ORIGINAL ARTICLE

Urethrocutaneous fistula following hypospadias repair: regional anesthesia and other factors

Raza H. Zaidi[1], Nina F. Casanova[2], Bishr Haydar[1], Terri Voepel-Lewis[1] & Julian H. Wan[2]

1 Department of Anesthesiology, University of Michigan, Ann Arbor, MI, USA
2 Department of Urology, University of Michigan, Ann Arbor, MI, USA

What is already known

- Urethrocutaneous fistula is a well-known complication of hypospadias surgery. A recent prospective study suggested that caudal anesthesia might increase the risk of fistula formation in children.

What this article adds

- Our case series that reviewed patients over a 19-year period showed that the use of caudal regional anesthesia in children undergoing primary hypospadias repair was *not* associated with urethrocutaneous fistula formation.

Summary

Background: Urethrocutaneous fistula is a well-known complication of hypospadias surgery. A recent prospective study by Kundra *et al.* (Pediatr Anesth 2012) has suggested that caudal anesthesia may increase the risk of fistula formation. We sought to evaluate this possible association and determine if any other novel factors may be associated with fistula formation.
Methods: Children who underwent primary hypospadias repair between January 1, 1994 and March 31, 2013 at our tertiary care center were included in this study. Reviewed surgical data included repair type, duration of procedure, use of local anesthetic infiltration, and subcutaneous epinephrine. Analgesic factors included use of caudal and/or penile block, opioid usage, postoperative pain scores, and nausea/vomiting. Postoperative surgical complications and estimates of family household median income by zip code were also reviewed.
Results: Fistula occurrence was not associated with caudal or penile block, severity of postoperative pain, or surgeon experience. A more proximal location of the urethral meatus, longer operating time, and use of subcutaneous epinephrine were significantly more common in patients who developed fistula. As assessed by home address zip code, distance of more than 100 miles and median household income in the bottom 25th percentile of our study population were not associated with fistula, as compared to closer distance or higher income.
Conclusion: In this series, we found no association between the use of caudal regional anesthesia and fistula formation. Location of the starting urethral meatus, prolonged surgical duration, and subcutaneous epinephrine use were associated with fistula formation. Our findings call into question the routine use of epinephrine in hypospadias repair.

Introduction

Hypospadias repair aims to straighten the phallus and create a urethral opening on the glans with resultant acceptable cosmesis. While these aims seem straightforward, it is a highly technical procedure that remains associated with significant complications such as meatal stenosis, urethral fistulae, and strictures. Urethrocutaneous fistulae are among the most troublesome complications with rates ranging from 4% to 28% being reported in recent years (1–3), and the reoperations necessary to correct this carry financial, social, and possibly neurocognitive harm to the patient and family (4,5).

The formation of fistulae is unequivocally associated with the original location of the urethra (1,3). The more proximal the starting point, the greater the risk of fistulae. Surgeon volume, use of vascularized tissue interposition, and older patient age (>4–10 years) may also be factors (3,6,7). In addition, recent data from Kundra *et al.* (8) in 2012 demonstrated an association between use of caudal epidural blocks and fistula formation. This finding was attributed to penile engorgement, a known consequence of caudal epidural blocks. These investigators theorized that increased penile edema could result in inadequate or delayed tissue healing; however, they did not specifically assess for this. In addition, this study included children in the care of urologic *or* plastic surgeons, a factor that was not accounted for in their analysis. Therefore, we reviewed our series of children who underwent primary single-stage hypospadias repair under the care of academic pediatric urologic surgeons with an aim to evaluate multiple factors, including those related to anesthesia as proposed by Kundra *et al.*, which may influence fistula formation.

Methods

Children who underwent primary hypospadias repair performed by a fellowship-trained pediatric urologist between January 1, 1994 and March 31, 2013 at our tertiary care center were included in this retrospective, nested case–control study. Institutional review board approval was obtained with a waiver of consent for the use of retrospective, de-identified data. All cases of fistulae were identified by independent chart review of children who had undergone multiple repairs, and the diagnosis was validated by a secondary, independent review by an investigator blinded to the first. As the recognition of fistula formation may not occur for up to 6 months following repair (9), only cases performed more than 6 months prior to the initiation of data review were included. Two controls for every case of fistula were randomly selected from the remaining list. The

subjects were excluded if they underwent multi-staged or buccal flap repairs, or had disorders of sex development, connective tissue, or bleeding disorders.

Reviewed data included preoperative, surgical, analgesic, and postoperative data. Preoperative data included age, medical history, surgeon experience (time since graduation of residency), and location of urethral opening. Urethral opening was defined as distal (at the glans/shaft junction or just beneath the glans), proximal (at or proximal to the penoscrotal junction), or midshaft. Patient zip code was collected to evaluate socioeconomic factors, including median income by zip code and distance from our center. Median income by zip code was found by referencing United States Census data (10). Surgical data included repair type, duration of procedure, use of local anesthetic infiltration with or without subcutaneous epinephrine, and placement of urinary catheter. Analgesic factors included use of caudal (0.25% bupivacaine ± epinephrine) and/or penile block (1% lidocaine or 0.25% bupivacaine ± epinephrine), intraoperative and postoperative opioid usage, postoperative pain scores (i.e., FLACC behavioral scores (11)), and nausea/vomiting. Postoperative data reviewed the first and last postoperative clinic visits, focusing on infection, hematoma, meatal stenosis, and fistula formation, as well as time to any subsequent urologic procedure.

Statistical analyses

Univariate analysis using chi-square test with Fisher's exact tests, as appropriate, were used to evaluate the association between fistula occurrence and various perioperative and socio-demographic factors. Variables of interest from the univariate analysis were placed in a multivariate logistic regression model of a predefined subgroup consisting of only distal tubularized repairs to standardize the cohort. All tests were two-sided, and *P* values <0.05 were considered significant. The data were analyzed using SPSS version 22 (IBM Corporation, Armonk, NY, USA).

Results

Forty-five cases of fistula were identified and 90 controls were randomly selected from the remaining 1647 hypospadias procedures that met screening criteria as likely single-stage hypospadias repairs in the database. Characteristics of the study sample are summarized in Table 1. There were no statistically significant differences between the fistula and control groups with regard to age or ASA physical status. The sample consisted primarily of healthy ASA 1 patients undergoing repair of distal hypospadias using the tubularized incised plate

approach. All patients were circumcised during the repair. Caudal analgesia was provided for 101 patients and only one caudal failure was noted, defined as an increase in HR ≥ 15% following incision. Six surgeons' cases were included in the dataset, all having both fistula and control patients. Surgeon experience was not different between the fistula and control group (162.6 ± 74.4 vs 166.7 ± 73.2 months, $P = 0.763$).

Table 2 describes the univariate analyses comparing perioperative factors between outcome groups (children with vs without fistula). These analyses showed that fistula occurrence was not associated with age, caudal or penile block, severity of postoperative pain, or surgeon experience. A more proximal location of the urethral opening, longer operating time, and use of subcutaneous epinephrine were more common in patients who developed fistula. An association between local anesthetic use and fistula was not found to be significant after excluding those who received epinephrine in the local infiltration ($P = 0.452$). The mean volume of local anesthetic with or without epinephrine use was 1.9 ml (±1.94 ml, range: 0.2–10 ml).

Hematoma, urinary tract, and wound infections were rare occurrences, but found only in the fistula group. Wound infections were found to have a statistically significant association with fistula formation (Table 2). The patients with fistula had slightly higher total perioperative opioid consumption compared with controls

(mean difference: 0.05 [95% CI 0.02–0.09] mg·kg^{-1} oral morphine equivalents $P = 0.004$). There were no statistically significant differences between the fistula and control groups with regard to postoperative vomiting or severe pain (FLACC ≥ 5).

Given the marked differences between the control and the fistula group in opening of urethra, we sought to study a more homogenous group in a *post hoc* fashion. Including only the subgroup that underwent tubularized repair of distal urethral openings, we created a logistical regression model to examine the predictive power of the covariates of interest (i.e., caudal analgesia, subcutaneous epinephrine, and surgical duration) on the outcome, fistula formation. To account for potential differences between surgeons, we included a coded surgeon variable at a second step in our model. The first step of this model was significant ($\chi^2 = 38.44$; $P < 0.001$), showing significant main effects for subcutaneous epinephrine and duration of the procedure, but not for use of caudal analgesia (Table 3). Adding the surgeon covariate to the model at step 2 did not improve the model, but reduced slightly the effects of the covariates.

Socioeconomic factors including the median income and travel distance to hospital were evaluated using home address zip code. Travel distance >100 miles or median household income in the bottom 25th percentile of our population dataset (≤$40 702) was not associated with fistula compared with closer travel distance ([95% CI 0.266–1.783], $P = 0.496$) or higher income ([95% CI 0.393–2.014], $P = 0.835$).

Discussion

Urethrocutaneous fistula formation after hypospadias repair is a costly and troublesome complication for both the patients and the surgical providers. While changes in surgical technique have significantly decreased the overall rate of fistula formation over the last two decades (12–14), identifying specific modifiable risk factors is necessary to further improve the outcomes for children.

To address this issue, we retrospectively reviewed primary hypospadias repairs at our tertiary care institution. We found that fistula formation was associated with longer surgical duration and, in keeping with the literature, a more proximal location of the urethral opening (1,3). In addition, the use of subcutaneous epinephrine was also identified as a risk factor for fistula formation. Alternatively, we found no association between the caudal analgesia use and the urethrocutaneous fistula formation, in contrast to Kundra's study (8). Their proposed mechanism of action, being that caudal analgesia promotes penile edema, has not been previously described. In contrast, it could be argued that a decrease

Table 1 Study population characteristics

Age (years)	Median years ± SD
Control group	1.56 ± 1.55
Fistula group	1.92 ± 2.79

	n (%)
Hypospadias location	
Distal	114 (84.4)
Midshaft	8 (6)
Proximal	13 (9.6)
Analgesic technique	
Caudal	101 (74.8)
Penile block	22 (16.3)
Local infiltrate	84 (62.2)
Subcutaneous epinephrine	72 (53.3)
Surgical repair type	
Tubularized incised plate	107 (79.2)
Meatal advancement and glanuloplasty (MAGPI)	26 (19.3)
Preputial island onlay	2 (1.5)
Postoperative complications	
Urinary tract infection (UTI)	1 (0.7)
Wound infection	3 (2.2)
Hematoma	1 (0.7)
Vomiting/retching	5 (3.7)

Table 2 Associations between perioperative factors in patients with and without fistula following hypospadias repair

Variable	Fistula		No fistula		OR (95% CI)	*P*-value
	n	%	*n*	%		
Analgesic factors						
Caudal	32	71.1	69	76.7	0.749 (0.334–1.682)[b]	0.483
Penile Block	9	20	13	14.4	1.481 (0.580–3.781)[b]	0.410
SC local ± epinephrine	37	82.2	47	52.2	4.231 (1.775–10.089)[b]	0.001*
SC local with epinephrine	34	75.6	38	42.2	4.230 (1.904–9.397)[b]	<0.001*,**
SC local without epinephrine	3	6.7	9	10		
Location						
Distal	25	55.6	89	98.9	0.014 (0.002–0.110)[b]	<0.001*
Proximal/midshaft	20	44.4	1	1.1		
Surgical factors						
Mean surgical duration (min)	156.3		90.1[c]			<0.001*
Mean surgical experience (months)	162.6		166.7[c]			0.763
Composite: local/regional						
With SC epinephrine						
No regional technique	5	11.1	3	3.3		0.560[b]
Penile block	5	11.1	4	4.4		
Caudal	24	53.3	30	33.3		
Caudal and penile block	0	0	1	1.1		
Without SC epinephrine						
No regional technique	1	2.2	6	6.7		0.019[b]
Penile block	2	4.4	8	8.9		
Caudal	6	13.3	38	42.2		
Caudal and penile block	2	4.4	0	0		
Patient factors						
Median age (days)	482 (282–789)		407 (283–594)[c]			0.343
Postoperative issues						
Urinary Tract Infection	1	2.4	0	0.0	1.024 (0.977–1.074)[a]	0.344
Wound infection	3	7.1	0	0.0	1.077 (0.990–1.171)[a]	0.039*
Hematoma	1	2.4	0	0.0	1.023 (0.979–1.069)[a]	0.333
Vomiting/Retching	3	6.8	2	2.3	3.073 (0.494–19.115)[a]	0.208
Postoperative Pain (FLACC score)						
None/mild (0–4)	33	73.3	59	65.6	0.692 (0.314–1.526)[a]	0.361
Moderate/severe (≥5)	12	26.7	31	34.4		

SC, subcutaneous.
[a]Fisher's exact two-sided test.
[b]Chi-square test.
[c]Student's *t*-test.
*Statistically significant result (*P* < 0.05) **vs all patients not receiving epinephrine.

in peripheral edema might be expected in infants, given the increase in cardiac output and decrease in systemic vascular resistance demonstrated with epidural administration of bupivacaine (15). The association between the urethral fistula and the caudal analgesia that Kundra *et al.* identified, while concerning, may instead reflect other, more important factors not controlled for by the authors. For example, they did not control for either surgical service or surgical technique when comparing the caudal analgesia with penile block. Surgical technique has been implicated in urethral fistula formation by previous studies (1,16) and calls into question the finding of the Kundra study.

To our knowledge, this is the first association shown between subcutaneous epinephrine infiltration and urethral fistula formation in hypospadias in humans. Subcutaneous epinephrine and tourniquets are used in hypospadias surgery to reduce bleeding in the operative field, improve surgical visualization of delicate structures, and decrease hematoma formation. Ischemia/reperfusion injury is a concern with either technique, and can lead to poor outcomes (17). While the vasoconstrictive properties of epinephrine help with hemostasis, it lowers subcutaneous wound oxygen tension (18) and may jeopardize tissue healing. Catecholamines can negatively affect macrophage function (19), which is

Table 3 Two-step logistic regression model examining the effects of perioperative factors on fistula development in children undergoing distal tubularized repair

Risk factor	Step 1			Step 2		
	χ^2 = 38.44; df (3); *Nagelkerke r^2 = 0.537; P < 0.001*			χ^2 = 1.18; df (1); *Nagelkerke r^2 = 0.55; P = 0.276*		
	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Anesthetic						
Caudal	0.28	0.06, 1.45	0.129	0.27	0.048, 1.48	0.132
Surgical						
Use of subcutaneous epinephrine	7.44	1.4, 40.7	0.021	5.12	0.83, 31.36	0.078
Intraoperative issues						
Duration of procedure (min)	1.04	1.02, 1.06	<0.001	1.04	1.01, 1.06	0.001
Surgeon				0.42	0.09, 1.98	0.275

necessary for wound healing (20). Stratford *et al.* (21) showed that the use of subcutaneous epinephrine at the operative site in a guinea pig model was associated with increased wound infection. They proposed that epinephrine-induced vasoconstriction resulted in tissue hypoxia, interfering with the ability of macrophages, neutrophils, and other innate defense mechanisms from protecting damaged tissue, leading to wound breakdown. A study by Kajbafzadeh *et al.* (22) compared different hemostatic techniques in a rabbit model of hypospadias repair using the index of apoptotic myocytes and tissue remodeling under electron microscopy. These techniques included continuous vs intermittent tourniquet application and injection of epinephrine vs saline into the repair site. While both tourniquet application and epinephrine use caused urethral wall tissue damage, as compared with no hemostatic technique, cellular damage and the number of apoptotic myocytes were significantly higher following epinephrine hemostasis. The only urethral fistula was found in the epinephrine arm of the study, although this difference lacked power to show significance. They postulated that compared with tourniquet application, epinephrine use likely created an environment of ischemia for an unknown and uncontrolled duration causing prolonged ischemia and tissue damage. As a result, it can be hypothesized that this more extensive tissue damage may leave the tissue more susceptible to fistula formation. In light of these investigations and our results, the association between epinephrine and urethral fistula calls into question the routine use of subcutaneous epinephrine in hypospadias surgery.

We also found that increased duration of surgery is associated with urethral fistula formation. One possible explanation is that longer operating time indicates a more difficult repair. Longer cases are also more likely to have proximal defects. The creation of a neourethra for a proximal repair is more extensive and requires longer suture lines, which increases the risk for urethral fistula. Unexpected anatomical or procedural issues may also predispose to both increased length of surgery and likelihood for urethral fistula.

Hypospadias repair is a highly technical operation that requires a skilled and experienced surgeon. Higher surgeon case volume is associated with lower morbidity and improved patient outcomes across a number of surgical procedures (23). Lower surgeon volume has been implicated to play a role in postoperative hypospadias complications such as meatal stenosis, urethral fistulae, and strictures (6). For many patients, access to a 'center of excellence' where skilled fellowship-trained pediatric urologists perform high volume of hypospadias repairs is limited, especially in rural areas. While some prior studies have shown that travel distance negatively affects health outcomes (24), others have shown the opposite (25). We did not find an increase in urethral fistula formation in patients traveling >100 miles from their home to our medical center. Our findings suggest that traveling to a 'center of excellence' can be done successfully without an increase in procedure-specific complications for highly technical and less commonly performed surgeries, such as hypospadias repair.

Our results also showed no association between the median income and the urethral fistula. Given the shortage of both generalists and specialists in poorer rural areas, the benefit of traveling even long distances to high volume centers for a technical treatment such as hypospadias surgery may be good for the patient and also cost effective.

Strengths/limitations

We reviewed 19 years of data containing a large series of cases, which allowed us to examine multiple different outcomes. Our data were rigorously reviewed by trained reviewers, and subjected to secondary chart review by blinded investigators. This high-quality review was used to ensure the integrity of our findings, and is a notable strength of our study. The potential for selection bias,

underreporting of outcomes, and loss to follow-up, however, are potential limitations of our retrospective study. In addition, we did not examine some potential risk factors for fistula, including the presence and the severity of chordee or type of urethral dressing utilized, which may impact hemostasis, swelling, blood flow to the tissue, and increase susceptibility to tissue ischemia. Among the six different surgeons who performed the hypospadias repairs, selection bias might have occurred. We did not match for surgeon, and noted significant inter-surgeon variability in distribution of fistula cases and controls. To address the differences between the control and fistula groups, we studied a more homogenous sample in a *post hoc* fashion by doing a subgroup analysis of the patients who underwent tubularized repair of distal urethral openings. Finally, the retrospective nature of this study limits the ability for us to show a causal relationship between the subcutaneous epinephrine and the urethral fistula formation. Prospective trials are necessary to confirm whether the subcutaneous epinephrine use in hypospadias surgery is a risk factor for urethral fistula formation.

Conclusion

Hypospadias repair is a highly technical procedure performed to move the urethral meatus to the glans penis and improve penile cosmesis. While improvements have been made, urethrocutaneous fistulae remain a problematic complication of repairs. We found no association between the use of caudal regional anesthesia and fistula formation. Location of the urethral opening, increased surgical duration, and subcutaneous epinephrine use were associated with fistula formation in this series. This last observation calls into question the routine use of epinephrine in hypospadias repair surgery and is a potentially modifiable risk factor. The travel distance from home to the surgical center and the median income were not significant factors. This suggests that tertiary care involving technical interventions, such as hypospadias repair, can effectively be carried out despite long distances and wide variations in local health care quality, possibly resulting in improved outcomes when focused at 'centers of excellence'.

Ethics approval

Local Institutional Review Board oversight and exemption was sought and obtained (University of Michigan HUM# 00075845). This work complies with the ethics policy of this journal.

Funding

Conflict of interest

The authors report no conflict of interest.

Acknowledgments

References

1 Chung JW, Choi SH, Kim BS *et al*. Risk factors for the development of urethrocutaneous fistula after hypospadias repair: a retrospective study. *Korean J Urol* 2012; **53**: 711–715.

2 Nuininga JE, De Gier RP, Verschuren R *et al*. Long-term outcome of different types of 1-stage hypospadias repair. *J Urol* 2005; **174**: 1544–1548.

3 Eassa W, Jednak R, Capolicchio JP *et al*. Risk factors for re-operation following tubularized incised plate urethroplasty: a comprehensive analysis. *Urology* 2011; **77**: 716–720.

4 Woodhouse CR, Christie D. Nonsurgical factors in the success of hypospadias repair. *BJU Int* 2005; **96**: 22–27.

5 Mondaini N, Ponchietti R, Bonafe M *et al*. Hypospadias: incidence and effects on psychosexual development as evaluated with the Minnesota Multiphasic Personality Inventory test in a sample of 11,649 young Italian men. *Urol Int* 2002; **68**: 81–85.

6 Lee OT, Durbin-Johnson B, Kurzrock EA. Predictors of secondary surgery after hypospadias repair: a population based analysis of 5,000 patients. *J Urol* 2013; **190**: 251–255.

7 Yildiz T, Tahtali IN, Ates DC *et al*. Age of patient is a risk factor for urethrocutaneous fistula in hypospadias surgery. *J Pediatr Urol* 2013; **9**: 900–903.

8 Kundra P, Yuvaraj K, Agrawal K *et al*. Surgical outcome in children undergoing hypospadias repair under caudal epidural vs penile block. *Pediatr Anesth* 2012; **22**: 707–712.

9 Snodgrass W, Villanueva C, Bush NC. Duration of follow-up to diagnose hypospadias urethroplasty complications. *J Pediatr Urol* 2014; **10**: 208–211.

10 United States Census Bureau/American Fact Finder. "Median income in the past 12 months (In 2012 Inflation-Adjusted Dollars)." *2008–2012 American Community Survey 5-Year Estimates*. Available at: http://factfinder2.census.gov. Accessed 11 April, 2014.

11 Merkel SI, Voepel-Lewis T, Shayevitz JR *et al*. The FLACC: a behavioral scale for scoring postoperative pain in young children. *Pediatr Nurs* 1997; **23**: 293–297.

12 Gapany C, Grasset N, Tercier S *et al*. A lower fistula rate in hypospadias surgery. *J Pediatr Urol* 2007; **3**: 395–397.

13 Cheng EY, Vemulapalli SN, Kropp BP *et al*. Snodgrass hypospadias repair with vascularized dartos flap: the perfect repair for virgin cases of hypospadias? *J Urol* 2002; **168**: 1723–1726.

14 Djordjevic ML, Perovic SV, Vukadinovic VM. Dorsal dartos flap for preventing fistula

in the Snodgrass hypospadias repair. *BJU Int* 2005; **95**: 1303–1309.

15 Monsel A, Salvat-toussaint A, Durand P *et al*. The transesophageal Doppler and hemodynamic effects of epidural anesthesia in infants anesthetized with sevoflurane and sufentanil. *Anesth Analg* 2007; **105**: 46–50.

16 Bhat A, Mandal AK. Acute postoperative complications of hypospadias repair. *Indian J Urol* 2008; **24**: 241–248.

17 Cakmak M, Caglayan F, Kisa U *et al*. Tourniquet application and epinephrine injection to penile skin: is it safe? *Urol Res* 2002; **30**: 268–272.

18 Jensen JA, Jonsson K, Goodson WH III *et al*. Epinephrine lowers subcutaneous wound oxygen tension. *Curr Surg* 1985; **42**: 472–474.

19 Abrass CK, O'Connor SW, Scarpace PJ *et al*. Characterization of the beta-adrenergic receptor of the rat peritoneal macrophage. *J Immunol* 1985; **135**: 1338–1341.

20 Mahdavian Delavary B, Van der veer WM, Van Egmond M *et al*. Macrophages in skin injury and repair. *Immunobiology* 2011; **216**: 753–762.

21 Stratford AF, Zoutman DE, Davidson JS. Effect of lidocaine and epinephrine on Staphylococcus aureus in a guinea pig model of surgical wound infection. *Plast Reconstr Surg* 2002; **110**: 1275–1279.

22 Kajbafzadeh AM, Payabvash S, Tavangar SM *et al*. Comparison of different techniques for hemostasis in a rabbit model of hypospadias repair. *J Urol* 2007; **178**: 2555–2560.

23 Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. *Ann Intern Med* 2002; **137**: 511–520.

24 Chou S, Deily ME, Li S. Travel distance and health outcomes for scheduled surgery. *Med Care* 2014; **52**: 250–257.

25 Lamont EB, Hayreh D, Pickett KE *et al*. Is patient travel distance associated with survival on phase II clinical trials in oncology? *J Natl Cancer Inst* 2003; **95**: 1370–1375.