Int Urol Nephrol (2017) 49:183–189
DOI 10.1007/s11255-016-1464-z

UROLOGY - ORIGINAL PAPER

Comparing the bulking effect of calcium hydroxyapatite and Deflux injection into the bladder neck for improvement of urinary incontinence in bladder exstrophy–epispadias complex

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Received: 15 October 2016 / Accepted: 17 November 2016 / Published online: 28 November 2016

Abstract
Objectives The aim of this study was to evaluate the efficacy of the endoscopic injection of calcium hydroxyapatite (CaHA) into the bladder neck (BN) region of patients with urinary incontinence and bladder exstrophy–epispadias complex (BEEC).
Patients and methods We designed a retrospective cohort study in which we retrospectively studied medical charts of female and male patients of BEEC who had undergone CaHA or Deflux injection for continence improvement between 2009 and 2014. Sixteen incontinent patients with a mean ± SD age of 8.09 ± 3.5 years received an endoscopic submucosal injection of 5.4 ml of pure CaHA powder with autologous plasma (group A). Patients in group B ($N = 21$), control group, with a mean ± SD age of 7.51 ± 2.8 years received Deflux injection (5.1 ml). The mean follow-up after injection was 38 ± 5.2 and 33 ± 4.1 months in groups A and B, respectively.
Results No post-injection complication was detected in none of the patients during the follow-up. Eleven patients (68.75%) in group A became socially dry following 1–2 injections, the degree of incontinence was improved in 4 patients (25%), and there was no change in one patient (6.25%). However, Deflux injection resulted in complete dryness in 14 (66.66%), improvement in the degree of incontinence in 5 (23.81%) and no change in 2 patients (9.52%), leading to no significant difference in continence achievement between CaHA and Deflux groups ($p = 0.9$). The statistical analysis was not significantly different in terms of bladder capacity ($p = 0.7$) or Q max ($p = 0.8$).
Conclusion The preliminary results of this study revealed that CaHA may be applied as an affordable bulking agent in treatment of urinary incontinence in BEEC.

Keywords Calcium hydroxyapatite · Deflux · Bladder exstrophy · Urinary incontinence

Abbreviations

CaHA	Calcium hydroxyapatite
BEEC	Bladder exstrophy–epispadias complex
BN	Bladder neck

Introduction

Long-term goals in children with bladder exstrophy–epispadias complex (BEEC) are provision of a successful bladder and abdominal wall closure along with cosmetic genitalia, preservation of renal function and urinary reservoir, and achievement of urinary continence for proper urine storage [1]. Bladder augmentation, clean intermittent catheterization (CIC) and concomitant continent stoma creation is a sufficient salvage process for BEEC patients with urinary incontinence, constant upper urinary tract changes and small bladder capacity [2]. However, standard bladder neck (BN) repair was suggested to be insufficient to establish volitional continence with good bladder capacity in children with BEEC [3]. Several factors including multiple failed closure,

Electronic supplementary material The online version of this article (doi:10.1007/s11255-016-1464-z) contains supplementary material, which is available to authorized users.

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inadequate bladder capacity, bladder calculi and intermittent infection can contribute to incontinence [4].

The application of urethral bulking agents is a less invasive therapy that was first described in 1938 by using sodium morrhuate for urethral resistance augmentation [5]. Recently, the largest study with longest follow-up revealed promising outcomes regarding Deflux injection for treatment of urinary stress incontinence [6]. Calcium hydroxyapatite (CaHA) gained FDA approval in 2005 and was showed to have 63.4% improvement in urinary incontinence in the largest published multicenter randomized clinical trial [7]. Deflux, as the frequently applied material for incontinence management, is a biocompatible, non-toxic and non-migratory material that are the characteristics of an ideal bulking agent. Considering its expensiveness and temperature limitation, researchers are still making attempts for the development of other safe and effective biomaterials.

Our purpose was to identify the role of CaHA injection on the fate of the lower urinary tract and continence status in patients with BEEC. The results of CaHA injection were also compared with Deflux application as the technique of choice.

Patients and methods

Patients

We designed a retrospective cohort study in which we reviewed medical charts of patients who have undergone CaHA or Deflux injection for continence improvement from December 2009 until August 2014. Patients with history of BEEC who have been repaired surgically prior to CaHA or Deflux injection were included in this study. Exclusion criteria were urinary incontinence caused by other underlying conditions including myelomeningocele and detrusor sphincter dyssynergia (DSD). All patients had undergone a single-staged bladder closure procedure without osteotomy before injection.

The series consists of two groups of patients: group A, who received CaHA injections, and group B or control group, who received Deflux injections according to a surgeon level decision with a single surgeon managing these two groups (senior author). The procedure and its experimental nature was explained for the patients' guardians, and it was assured that they have fully understood the procedure and its complications, after that an informed consent was obtained from guardians. Initial evaluation of both groups included a medical history, estimate of the level of incontinence (totally continent, partially continent and incontinent), urine examination and urine culture, renal ultrasound and uroflowmetry.

Preparation of CaHA

To prepare an injectable form of CaHA, 2.3 g of CaHA powder (Merck Chemicals, Darmstadt, Germany) was poured into 5-ml syringes and was compressed, while the plungers were removed. Then, the syringes and their plunges were all sterilized by gamma radiation. Following these steps, the pure CaHA powder was mixed with autologous plasma and prepared for the intervention.

Scanning electron microscopy (SEM) of CaHA powder was performed before injection in order to evaluate the size and shape of particles.

Surgical technique

In order to minimize the bias on outcomes based on surgeon technique, all the injections were performed by one surgeon (senior author). After completing the preparation of CaHA, as outlined above, a 6- to 7.5-Fr Wolf neonatal cystourethroscope (GmbH, Knittlingen, Germany) with a 3-Fr working channel for needle insertion was inserted into the urethra under general anesthesia. The entire procedure was meticulously performed under direct vision. CaHA or Deflux was injected at the level of the proximal urethra just distal to the BN by the application of the cystoscope with endoscopic injection setup. The cystoscope was inserted into the mid-urethra, and the tip of the needle was inserted beneath the urethral mucosa in order to infiltrate CaHA/Deflux beneath the urethral mucosa. Before pulling back the needle tip, an average of 0.5 ml CaHA and 0.5–0.8 ml of autologous plasma were injected until the volcanic appearance was observed following injection.

The bulking agent was deposited into the submucosal tissues until complete coaptation of the urethral mucosa was visualized. After completion of procedure, a silicon catheter was inserted and fixed in urethra. The procedure was performed at 3–6 regions in both groups with an average volume of 5.4 and 5.1 ml of CaHA and Deflux.

Patients were followed up with 2-month intervals for the first year and with 6-month intervals afterward. Ultrasound was performed at 1, 6 and 12 months and then twice yearly. Functional bladder capacity was determined by cystometry. An experienced clinical pediatric urodynamic nurse specialist performed urodynamic (Duet®) and uroflowmetry studies in accordance with the International Children's Continence Society protocol on an annual basis. Patients who were dry at night and continent for at least 6 h during the day were defined as totally continent. Children who were dry for at least 3 h throughout the day with occasional nighttime leakage were defined as partially continent. Those with leakage or a severe urinary bother that warranted further reconstruction were defined as incontinent SPSS®,

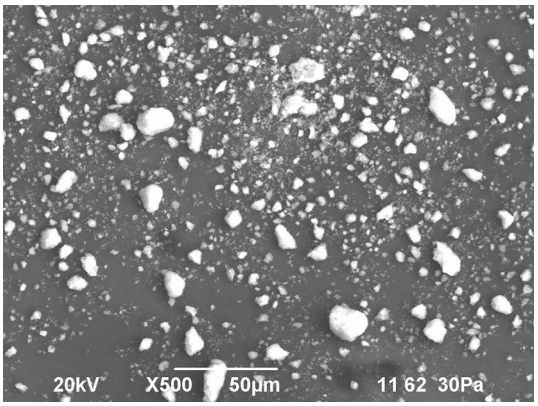

Fig. 1 SEM analysis of CaHA particles

Table 1 Patient demographic characteristics

	Group A ($n = 16$)	Group B ($n = 21$)
Age (months)	8.09 ± 3.50	7.51 ± 2.80
	Range 2.5–13.91	Range 3.71–12.50
Gender (male)	12	15
Follow-up (months)	38 ± 5.2	33 ± 4.1
Injected bulking agent (ml)	5.4	5.1

version 16.0, was applied for statistical analysis. Chi-square and paired Student t tests were used to compare categorical and continuous variables. Data are expressed as mean ± SD, and $p < 0.05$ was considered statistically significant.

Results

SEM revealed homogeneous shape of CaHA particles which was above the threshold for migration. The homogeneity of particles may cause less inflammation at the site of injection (Fig. 1).

Demographic characteristics of children are summarized in Table 1. Group A consisted of 16 patients, 4 females and 12 males, with a mean ± SD age of 8.09 ± 3.50 years (min 2.50, max 13.91) at the time of intervention. Group B consisted of 21 patients, 6 females and 15 males, with a mean ± SD age of 7.51 ± 2.80 years (min 3.71, max 12.50) at the time of Deflux injection. All patients were totally incontinent prior to therapy.

Clinical characteristics of children before and after the injection of bulking agent in each group are outlined in Table 2. Follow-up consisted of renal ultrasonography, uroflowmetry, bladder capacity measurements and investigating patients' continence status (Fig. 2). The mean ± SD duration of follow-up was 38 ± 5.2 months in group A and 33 ± 4.1 months in group B.

No complications related to the injection of CaHA/Deflux or postoperative complications were developed in the patients of groups A and B. Follow-up ultrasounds in both groups were normal, and no hydronephrosis was observed in any of the patients of these groups. Nearly, symmetrical renal function was observed in DMSA renal scan in patients of both groups without any statistical significant difference. The UTI rate was 25% in group A (4 none febrile UTI) and 23.8% in group B (5 none febrile UTI) after the injection of the respected bulking agent. However, the statistical analysis was not significantly different ($p = 0.8$). UTI occurred in patients that were incontinence or partially continent. None of the patients with complete continence experienced febrile or non-febrile UTI.

Moreover, 11 patients in group A (68.75%, 8 males and 3 females) and 14 children in group B (66.66%, 10 males and 4 females) were completely continent after CaHA and Deflux injection, respectively. Statistical analysis revealed that 4 patients (25%, 3 males and 1 female) in group A and 5 children (23.8%, 4 males and 1 female) in group B

Table 2 Patient clinical characteristics before and after the bulking agent injection

	Group A ($n = 16$)				Group B ($n = 21$)			
	Before		After		Before		After	
	Male	Female	Male	Female	Male	Female	Male	Female
Continence								
Totally continent	0	0	8 (50%)	3 (18%)	0	0	10 (47.6%)	4 (19%)
Partially continent	3 (18%)	2 (12.5%)	3 (18%)	1 (6.2%)	5 (23.8%)	2 (9.5%)	4 (19%)	1 (4.7%)
Incontinent	9 (56.2%)	2 (12.5%)	1 (6.2%)	0	10 (47.6%)	4 (19%)	1 (4.7%)	1 (4.7%)
Bladder capacity (ml)	120 ± 37.5	144 ± 17.4	209.3 ± 20.1	239.1 ± 10.2	187.3 ± 30.8	155.1 ± 32.4	256.2 ± 38.7	222.7 ± 43.5
Q max (ml/s)	9 ± 3.8	10 ± 5.2	17 ± 5.4	15 ± 4.9	8 ± 5.1	8 ± 5.8	20 ± 6.9	15 ± 5.8

In spite of a statistically significant difference before and after injection in each group, the differences between groups and genders were not significant ($p > 0.05$)

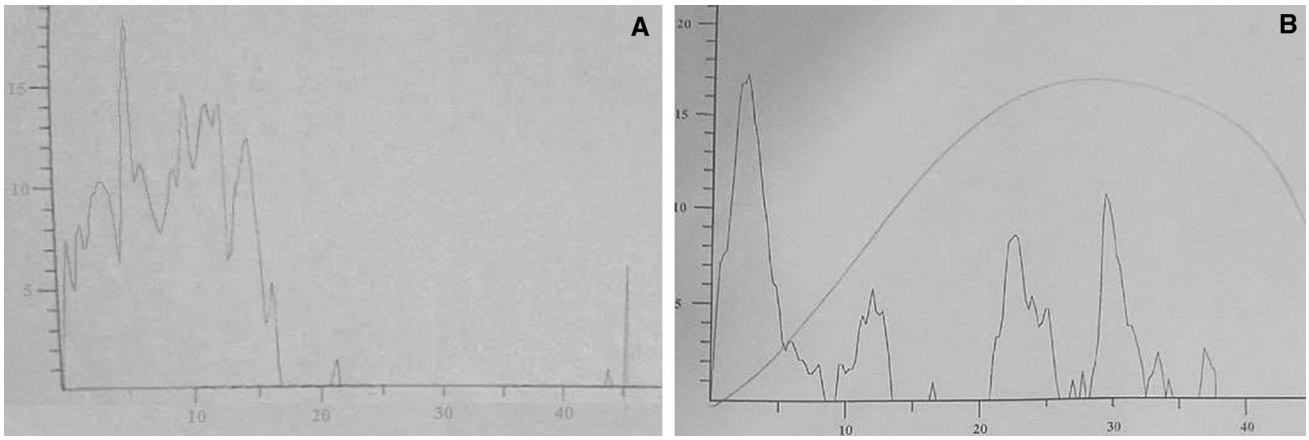

Fig. 2 Postsurgical uroflowmetry **a** 4 months after hydroxyapatite injection in a 5-year-old boy with voiding volume of <1 cc before the operation, **b** 3.5 months after Deflux® injection in a 4-year-old boy

were partially continent at the end of the study. There was no change in degree of continence in 1 patients of group A (6.25%, 1 male patient) and 2 patients of control group (9.52%, 1 male and 1 female). In spite of the fact that the continence rate improved significantly after the injection of bulking agents in each group ($p = 0.01$), statistical analysis showed no significant difference in continence achievement between two groups ($p = 0.9$). In addition, no statistically significant difference was detected between genders in terms of continence improvement between groups ($p = 0.8$).

Bladder capacity reached from 132 ± 27.5 to 224.2 ± 30.3 ml after CaHA injection, while it reached from 146.1 ± 34.90 to 239.4 ± 40.2 ml after Deflux injection. While the bladder capacity improvement was statistically significant in each group ($p = 0.03$), no significant difference was detected between the groups ($p = 0.7$). Similar results were found in Q max measurement confirming that improvement of uroflowmetry elements was not significant between groups $p = (0.8)$, while the differences were significant within each group ($p = 0.04$). Table 2 depicts the clinical characteristics of patients prior and after the intervention in each gender subgroups. Regarding the bladder capacity and Q max, the differences between genders were not significant between groups ($p = 0.8$ and $p = 0.6$, respectively). No ureteral obstruction or pyelonephritis was detected in none of the patients during the follow-up. Normal voiding was observed in all patients after injection of CaHA and Deflux. Video 1 shows voiding of a patient in group A, 2 years after injection of CaHA.

Discussion

Continence is the foremost goal in the management of BEEC patients, the prognosis of which is essentially long term. Urinary incontinence is an incapacitating condition affecting both physical and emotional well-being of patients. First female patient with BEEC and subsequent successful closure and urinary continence was described by Young in 1942 [8]. With the acceleration in efforts for complete bladder reconstruction, the rates of continence and successful total reconstruction reached 20% in the early 1970s. Continence rate reached 80% with contributions of Jeffs, Kelalis and Ransley [9–11].

Successful primary bladder closure is important in the development of sufficient bladder capacity and ultimate continence in patients with BEEC, apart from the surgical technique. Respectively, long-term outcomes of BEEC treatment should be reviewed with regard to the management of urinary continence and resulting complications. Achievement of urinary continence is a long-term aim in patients with BEEC. Several factors including urodynamic parameters, bladder capacity at the time of BN repair, and surgeon's skill are crucial in the achievement of urinary continence. It has been noted previously that a median bladder capacity of 85 cc in patients undergoing staged reconstruction of BEEC increases the likelihood of achieving continence following BN reconstruction [12]. This procedure is usually performed as soon as the child is able to cooperate with a voiding program in order to be dry. The majority of children are at age 4–5 years when undergoing this technique. By the application of this procedure, excellent continence rate with spontaneous voiding per urethra is usually achievable. However, attainment of urinary continence after a failed primary closure decreases compared to a successful bladder closure. In spite of the fact that successful re-closure and bladder development may be achieved, the chance of long-term continence is dramatically reduced if the second bladder closure is failed. According to a recent series of children with failed primary

closure and a subsequent successful re-closure, only 18% were eventually continent and voiding per urethra [13, 14]. According to the study of Gearhart et al. [13], the bladder ability to reach adequate capacity for further continence achievement after BNR is markedly decreased after 2 closures, while the majority of patients will necessitate BN closure, augmentation and/or continent diversion after 3 closures. These statistics motivated us to find a safe, easy and cost-effective alternative method for achieving urinary continence in order to improve the quality of life in these patients.

In spite of the fact that studies have shown the successfulness of osteotomy in enhancing the chance for continence attainment [13], the results of our studies showed promising outcomes without osteotomy [15, 16]. In another study in which the results of osteotomy were directly compared to no osteotomy, no difference was found in continence rates [17]. Immediate continent diversion is a substitute which was not applied in the patients of the present study considering the young age of these children.

Postoperative continuous dribbling is usually considered as an indicator of further interventions. Undoubtedly, increasing outlet resistance and protecting the upper tract is a crucial point in maximizing bladder function. It was proposed that the application of bulking agents may play a role in improving bladder capacity by increasing outlet resistance [18]. In spite of the effectiveness, safeness and simplicity of bulking agent injection into the BN after modified Young-Dees-Leadbetter BN reconstruction, the success rate is about 45% [19, 20]. In the study of Surer et al., BN collagen and autologous fat injection was performed in 12 and 1 patients, respectively, at the time of augmentation and continent diversion [21]. Regular anticholinergics and α-agonists administration was required in all of these patients for remaining dry between stomal catheterizations. In another study, periurethral collagen injection was performed in two patients after BN reconstruction in order to achieve continence. However, 2-year follow-up of these patients revealed unsuccessful periurethral collagen injection and these children were incontinence [22]. As a final point, the role of periurethral collagen injections in increasing outlet resistance may be limited.

In a 10-year-old patient with pelvic osteotomies and a modified Young-Dees-Leadbetter procedure who had minimal stress incontinence, transurethral bovine collagen injection was successfully applied [23]. Periurethral injection of collagen for intermittent incontinence was applied in a male newborn of duplicate BEEC with dry intervals between catheterizations [24]. In the study of Frimberger et al. [25], collagen was injected at the BN in an attempt to stimulate bladder growth in one patient without any complication. Complete dryness was also achieved in one patient with BEEC by collagen injection in the study of Mathews et al. [26]. Similar results were obtained in another study in which 4 children received collagen injections in an effort to improve bladder capacity and increase outlet resistance [27]. Continence was improved by endoscopic collagen injection in 64% of a mixed population of children with intrinsic sphincter deficiency, some of whom had BEEC [28]. Submucosal cross-linked bovine collagen injection in the BN or sphincteric urethra was performed before BNR in order to enhance bladder outlet resistance [29]. The results of their study showed the effectiveness of this complementary procedure in increasing bladder capacity and outlet resistance, improving continence and decreasing the need for further bladder augmentation. Similar results were obtained in the study of Ben-Chaim et al. [19] in which improvement of continence was achieved in 53% of patients after transurethral injection of cross-linked bovine collagen. Nevertheless, after repeated collagen injections, 90% of children had additional improvement.

Subureteral Deflux injections can be considered as a prudent approach to temporize the situation of patients until a further need for BN reconstruction. In spite of the fact that Macroplastique injection is a promising and safe endoscopic modality for incontinence correction [30], longer follow-up and larger series are required to ensure their effectiveness of such bulking agents.

Recently, we managed urinary incontinence in a patient with complete bladder duplication by CaHA injection at BN with satisfactory outcomes [31]. The results of the current study were incompatible with our previous findings, revealing that submucosal injection of CaHA for the purpose of increasing the outlet resistance and improving continence is a simple and safe procedure with reasonable success rate. Consequently, this bulking agent may be applied for continence improvement in patients with BEEC who lack full continence after reconstructive surgery. Undoubtedly, this procedure should only be applied as an adjunct therapy to BN reconstruction to improve continence. It should be also taken into consideration that in the present study autologous blood was added to the pure CaHA as a safe an economical career in combination with ringer lactate to increase the stability of the injected bulking agent. The blood clot may enhance healing process by facilitating fibroblast growth and extracellular matrix formation [32]. As a result, better ureteral cooptation may be obtained as the newly formed extracellular matrix could prevent the possible migration of injected CaHA. Additionally, one of the main superiorities of applying CaHA is its cost-effectiveness compared with Deflux. As estimated, Deflux is approximately 19 times more expensive than CaHA (1900 USD vs. 100 USD).

It is not outlandish to conclude that injection of CaHA may be as effective as Deflux injection which is usually considered as the gold standard technique for patients with urinary incontinence. However, more evaluations with longer follow-ups are needed to draw firm conclusions.

Conclusion

Continence achievement in children BEEC is still difficult to predict. It is important to realize that extensive experience and understanding of the continence mechanisms are required for management of these patients. However, choosing the most applicable and efficient bulking agent may be vital in achieving complete dryness or improving the grade of continence. Long-term results of the current study confirmed that the injection of CaHA for urinary incontinence in children with BEEC is relatively reliable, safe and effective. Our data reveal that CaHA may be applied with valid and promising outcomes in patients with urinary incontinence.

Compliance with ethical standards

Conflict of interest None of the authors has direct or indirect commercial financial incentive associating with publishing the article and does not have any conflict of interest.

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