# Safety, Efficacy and Health Related Quality of Life of Autologous Myoblast Transplantation for Treatment of Urinary Incontinence in Children With Bladder Exstrophy-Epispadias Complex

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**Purpose:** Children with bladder exstrophy-epispadias complex undergoing endourethral autologous myoblast transplantation to treat urinary incontinence were evaluated at 4 years of followup regarding the safety, efficacy and durability of the procedure, and health related quality of life.

**Materials and Methods:** Seven boys underwent autologous myoblast transplantation between May and December 2006. All patients had persistent urinary incontinence after bladder neck reconstruction and bulking agent injection. Patients were followed for 4 years after autologous myoblast transplantation regarding clinical outcomes and cystometric, urodynamic, uroflowmetric and urethrocystoscopic evaluations. Health related quality of life was also measured before treatment and at final followup.

**Results:** No evidence of urinary obstruction was observed. Five children (71%) were completely continent and 2 (29%) were socially dry with complete daytime dryness at final followup. Health related quality of life was improved significantly. Urodynamic studies revealed a progressive increase in bladder capacity ($p < 0.001$). Mean detrusor leak point pressure showed a 27 cm $H_2O$ (158%) increase during 4-year followup. Uroflowmetry parameters of voided volume and average maximum flow rate were improved significantly ($p < 0.001$).

**Conclusions:** The 4-year outcomes demonstrate that autologous myoblast transplantation for urinary incontinence in children with bladder exstrophy-epispadias complex is relatively reliable, reproducible, safe and effective with minimal morbidity. This novel treatment represents a promising therapeutic approach in patients with urinary incontinence. Further randomized trials with larger numbers of patients and longer followup are needed.

**Key Words:** bladder exstrophy, myoblasts, quality of life, stem cells, urinary incontinence

**Abbreviations and Acronyms**

AMT = autologous myoblast transplantation

BEEC = bladder exstrophy-epispadias complex

BNR = bladder neck reconstruction

DLPP = detrusor leak point pressure

HRQol = health related quality of life

Qmax = maximum urine flow rate

UI = urinary incontinence

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CONTINENCE remains a challenging goal in the treatment of children with bladder exstrophy-epispadias complex. Most children with this condition undergo several surgical procedures for the management of sphincteric incompetence, including bladder neck reconstruction, sling surgery and artificial sphincter placement.[1,2] Patients who remain incontinent usually undergo urinary reservoir reconstruction. The reported success rate for achieving continence with normal voiding varies from 21% to 83%.[3] These results may include patients with urinary diversion or those who have undergone bladder augmentation.

Endoscopic injection of bulking agent has emerged as a therapeutic ap-

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proach in the treatment of UI.[4] This procedure seems to be economical, with shorter hospitalization and fewer major complications. On the other hand, degradation, migration, reabsorption, overbulking, bladder outlet obstruction and hypersensitivity are frequently reported complications of bulking agents.

Recent human and animal studies have revealed a role for skeletal muscle derived stem cells in the treatment of UI.[5–8] Muscle precursor cells (myoblasts) are characterized by the capability of proliferation, differentiation and final fusion to form new myofibers competent for muscle contraction. One important feature of these cells is that they do not expand beyond the required repair need due to the post-mitotic nature of myotubes.[9]

We have previously proposed a management approach using AMT for treatment of urinary incontinence in children with BEEC. The preliminary data confirmed the efficacy and reliability of AMT to improve the structure and contractile function of sphincter in UI.[10] However, to our knowledge long-term results of cell based therapy for UI have not yet been studied in children. We present our findings at 4-year followup regarding health related quality of life and the safety, durability and efficacy of autologous myoblasts for treatment of urinary incontinence in children with BEEC.

## PATIENTS AND METHODS

The initial study included 1 girl and 7 boys with a mean age of 8.8 years who were considered for AMT between May and December 2006.[10] All patients were referred to us following multiple failed treatments, including bladder closure, pelvic bone osteotomy, BNR and epispadias surgery.

The study was approved by the institutional review board, and written informed consent was obtained from the parents. Each patient underwent cystoscopic injection of $7 \times 10^6$ to $4 \times 10^7$ autologous cells into 8 to 10 sites in the area of the external sphincter.[10]

Treatment efficacy was assessed at 4 years in the 7 boys. Treatment in the girl was considered a total failure due to the initial failed improvement in continence, and the patient was lost to followup.

Evaluations included grading of incontinence, voiding diary, urine culture, renal ultrasound, voiding cystogram and urodynamic study. Daytime continence was determined by dry intervals after voluntary voiding.[11] Continence was defined as day and night dryness for periods longer than 3 hours with voiding per urethra. Incontinence grade was based on a scale of 0 to 3.[10] Patients were considered socially dry if the dry periods were longer than 3 hours during the day with or without nocturnal incontinence or clean intermittent catheterization.

Patients were evaluated by ultrasound at 1, 6 and 12 months, and then twice yearly. Cystometry was used to determine functional bladder capacity. Urodynamic and uroflowmetry studies were also performed on an annual basis. Urodynamic study (Duet®) was performed in all children in accordance with the International Children's Continence Society protocol by an experienced clinical pediatric urodynamic nurse specialist. DLPP was defined as pressure at urinary leakage around the catheter. Maximum voiding detrusor pressure and maximum flow rate were determined.

In accordance with our previous study we defined normal bladder compliance as end filling pressure less than 20 cm $H_2O$ and bladder stability as absence of uninhibited detrusor contraction (greater than 15 cm $H_2O$) during filling. Normal voiding was considered as normal filling dynamics (bladder compliance and stability) along with demonstrable voiding detrusor contraction. Simultaneous uroflowmetry was performed in all children and Qmax was determined. Urethrocystoscopy was performed at the end of first and the fourth year to evaluate any further abnormalities, inflammations or mass formation.

Generally there are no accepted outcome criteria to evaluate treatment success. In this study 3 criteria were assessed before and after therapy to measure success. First, incontinence was graded according to dry intervals as assessed by patient questionnaire. Next, HRQol was assessed by incontinence quality of life instrument before and 4 years after AMT to evaluate the outcome of myoblast therapy. The Kid-KINDL (for 8 to 12-year-olds) and Kiddo-KINDL (for 13 to 16-year-olds) self-report questionnaires and the proxy version KINDL for parents (for 8 to 16-year-olds) were used to determine HRQoL. These 3 questionnaires consist of 24 items associated with 6 dimensions. The total sum of all 24 answered questions ranges from 24 to 120. The scores are transformed to values between 0 and 100,[12] with higher scores indicating better HRQoL. Finally, urodynamics were evaluated via uroflowmetry and pressure-flow studies.

All statistical analysis was performed using SPSS®, version 16.0. Categorical variables were compared with the chi-square test. The paired Student t test was used to compare continuous variables, and the Wilcoxon signed rank test was executed for nonparametric statistical comparisons before and after treatment. Data are expressed as mean $\pm$ SD, and $p < 0.05$ was considered statistically significant.

## RESULTS

Demographic and clinical characteristics of children before AMT and after mean followups of 15.3 months and 4 years are outlined in table 1. Continence was improved significantly in all patients at final followup. Before AMT 2 patients (29%) were totally incontinent and 5 (71%) were frequently wet with dry intervals lasting less than 30 minutes. At 15 months after cell injection 4 patients became socially continent and 3 were completely dry. At the current followup 5 boys (71%) were completely dry and were voiding per urethra without intermittent catheterization, and 2 (29%) were socially continent (grade 1). There were 3 episodes of bacteriuria in 2 patients, although no evidence of urinary outlet obstruction or hydronephrosis was observed. It is note-