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Role of urethral bulking agents in epispadias—exstrophy complex patients

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Abstract *Objective:* Injection of urethral bulking agents (UBA) has been used to increase bladder capacity prior to bladder neck reconstruction (BNR) or as an adjuvant therapy following BNR to improve continence. The purpose of this study was to determine the effectiveness of urethral injections in the exstrophy population.
Materials and methods: A review was performed of patient characteristics, bladder capacity, and continence status of all patients with the exstrophy—epispadias complex who underwent injection of UBA between 1980 and 2008.
Results: Among 66 patients with a median follow-up of 8 years, 41 underwent injections prior to BNR, and 25 had injections after BNR. Only 24% of patients who underwent injections prior to BNR were continent on last follow-up. Among 25 patients who underwent BNR prior to injection(s), 16 were partially continent and nine were incontinent prior to first injection. Patients who were partially continent attained social continence (dry interval greater than 3 h) at a significantly higher rate than those who were incontinent (63% vs. 13%, $p = 0.047$). No patient with cloacal exstrophy in either group attained urethral continence.
Conclusion: UBAs do not appear to have a role prior to BNR. However, they may provide benefit when given adjunctively following BNR in patients who are partially continent.
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Introduction

Obtaining urinary continence in children with the bladder exstrophy—epispadias complex (BEEC) remains a challenge for pediatric urologists. Early closure of the bladder and posterior urethra with epispadias repair (in males) either at the time of closure or at 6—12 months of age is the first step in attaining continence [1]. Regardless of the method or closure, most individuals who develop a bladder capacity (BC) greater than 85 cc will undergo a bladder neck reconstruction (BNR) that is designed to reproduce outlet control of the bladder reservoir and ultimately achieve urethral continence [2,3]. Classically, if the patient is unable to achieve a dry interval of greater than 3 h after BNR, the BNR is considered a failure and the child may undergo further continence procedures, including a continent urinary diversion (CUD) with or without bladder augmentation [2].

In 1982, Politano et al. first reported the use of urethral injections to treat stress incontinence in women [3]. Since then, urologists have attempted to use these agents in the exstrophy population. It was theorized that adding bulk to the bladder neck and adjacent urethra would result in an increase in outlet resistance. This increased resistance would allow the bladder neck to oppose changes in intravesical pressure resulting in normalization of bladder cycling and an enhancement in bladder growth and capacity [4]. Thus, in the exstrophy population, urethral bulking agents (UBA) have primarily been used for one of two reasons: 1) to increase bladder capacity in the hope of making the child a better candidate for BNR, or 2) as a minimally invasive adjunct to an unsuccessful BNR [5].

Overall, data on the efficacy of UBA in the exstrophy population are lacking. In this study, the authors aimed to identify which individuals with bladder exstrophy will benefit most from UBA.

Materials and methods

Following approval from the institutional review board, all patients with complete proximal epispadias, classic bladder exstrophy, or cloacal exstrophy born between 1980 and 2008 with a history of UBA injection into the urethra or bladder neck were identified from our institutionally approved exstrophy database. Patients were excluded from the study if UBA was injected for reasons other than to increase BC prior to BNR or improve continence after BNR, or if epispadias was distally located in a complete epispadias patient. All patients who underwent augmentation cystoplasty prior to UBA injection, had less than 6 months of follow-up after first UBA injection, or had their UBA injections performed at an outside institution, were also excluded. Each patient's medical record was reviewed for gender, exstrophy diagnosis, continence procedures required, bladder capacity measurements, and continence status.

Two different groups of subjects were evaluated: patients who received UBA prior to BNR with the intention of increasing BC and those who received UBA as an adjunct after BNR with the intention of improving continence. In both groups, patients who eventually attained social continence were compared with those who remained partially incontinent or incontinent (including those who underwent subsequent CUD). Additionally, all patients with cloacal exstrophy were separated from subgroup continence analysis and instead analyzed independently. All categorical and continuous variables were evaluated by Fisher's exact test and student's two-tailed *t* test, respectively. Receiver operating characteristic (ROC) curves were plotted to analyze predictive cutpoints of any relevant statistically significant factors found via univariate analysis. Because of the small sample size, multivariate logistic regression analysis was not feasible. All statistical analyses were performed with Microsoft Excel 2007 and Stata IC 12. A *p* value of less than 0.05 was considered statistically significant.

Bladder capacities recorded at our institution are generally performed on a yearly basis between the time of closure and the time of BNR, including just prior to injection of bulking agents and at the time of BNR by gravity cystogram under general anesthesia. This procedure involves placement of a Foley catheter into the bladder, over-inflation of the catheter balloon to prevent leakage of urine from the bladder neck, and gravity instillation of normal saline at 30 cm of water pressure into the catheter. Dextranomer-hyaluronic acid and collagen were the primary forms of UBA used at our institution and 4—8 mL were typically injected using a 20 gauge needle under general anesthesia. Autologous fat was sometimes injected instead in patients with identified collagen allergies. UBAs were injected in a retrograde fashion circumferentially around the bladder neck and urethra by transurethral route or at the 3, 6, 9, and 12 o'clock positions using the periurethral injection technique.

Partial continence was defined by volitional voiding through the urethra with a daytime interval between 1 and 3 h of dryness. Social continence was defined as a dry interval of greater than 3 h during the day [2]. Incontinence was defined by a daytime continence interval of less than 1 h. BNR was considered successful if the patient reported a dry interval of greater than 3 h and unsuccessful if the patient continued to have a dry interval of less than 3 h or underwent CUD.

Results

After review of the institutional exstrophy database containing 1178 patients, 69 (44 male, 25 female) patients with a history of one or more UBA injection(s) into the bladder neck or urethra were identified. At least 6 months of follow-up data were unavailable for one patient and two additional patients were found to have had their initial bulking agent injections performed at an outside institution. These three patients were deleted from the analysis. The remaining 66 patients had a mean (range) follow-up time of 105 (11—266) months after their first UBA injection. Among those patients who underwent BNR, mean (range) follow-up time after BNR was 103 (11—266) months. Among all patients injected with urethral bulking agents, continence rates based on type of bulking agents used at first injection were: 31% in 39 patients injected with collagen, 27% in 22 patients injected with dextranomer-hyaluronic acid, and 0% in two patients injected with autologous fat, one patient injected with polytetrafluorethylene, two patients injected with collagen on first injection followed

by dextranomer-hyaluronic acid on subsequent injections, and one patient injected with collagen on first injection and with silicone during subsequent injections.

Forty-one patients (22 male, 19 female) underwent injection(s) prior to BNR. Eleven (three male, eight female) of these patients had complete epispadias, 27 (17 male, 10 female) had classic bladder exstrophy (CBE), and three (two male, one female) had cloacal exstrophy or a skin covered cloacal variant. Among the 38 epispadias and CBE patients, 19 (50%) ultimately underwent BNR; the remaining 19 (50%) were judged to have a BC that was too small for BNR. Among the patients who underwent BNR, nine (47%) were socially continent on last follow-up. A difference was seen between median initial BC and median BC increase in patients who did not undergo BNR (initial: 55; increase: 31), patients who underwent unsuccessful BNR (initial: 60; increase: 18), and patients who underwent successful BNR (initial: 99, increase: 61).

No difference in continence rates was observed between patients with complete epispadias and those with classic bladder exstrophy. No patient with cloacal exstrophy attained social continence. Fig. 1 depicts the continence outcomes in each group of patients.

Table 1 compares demographical and clinical characteristics between patients who achieved social continence and those who either remained incontinent or underwent a CUD. Age at first injection ($p = 0.032$), BC at the time of initial injection ($p = 0.002$) and volumetric change in BC before and after injections ($p = 0.009$) were the only statistically significant variables associated with success of BNR. No statistically significant association with continence outcomes was seen with gender or number of injections.

Sensitivity and specificity measurements identifying the predictive ability of pre-injection BC at various cutpoints are plotted as an ROC curve in Fig. 2, demonstrating an optimal pre-injection BC cutoff of 70 mL, above which urethral continence can be predicted with a sensitivity of 100% and a specificity of 76%.

Twenty-five patients (20 male, five female) underwent UBA injections after BNR as an adjunctive continence procedure. Four of these patients had complete epispadias (four male, zero female), 20 had CBE (16 male, four female), and one had cloacal exstrophy (one female). Among the 24 epispadias and CBE patients, 10 (42%) achieved social continence. As reported in Table 2, 16 patients were partially continent prior to their first bulking agent injection. After the addition of UBA, nine (63%) of these patients achieved social continence, three (19%) showed no change in continence status, two (13%) regressed to a state of incontinence, and two (13%) underwent CUD at last follow-up. Of the eight that were incontinent after BNR, one (13%) achieved social continence after injection, five (63%) underwent CUD, one (13%) improved to partial continence, and one (13%) remained incontinent at last follow-up. A significant difference ($p = 0.047$) was found when comparing rates of social continence between patients who had partial continence and patients who were incontinent before injection.

Discussion

It is widely known that in children incontinence is strongly associated with poor integration into peer groups and worsening mental health [6]. Although urinary incontinence in the general population is treated pharmacologically or with behavioral modification, these therapies are less effective in the exstrophy population. Children with BEEC typically require multiple surgical procedures to become continent. If satisfactory urinary continence cannot be achieved with a BNR, most children will undergo enterocystoplasty with CUD.

It is well known that the success of a BNR is highly dependent on the patient's BC. Chan et al. showed that patients with a BC of at least 85 mL prior to BNR had higher success rates [2]. Patients with poor bladder growth and capacity or those with poor bladder quality are not candidates for BNR and are better suited for CUD [7].

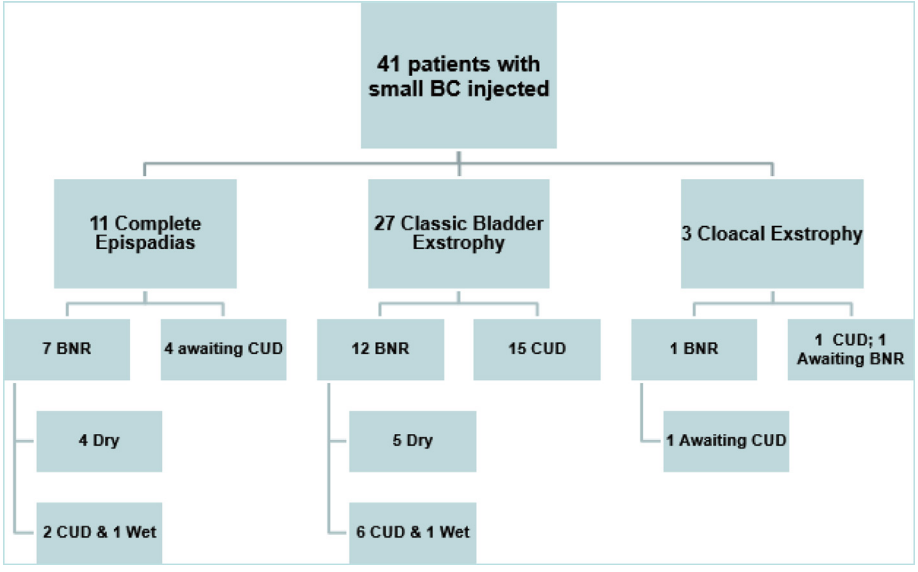

Figure 1 Outcome stratified by diagnosis (urethral bulking agent given prior to bladder neck reconstruction).

Table 1 Comparison of epispadias and classic bladder exstrophy patients who attained continence vs. those who remained incontinent at last follow-up.

	Continent $n = 9$	Incontinent/UD $n = 29$	p
No. male (%)	4 (44)	13 (45)	0.2970[a]
Median age (range) at initial injection in months	65 (53–120)	56 (29–102.5)	0.0315[b]
No. of injections (%)			
One	6 (67)	15 (52)	0.2351[a]
Two	2 (22)	7 (24)	0.3469[a]
Three or more	1 (11)	7 (24)	0.2702[a]
Median BC increase (range[c])	61 (−10 to 146)	12 (−25 to 56)	0.0085[b]
Median BC at first injection (range)	99 (70–128)	59 (25–155)	0.0017[b]

BC, bladder capacity.
[a] Fisher's exact test.
[b] Student's t test.
[c] A negative range signifies a decrease in BC between first injection and BNR.

In 1982, Jeffs et al. first pioneered the concept of increasing outlet resistance prior to BNR [8]. Since then, several studies have looked at using injectable bulking agents to increase bladder growth in exstrophy patients with small capacities. Duffy and Ransley used bulking agents in 12 males with primary epispadias, none of whom had prior BNR [9]. Using ultrasound imaging, they showed a median increase in BC of 130 mL. Caione et al. looked at six patients with known exstrophy who received bulking agents prior to BNR, reporting a 47% increase in BC among these patients [10]. Lottmann et al. evaluated 33 patients, 13 of whom had a diagnosis of exstrophy, and reported that 12 of 18 patients with an initially small bladder size had at least a 50% increase in capacity [11].

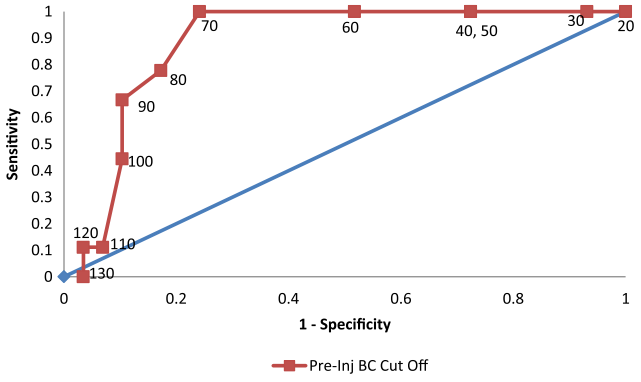

Figure 2 Receiver operating characteristic analysis curve for pre-injection bladder capacity in epispadias and CBE patients (urethral bulking agent given prior to bladder neck reconstruction).

Table 2 Outcomes stratified by pre-urethral bulking agent (UBA) continence (UBA given after bladder neck reconstruction).

		After injections		
		Socially dry	Partial/ non-continence	CUD
Before injections	Partially dry	9	5	2
	Incontinent	1	2	5

CUD, continent urinary diversion.

Both Caione and Lottmann noted that any improvement in bladder capacity may be secondary to natural bladder growth rather than the direct impact of the UBA.

In this study, a significantly higher BC at first injection and a significant increase in the bladder growth was seen in patients who ultimately attained continence after pre-BNR bulking agent injections when compared with those who did not attain continence. ROC analysis showed an optimal minimal pre-injection BC cutoff of at least 70 mL. No patient with a BC of less than 70 mL prior to their first bulking agent injection had a successful BNR. In contrast, nine of 16 (56%) patients who had a BC of at least 70 mL prior to their first injection underwent BNR and had a successful outcome. Because it has been shown that larger bladders are more likely to go through their natural progression of growth whereas smaller bladders more often fail to increase in size, this direct association between higher pre-injection BC and improved continence rate may have occurred despite the UBA rather than because of it [12]. Bladder capacity and successful primary closure remain the primary independent predictors of continence after BNR, and urethral bulking agents have shown no definite effect on bladder growth or success of BNR [13].

Our 47% success rate among patients who had BNR after bulking agent injection compares unfavorably with the 70%–80% rate that has been reported in patients who do not undergo UBA injections [14]. It is plausible that these bulking agent injections may have negatively impacted the BNR procedure. One could also argue that many patients underwent UBA injection because of a small bladder capacity and thus were more inclined to have poor bladder growth and an unsuccessful BNR outcome. Published literature shows conflicting views as to whether UBA injections negatively impact future bladder neck surgeries [15]. It is the authors' opinion that UBAs distort the natural tissue planes of the bladder neck, which makes a BNR performed at a later time arduous and perhaps ultimately less likely to succeed.

The use of bulking agents as salvage therapy after an unsuccessful BNR has been reported in several studies. Caione et al. first hinted at the importance of having at least partial continence prior to injections. They reported 10 BEEC patients with prior BNR [10]. Of the three patients described as having poor continence before injection, one continued to have poor continence after injection and two attained fair continence. All seven patients described to initially have fair continence attained good continence after injection. Similarly, Burki et al. looked at 52 patients with BEEC who received UBAs [16]. Eighty-one per cent of the patients that had at least some continence prior to injections became either occasionally wet or completely

dry compared with only 44% of the patients in the group who were totally wet prior to injections.

In our series, bulking agents appeared helpful after BNR only in patients who were partially continent prior to injection. Sixty-three per cent of those patients who could maintain at least 1 h of continence prior to injection attained social continence, compared with only 13% of patients who were incontinent after BNR.

It has been well reported that there is no difference in efficacy between types of bulking agents [17]. In our study no patient who underwent UBA injections composed of polytetrafluorethylene, autologous fat, or silicone attained social continence.

There are some limitations to this study. Although continence status is meticulously noted during clinical follow-ups at this institution, the retrospective design of this study could lead to analytical bias. While patients were required to have at least 6 months of follow-up, longer follow-up in some of these patients could show different continence outcomes. Detailed operational notes regarding these patients' UBA injection were available and adequate follow-up was done at our institution.

Although it is true that variations in technique may influence outcomes, these differences did not appear to affect our results. Further analysis, which was done only to demonstrate differences in technique, did not influence overall study results, found no difference between periurethral and transurethral injections or different volumes.

Not until the last 5 years were urodynamics routinely performed at this institution in exstrophy patients. This information may have been helpful in finding further predictors of success, including detrusor contractility, compliance, and urethral pressure profile. At our institution, unfavorable urodynamics, evidence of upper tract deterioration, and parental preferences are the most common reasons not to perform BNR in patients with adequate BC. Eight patients in this series had urodynamics performed after BNR and before UBA injection. All patients demonstrated maximum detrusor and leak point pressures of less than 20 cm of water, an absence of uninhibited contractions, and normal detrusor function with voiding.

Our population included patients with known cloacal exstrophy. However, cloacal exstrophy patients were separated from subgroup analysis and analyzed independently. There appears to be no role for UBA in patients with cloacal exstrophy. In this series, none of the five (three injected before BNR; two injected after BNR) patients with cloacal exstrophy developed social continence.

Conclusion

To the best of our knowledge, this is the largest study examining the effectiveness of UBAs in the exstrophy population. It is also the only study to analyze the value of continence grades in post-BNR patients before and after the injection of UBAs. This study showed no definite role of UBA prior to BNR. However, these agents may lengthen the dry interval when given to patients who have already achieved some degree of continence following BNR.

Conflict of interest

None.

Funding

None.

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