The benefit of tissue sealant on urethroplasty in hypospadias patients – A systematic review and meta-analysis [version 1; peer review: 1 approved with reservations]

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Abstract

Background: Hypospadias was ranked second after undescended testis as the most prevalent congenital abnormality in newborn males. Hypospadias can be successfully repaired through multiple surgeries in the majority of children. Postoperative complications were not rarely seen after surgeries, such as urethrocutaneous fistula (UCF), meatal stenosis, and glans breakdown. Tissue sealant application in hypospadias repair serves as additional suture line coverage and reduces the post surgery complications. However, the effects of sealants usage during urethroplasty are still uncertain. This review aimed to know the effects of tissue sealant usage on patients with hypospadias who undergo urethroplasty.

Methods: The study was reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Literature was searched on PubMed, Embase, and Scopus following PRISMA guidelines. The search was conducted on October 12th, 2021, using the search term (“glue” OR “sealants” OR “tissue glue” OR “tissue sealant” OR “tissue adhesive”) AND (“hypospadias” OR “urethrocutaneous fistula” OR “urethral repair” OR “urethroplasty” OR “hypospadiology”).

Result: Systematic searching from all databases resulted in 160 potential articles. After a full-text review, eight articles were included in this study. UCF complication was reported in all studies. The occurrence of complication reported by all studies was urethrocutaneous fistula. Several studies also reported tissue edema and flap-related complications. Tissue sealant had no significant effect in reducing meatal stenosis.

Conclusions: This systematic review revealed additional benefits from several types of tissue sealant in hypospadias repair surgery. Fibrin sealant application over the urethroplasty suture line in hypospadias repair offers a water-proof coverage and may enhance the outcome from the surgery.
Keywords
Hypospadias, Urethroplasty, Tissue Sealant, Benefit

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Introduction
Hypospadias was ranked second after undescended testis as the most prevalent congenital abnormality in newborn males. Hypospadias is a displaced urethral opening at the penis ventral side because of incomplete penile structures closure during embryogenesis. At present, there are more than 300 known methods of surgical management of hypospadias however, hypospadias repair remains a complex procedure, even for sophisticated urologists and paediatrics surgeons.

Hypospadias can be successfully repaired through multiple surgeries in the majority of children. The overall success rate for first surgery was 55.9%. Postoperative complications were not rarely seen after surgeries, such as urethrocutaneous fistula (UCF), meatal stenosis, and glans breakdown.

In the recent past, the role of tissue sealants has been taken into consideration. Sealants are agents that can prevent the leakage of fluids by providing a physical barrier, which also aids in hemostasis. Tissue sealant application in hypospadias repair serves as additional suture line coverage and reduces the post surgery complications. However, the effects of sealants usage during urethroplasty are still uncertain. This review aimed to know the effects of tissue sealant usage on patients with hypospadias who undergo urethroplasty.

Methods

Eligibility criteria
Criteria for inclusion:

1. The study was published in full-text and written in English.
2. Published between 2002 and 2021.
3. Randomized controlled trials (RCTs) or prospective cohort studies.
4. Participants aged up to 18 years, who required operative repair for hypospadias.
5. The intervention included tissue sealants usage.
6. The comparison was made with patients without tissue sealant (Control).
7. The outcome of the studies was the number of children with complication after sealant use.

Guidelines
The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines was used in reporting this study. The flow diagram can be found in Figure 1.

Search strategy
The literature search was performed on PubMed, Embase, and Scopus following PRISMA guidelines (See reporting guidelines). The search was conducted on October 12th, 2021, using the search term (“glue” OR “sealants” OR “tissue glue” OR “tissue sealant” OR “tissue adhesive”) AND (“hypospadias” OR “urethrocutaneous fistula” OR “urethral repair” OR “urethroplasty” OR “hypospadiology”).

Data extraction
One reviewer (SS) performed literature selection and data extraction to an Excel database. Titles and abstracts were screened by two reviewers (SFS and AM) to determine the qualified articles. Next, the full text was reviewed to gather detailed information. Data were extracted by two reviewers (DK and SS) independently. Authors, study design, publication year, population, sample size, age, hypospadias severity, type of procedure performed, and characteristics of sealant information were extracted to Microsoft Excel. Any discrepancies among the observers were discussed until consensus was reached.

Result

Study selection
Systematic searching from all databases resulted in 160 potential articles (Figure 1). Duplicates were checked and excluded, leaving 79 articles. A total of 13 articles were qualified in this study. After a full-text review, eight articles were selected for review. These studies used various tissue sealant types. All the studies reported the procedure.
Study characteristics and key findings
The general characteristics of reviewed articles are listed in Table 1. All studies are prospective in study design. A total of 863 subjects with hypospadias were included. They were divided into the sealant and non-sealant groups, with 494 and 369 participants.

Shenoy et al., Gopal et al., and Ambriz-González et al. used fibrin sealant in their study. There were several distinctions regarding the application of fibrin sealant. Shenoy et al. applied the sealant on the neo-urethra’s suture line, and no vascular cover was used. Then, Gopal et al. made a thin layer of the sealant in the urethral and dartos suture line. Whereas Ambriz Gonzalez et al. applied 2 ml of fibrin glue over the surgical site and suture line.

In another study, Guinot et al. applied autologous platelet-rich fibrin (PRF) over urethroplasty. Meanwhile, Kajbafzadeh et al. aimed to determine fibrin sealant efficacy for UCF repair after multiple hypospadias and epispadias surgery. Over the closure area, a fibrin glue cover was made, and the dartos fascia layer was placed over this area.

Other sealants used in the included study were cryocalcium glue, BioGlue, and cyanoacrylate. Hosseinpour et al. used cryocalcium glue as a thin urethral layer and dartos suture lines. Kocherov et al. applied BioGlue as a thin cover on the the neo-urethra second suture line. Lastly, Hosseini et al. poured cyanoacrylate over the glans. A rubbery consistency was formed in 60 seconds, then reapplied 4-6 times.

Key findings of reviewed articles are listed in Table 2. Postoperative follow-up ranges between 7 days to 2 weeks to evaluate immediate complications, and between 1 month to 5 years to evaluate late complications. Hypospadias location differs from coronal, subcoronal, distal penile, etc. Some studies reported statistically significant differences of complication between the sealant and non-sealant groups. A study by Shenoy et al. reported distinction in early
<table>
<thead>
<tr>
<th>Study number</th>
<th>Author et al.,</th>
<th>Study design</th>
<th>Mean age</th>
<th>Sample size</th>
<th>Sealant type</th>
<th>The volume of sealant and technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Shenoy et al., 2021</td>
<td>Prospective</td>
<td>S-3.8 years N-4.6 years</td>
<td>20</td>
<td>20</td>
<td>Fibrin sealant</td>
</tr>
<tr>
<td>2</td>
<td>Hosseinpour et al., 2019</td>
<td>Prospective</td>
<td>-</td>
<td>300</td>
<td>100</td>
<td>Cryocalcium glue</td>
</tr>
<tr>
<td>3</td>
<td>Guinot et al., 2013</td>
<td>Prospective</td>
<td>S- median 8 months</td>
<td>33</td>
<td>72</td>
<td>Autologous PRF</td>
</tr>
<tr>
<td>4</td>
<td>Kocherov et al., 2013</td>
<td>Prospective</td>
<td>S-32.1 months N-26.7 months</td>
<td>20</td>
<td>20</td>
<td>BioGlue</td>
</tr>
<tr>
<td>5</td>
<td>Hosseini et al., 2012</td>
<td>Prospective</td>
<td>13.5 months</td>
<td>20</td>
<td>41</td>
<td>Cyanoacrylate</td>
</tr>
<tr>
<td>6</td>
<td>Kajbafzadeh et al., 2010</td>
<td>Prospective</td>
<td>S-12.18 years</td>
<td>11</td>
<td>-</td>
<td>Fibrin glue</td>
</tr>
<tr>
<td>7</td>
<td>Gopal et al., 2008</td>
<td>RCT</td>
<td>S-28.02 months N-28.00 months</td>
<td>60</td>
<td>60</td>
<td>Fibrin glue</td>
</tr>
<tr>
<td>8</td>
<td>Ambriz-González et al., 2007</td>
<td>Prospective</td>
<td>S-33.5 months N-31.3 months</td>
<td>30</td>
<td>56</td>
<td>Fibrin glue</td>
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Table 2. Main findings.

<table>
<thead>
<tr>
<th>Study number</th>
<th>Author</th>
<th>Time to follow up</th>
<th>Hypospadias location/type Sealant group</th>
<th>Main finding</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Shenoy et al.</td>
<td>7 days after discharge, 1, 3, and 6 months</td>
<td>Coronal (1), subcoronal (9), distal penile (4), mid penile (4), proximal penile (1), penoscrotal (1)</td>
<td>- Complications in 5 patients</td>
<td>- Differences in early postoperative ooze, skin flap-related complications and torsion were significant (p&lt;0.05)</td>
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<td></td>
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<td></td>
<td>Coronal (4), subcoronal (5), distal penile (1), mid-penile (7), proximal penile (1), and penoscrotal (2)</td>
<td>- Complications: coronal fistula (3), poor cosmetic outcome (3)</td>
<td>• Complications in 9 patients</td>
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<td></td>
<td></td>
<td>• Complications: early postoperative ooze (2), skin flap-related complications (3), UCF (7), poor cosmetic outcome (7), penile torsion (5)</td>
</tr>
<tr>
<td>2</td>
<td>Hosseinpour et al., 13 2019</td>
<td>2 weeks of the procedure, then every 3 month</td>
<td>Distal penile (300)</td>
<td>• Complications: edema (24), fistula (5), meatal stenosis (10)</td>
<td>• Statistically significant differences in edema (p=0.02)</td>
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<td></td>
<td></td>
<td></td>
<td>Distal penile (100)</td>
<td></td>
<td>• Statistically significant differences in fistula (p=0.02)</td>
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<td></td>
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<td></td>
<td>• No case of allergic in the case group</td>
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<tr>
<td>3</td>
<td>Guinot et al., 11 2013</td>
<td>2 month and 6 months post-operative</td>
<td>Distal (33)</td>
<td>• Coronal fistula (2)</td>
<td>• No statistically significant difference between both groups (p=0.65)</td>
</tr>
<tr>
<td>4</td>
<td>Kocherov et al., 16 2013</td>
<td>15 ± 2.3 months after surgery (mean ± SD)</td>
<td>Distal shaft (7), mid-shaft (6), proximal shaft (1), penoscrotal (6)</td>
<td>• Complications: UCF (4), breakdown of the suture line (4), meatal stenosis (1), poor cosmetic (n=12.6%)</td>
<td>• Complications: UCF (3), breakdown of the suture line (1), meatal stenosis (1), poor cosmetic (n=19.95%)</td>
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<td></td>
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<td></td>
<td>Distal shaft (8), mid-shaft (5), proximal shaft (1), penoscrotal (6)</td>
<td></td>
<td>• Statistically significant differences in poor cosmetic (p=0.007)</td>
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<tr>
<td>Study number</td>
<td>Author</td>
<td>Time to follow up</td>
<td>Hypospadias location/type</td>
<td>Main finding</td>
<td>Other findings</td>
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<td></td>
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<td></td>
<td>Sealant group</td>
<td>Non-sealant group</td>
<td>Sealant group</td>
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<tr>
<td>5</td>
<td>Hosseini et al.,15 2012</td>
<td>2 weeks postoperative and six to twelve months</td>
<td>Type B and C hypospadias</td>
<td>Type B and C hypospadias</td>
<td>Complications: hematoma (1), skin necrosis (1)</td>
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<tr>
<td>6</td>
<td>Kajbafzadeh et al.,10 2010</td>
<td>First 3 months from the date of surgery</td>
<td>Proximal hypospadias (8), epispadias (1), bladder extrophy complex (1)</td>
<td>-</td>
<td>Wound dehiscence (1), subcutaneous hematoma (1)</td>
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<tr>
<td>7</td>
<td>Gopal et al.,9 2008</td>
<td>2 weeks of the procedure and then every 3 months for the 1st year, then every 6 months for next 5 years</td>
<td>Proximal shaft (8), medial shaft (7), distal shaft (15)</td>
<td>Proximal shaft (14), medial shaft (12), distal shaft (30)</td>
<td>Complications in 12 patients Complications: postoperative edema (10), fistula (6), infection (4), meatal stenosis (3), proximal stricture (3).</td>
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<tr>
<td>8</td>
<td>Ambriz-González et al.,10 2007</td>
<td>At least 6 months after surgery</td>
<td>Proximal shaft (8), medial shaft (7), distal shaft (15)</td>
<td>Proximal shaft (14), medial shaft (12), distal shaft (30)</td>
<td>Complications: urethrocatheter fistula (3), flap dehiscence (4), flap necrosis (2)</td>
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- Statistically significant differences in postoperative edema (p=0.039), fistula formation (p=0.027), and overall complication (p=0.003)
postoperative ooze, skin flap-related complications, and tension between the sealant and non-sealant groups (p<0.05). Hosseinpour et al. revealed differences between edema and fistula (p=0.002). Kocherov et al. reported differences in poor cosmetic outcomes (p=0.007).

Shenoy et al. and Kajbafzadeh et al. reported less complication in the fibrin glue than in the non-sealant group. In the non-sealant group, the complications included early postoperative ooze, skin flap-related complications, UCF, poor cosmetic outcome, penile torsion, postoperative edema, diverticulum, meatal stenosis, proximal stricture, flap dehiscence, and flap necrosis. Early postoperative ooze, skin flap-related complications, and torsion were significantly different in the sealant and non-sealant groups (p<0.05). However, in a study by Kajbafzadeh et al., the difference of complications between both groups was not statistically significant.

Hosseinpour et al., in their study about the application of Cryocalcium glue, revealed that there was no allergy found in the sealant group. Then, Kocherov et al. reported poorer cosmetic outcomes in the non-sealant group compared to the BioGlue group (p=0.007). Subsequently, Hosseini et al. found poorer results in the non-sealant group than the cyanoacrylate group. His study revealed some complications, including hematomas, painful dressing removal, and repeat dressing.

**Figure 2. Forest plot: the occurrence of complication after urethroplasty (A: urethrocutaneous fistula, B: tissue edema, C: meatal stenosis, D: Flap related complication).**
In addition, Ambriz-González et al. compared the use of fibrin sealant on proximal, medial, and distal hypospadias. No statistically significant differences were found in the use of fibrin glue in proximal hypospadias to prevent complications. For medial hypospadias, fibrin glue was found to significantly reduce the occurrence of urethrocutaneous fistula (p=0.03) and flap dehiscence (p=0.001). Then, for distal hypospadias, fibrin glue was also found to reduce the occurrence of urethrocutaneous fistula (p=0.04) and flap dehiscence (p=0.04).

The analysis of clinical and statistical findings were shown in Figure 2. We compared the occurrence of complication after hypospadias repair. The occurrence of UCF was reported in all studies. UCF with sealant complication was the occurrence of complication reported by all studies was urethrocutaneous fistula. The pool risk ratio (RR) for UCF was 0.47 (95% CI 0.30 – 0.73 p=0.001) compared to non-sealant group. Tissue edema and flap related complication also reported by several studies with pooled RR for tissue edema and flap related complication was 0.45 (95% CI0.29 – 0.71 p=0.0004) and 0.44 (95% CI 0.31 – 0.62 p<0.0001). Tissue sealant gave no significant effect in reducing meatal stenosis with Pool RR 0.9 (95% CI 0.38 – 2.15 p=0.8).

Discussion

Hypospadias is a congenital anomaly discovered in 1 of every 300 live births. About 2-15% of infants with hypospadias experienced complications following repair procedures. The most common complications found, in order, are fistula, stricture, and dan wound breakdown. The need for hypospadias repairing technique, especially for cosmetic issues, is very demanding. The most popular technique is 'tabularized incised plate urethroplasty' or TIP. Although superior in cosmetic issues, it is reported that the complication is as high as 20-30%. Various tissue sealants were offered to gain a better seal of neo-urethra formation in the urologic procedures.

This systematic review revealed five different sealant types were used in hypospadias repair. The sealants are classified into natural and synthetic. The natural sealants are made of albumin, fibrin, and cryocalcium, while the synthetic sealant is made of cyanoacrylate.

Fibrin glue

Fibrin glue contains fibrinogen-rich coagulation cascade, factor XII, dan thrombin. According to the coagulation cascade, scavenging macrophages will reabsorb the fibrin glue in 14 days so that it has a weak mechanical strength. Other complications are anaphylactic reaction and infection.

Fibrin sealant has been used in many surgical procedures for hemostasis (topical agent) and tissue approximation (as an adhesive). Its usage has expanded through numerous procedures, including urologic surgery. Urologic procedures need the fibrin glue's sealing power to improve wound healing in penile urethroplasty.

Tisseel, a fibrin glue preparation, was first utilized by Kinahan et al. to enhance hypospadias repair. In addition, Hick et al. stated that fibrin glue could be beneficial in promoting early catheter removal and accelerating the process of wound healing. Study from Barbagli et al. shared their experience using fibrin glue in the buccal mucosa graft urethroplasty for bulbar urethral stricture.

Better postoperative outcomes were found in patients with fibrin sealant usage during surgery. There were no flap necrosis or penile torsion found as early postoperative complications. Havex et al. stated this benefit might be influenced by the regeneration of the cellular and angiogenic of the tunica albuginea defect. Urethra-cutaneous fistula was found less in the sealant group. They also had a better cosmetic outcome. There is a statistically significant improvement in the overall outcomes.

Another complication assessed in the study was postoperative edema. A larger number of early postoperative edema incidences in the non-sealant group might be due to undiscovered microscopic leakage in the tissue spaces between the suture lines. This could lead to a fistula formation. The application of fibrin glue forms an additional layer over the urethral tube, seals minute cracks between sutures, and decreases post-surgery edema. Therefore, its application might accelerate the wound healing process.

Commercial fibrin sealants had a higher risk of allergic reactions compared to the homologous, blood bank product, fibrin sealants, which are prepared from single unit plasma. Risk of infection could be decreased by using autologous blood as the fibrinogen source. The setback is that the production took longer and created non-uniform fibrinogen concentration. Kajbafzadeh et al. described fibrin glue's benefits preventing further recurrence in patients with recurrent fistula after hypospadias or epispadias repair.
Autologous platelet-rich fibrin
Choukroun et al. developed platelet-rich fibrin (PRF) in the early 2000s that has been used to augment the process of tissue healing. The procedure is simple and less expensive than fibrin glue: the PRF patch is collected by centrifuging the autologous blood sample without any adjuvant. The patch creation could be done amid the urethroplasty procedure and used promptly.11,28

A study by Guinot et al. found no negative effect of PRF as there were no adverse effects or skin infections discovered. Unfortunately, PRF superiority over conventional covering technique has not been proven.

Cryocalcium glue
The use of cryocalcium glue has been limited in underdeveloped or developing countries. This is due to its higher risk of infection transmission than fibrin glue, despite having been through donor screening, heat-treating, and the use of solvent and detergent suspension.13 The preparation of cryocalcium glue is very simple and can be done during the urethroplasty procedure. It can be used shortly after its preparation.13 It is formed from combining a patient's cryoprecipitate and calcium gluconate.13

This cryocalcium glue could be a safe and less expensive alternative than commercial fibrin glue to reduce fistula formation. The case group showed a minimal incidence of fistula by using cryocalcium glue.13 It is also safe from allergic complications due to its autologous origin.13

BioGlue
In a prospective study, Kocherov et al. reported the efficacy of BioGlue in hypospadias repair.14 BioGlue does not carry a risk of infection transmissions, such as HIV, HBV, or HCV, different from natural human fibrin tissue sealant. Therefore, it appears to be an ideal sealant.13 BioGlue consists of two purified bovine serum albumin and glutaraldehyde.30 Glutaraldehyde acts to bridge the bovine serum albumin amine groups to the target tissue's extracellular matrix, forming a covalent bond between tissue and adhesive.30 However, the advantages of BioGlue in reducing fistula formation and reconstruction breakdowns were not shown in the Kocherov et al. study.13 No difference in fistula formation and surgical breakdown were seen in both groups.13 In addition, the BioGlue group tends to have a more prominent severe fibrotic skin reaction, therefore inferior in cosmetics than the control group. Other publicity stated some discouraged effects of BioGlue, such as toxicity to tissue, local inflammation, and postoperative wound complications.31,32 It is hypothesized due to glutaraldehyde toxicity.14

Cyanacrylate
In a study by Hosseini et al., cyanacrylate was used as a dressing in urethroplasty.15 This dressing has many purposes with others in edema restriction, hematoma formation, and wound stabilization if treated in several layers and lacks urine and feces permeability.15 There were no regular changes or pain upon removal. This type of dressing was more convenient for patients and the wound was kept hygienic at home. The occurrence of complications is less, 10% versus 30%; but late complications indirectly related to the dressing have been excluded.15

Prestipino et al. used cyanacrylate in four patients with UCF. Three of them had fistula healing.15 In another study, cyanacrylate was used for simple sharp wounds in various locations, including the face and extremities, inguinal and umbilical hernia, cleft lip, hypospadias, and post-hypospadias fistula repair. The results showed improvement in efficacy, cosmetics, procedure duration, and patient comfort.34

Tissue sealant effect
Based on our meta-analysis, tissue sealant can reduce urethroplasty complications during hypospadias repair. In our analysis, tissue sealant can reduce the occurrence of fistula urethocutan, tissue edema, and flap-related complication. This result is in line with the previous systematic review.5

Limitation
There are several limitations to this study. The included studies reported non-uniform complications. Information on the sealant and surgery cost of hypospadias repairment was limited. Moreover, several hypospadias types and various repair techniques used might serve as confounding factors as not all studies report on the complication and success rate based on the type of hypospadias.

Conclusion
This systematic review revealed additional benefits from several types of tissue sealant in hypospadias repair surgery. Fibrin sealant applied over the urethroplasty suture lines forms an adequate water-proof cover and improves outcomes in
hypospadias repair. Fibrin glue reduces the incidence of complications in medial and distal hypospadias but not in proximal hypospadias. The application of PRF had no harmful effects, but it did not demonstrate superiority over conventional covering techniques. Cryocalcium glue could be used as an alternative to fibrin glue to reduce fistula formation. It is also safe and less expensive than fibrin glue. The use of cyanoacrylate dressing lessens the immediate complication of hypospadias repair surgery. Meanwhile, BioGlue does not show any additional advantages in hypospadias repair in pediatric patients than the standard procedures. A conclusion cannot be made due to studies diversity. Therefore, randomized controlled trials with a significant sample size are necessary to precisely compare the sealant and non-sealant groups, types of sealants, and hypospadias location.

Data availability
All data used in the research are available as part of articles and no additional source are needed to disclose

Reporting guidelines
Figshare: PRISMA checklist for ‘The Benefit of Tissue Sealant on Urethroplasty in Hypospadias Patients – A Systematic Review and Meta-analysis’.

DOI: 10.6084/m9.figshare.19102184

Data are available under the terms of the Attribution 4.0 International license (CC BY 4.0)

Author contributions
SFS: Conceptualization, Methodology, Project administration, Supervision

SS: Data curation, Software, Writing original draft

AM: Conceptualization, Supervision, Validation, Writing review and editing

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Open Peer Review

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Version 1

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This systematic review deals with a very interesting and up-to-date topic, since successful hypospadias repair still presents a great challenge. Literature data on the use of tissue sealant in urethroplasty show quite heterogeneous results, and authors made a very good choice to assess this by a systematic review. The methodology is based on PRISMA guidelines, with detailed explanation on search strategy, as well as good illustration of results. However, I have to note that the rest of the manuscript is poorly written, in several points:

1. The manuscript should be copy-edited to improve the quality of the writing.

2. Rationale and objectives are poorly explained, and introduction section needs more details and corrections, especially about the use of tissue sealant in hypospadias repair. Is it indicated in every case and form? What type of tissue sealant and when...?

Introduction Section: The sentence "Hypospadias can be successfully repaired through multiple surgeries in the majority of children" has to be corrected. Today, most of hypospadias cases are repaired by a one-stage surgery.

Introduction Section: "The overall success rate for first surgery was 55.9%.". Please provide reference. The rate of success is much higher today.

Abstract Section: "UCF complication was reported in all studies." Do not start a sentence with an acronym.

3. Some sentences within the Results and Discussion sections are unclear and require copy-editing.

Section Discussion: "Although superior in cosmetic issues, it is reported that the complication is as high as 20-30%. I don't think this data is true, based on provided reference."
4. Diversity of the studies is large, and it should be primarily denoted in Conclusion section.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Partly

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Partly

Are the conclusions drawn adequately supported by the results presented in the review?
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Paediatric urology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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