain and use -Low risk of infection and allergic reactions	Lack of sufficient literature supporting its usage (limited sample size)
Tissue glues and sealants		
• Fibrin glue	-Easy availability -Biodegradable -Clotting time can be modulated	-Poor tensile strength -Risk of infection -Risk of anaphylaxis -Risk of coagulopathy
• Cyanoacrylate glue	-Strong adhesion & low dehiscence rates -Low risk of infection	-Poor strength on wet surfaces -Release of vapors -Risk of allergy
Acellular dermal matrices	Good coverage agents in terms of providing strength and elasticity. Strength and elasticity of human ADM > xenogeneic ADM	-Availability -Xenogeneic dermis is prone to rejection -Lack of sufficient literature supporting its usage (limited sample size)

Abbreviation: ADM, Acellular dermal matrix.

Advantages and limitations of different sealants

Fibrin glue is readily available and biodegradable. The main advantage associated with its usage is that its clotting and degradation time can be controlled (**Table 3**). However, poor tensile strength, risk of transmission of any infectious agent, coagulopathy due to autoantibodies against fibrin, and risk of anaphylaxis must be considered [12]. On the other hand, cryocalcium glue utilizes the patient's own blood. Therefore, the complications including infectious disease transmission, risk of autoimmunity, and anaphylaxis do not occur [16].

Compared to fibrin glue, cyanoacrylate glue has strong adhesion and low dehiscence rates. In addition, the wound infection rates are very low (**Table 3**). Its disadvantages include poor mechanical strength on wet surfaces, the release of toxic vapours during exothermic polymerization, and the risk of allergy in certain individuals [12]. Lastly, BioGlue has excellent tensile strength and undergoes fast polymerization. Also, it is biodegradable. However, a low viscosity, difficult application procedure, and risk of serious adverse effects make it unsuitable for routine use [12].

Findings from the previous studies

A total of twelve studies were identified from previously published literature [7, 13-23]. Of these, ten demonstrated sealant application during urethroplasty while only three showed sealant usage for closure of UCF. The different types of sealants used and the main findings of these studies are depicted in **Table 2**. Although most of these studies highlight a therapeutic benefit(s) of sealant application, there is a paucity of high-level of evidence (only three studies are randomized trials). A recent systematic review of the available comparative studies has highlighted similar limitations [22], and the issues of limited sample size, variations in the protocols of sealant application, and non-uniform outcome reporting need to be taken into account in future studies.

Acellular dermal matrix grafts

Acellular dermal matrix (ADM) grafts have been commonly used for reconstructive surgeries involving the genitourinary tract. Studies have shown promising results with allogenic or xenogeneic ADMs for the coverage of skin defects due to Fournier's gangrene, necrotizing fasciitis of the scrotum, burns in the genital areas, etc. [24, 25]. In patients with severe hypospadias, ADMs have been previously used for penile orthoplasty. Previous studies have demonstrated favorable results in the correction of severe chordee [26, 27]. However, the application of ADM as a coverage agent is seldom explored.

Types of acellular dermal matrices

Depending upon the source, these can be divided into xenogeneic, allogeneic, and autologous. Xenogeneic ADMs can be bovine or porcine in origin [4]. Allogeneic ADM is derived from human cadaveric tissue [26]. Although an autologous ADM must be derived from the patient's tissues, there are no studies on the usage of true autologous ADM as a coverage agent in hypospadias. However, Fossum et al. [28] have shown that it can be imitated by implanting a layer of cultured urothelial cells (retrieved by bladder wash) on an allogeneic ADM.

Mechanism of action

ADMs are scaffolds that are devoid of any cells and their antigenic properties. However, all the growth factor receptors and vascular channels are still present in these matrices. This promotes the migration of inflammatory cells and neovascularization after implantation, thus, ensuring an efficient wound healing [27].

Advantages and disadvantages

Although porcine and bovine ADMs have shown promising results, whether allogeneic or autologous, human ADMs should always be preferred. Compared to the human dermis, the porcine dermis is abundant in type I collagen and poorer in type III collagen and elastin fibers. It results in poorer elasticity and stretchability [27]. Also, the xenogeneic ADMs have a relatively denser structure than the human ADM. This delays the infiltration of the inflammatory cells and neovascularization, subsequently leading to a delayed graft uptake and poorer graft survival [27]. In addition, the xenogeneic dermis is prone to hyperacute and acute rejections (**Table 3**).

At present, there is a shortage of literature on the comparison of ADMs with other covering biomaterials. To our best knowledge, only one prospective study highlights the graft superiority of bovine ADM over dartos fascia in terms of the incidences of UCF and overall complications following urethroplasty [4].

Findings from the previous studies

Fossum et al. [28] treated six patients with severe hypospadias (scrotal or perineal meatus). A layer of cultured autologous urothelial cells was implanted on human ADM. The transplant was done so that the urothelial layer faced the lumen. Subsequently, the graft urethroplasty was performed. Half the urethral tube was made up of the penile shaft skin and the remaining half was transplanted in origin. During follow-up, two cases developed UCF while two had stricture formation. Cosmetic appearance and patient satisfaction were good in all cases. However, the biopsy showed urothelial lining in only 3/6 cases.

Lin et al. [4] have also demonstrated their experience of using bovine ADM as a coverage agent in 35 cases of proximal hypospadias. The outcomes were compared with the control group (80 patients) where the dartos fascia was used for coverage. A transverse preputial island flap urethroplasty was performed in both groups. The incidences of overall complications and UCF were significantly lower in the ADM group. However, all other complications including wound infection, urethral stricture, and diverticulum formation showed no significant difference among the two patient groups.

Recently, in a proof of concept study, Morgante et al. [29] showed the anti-inflammatory and tissue integrative properties of two different porcine ADMs. These ADMs were implanted in a peri-urethral location as on-lay grafts in male pigs. In this study, the porcine acellular bladder matrix (PABM) showed better stromal infiltration, neovascularization, and overall incorporation than the cross-linked acellular dermal matrix (Permacol™). Although ADMs have a great potential in reconstructive surgeries, a detailed exploration of their properties in in-vivo studies is mandated before any conclusions regarding their role as routine adjuvants in hypospadias surgery are drawn.

Anatomic justification and extent of application of adjuvants

Based on the current anatomic knowledge, it is clear that the male urethra is not a uniform tubular structure. The diameter and configuration of the urethra differ in its different parts [30]. Moreover, magnetic resonance imaging (MRI) findings of the normal glans have revealed that the glans wings are not fused in the midline but are separated by the septum glandis and frenulum [30]. There is only a lower

median septum and no additional tissue coverage at the glandular and sub-coronal levels. As a result, it is imperative to replicate the normal anatomy (recreate the frenular triangle) rather than focusing the attention on extensive glanular dissection and tight closure over the urethral stent [31]. Therefore, any covering layer (tissue glue/PRP/dermal matrix) right up to the meatus is non-anatomical and redundant.

However, their application over the proximal urethral suture line alone to complement/substitute the ideal covering agents (dartos, tunica vaginalis, etc.) needs to be studied further. Adequately powered comparative studies in the future may highlight therapeutic benefits of these biomaterials, especially in redo cases where there is no intervening layer between the urethra and penile skin.

Conclusions and future perspectives

The present review summarizes the available literature on common adjuvant covering agents in hypospadiology. The number of published studies is maximum for tissue sealants (or glues), followed by platelet-rich concentrates and ADMs. Although individual studies on these adjuvants have demonstrated promising results, the level of evidence is limited. In addition, there is a shortage of literature on comparison between these adjuvants and between adjuvants and ideal covering agents (dartos fascia or tunica vaginalis). Well-designed randomized controlled trials need to be conducted before a definite conclusion is drawn.

Future studies must also utilize the relatively less explored tissue engineering area to create newer autologous in-vitro expanded covering tissues. Apart from being useful in complicated cases of hypospadias, these newer adjuvants will be highly resourceful in complex reconstructive urogenital surgeries, e.g. exstrophy bladder, urethral stricture, etc.

Disclosure of conflict of interest

None.

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