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ORIGINAL ARTICLE

A prospective, multi-center, open-label, single-arm phase 2b study of autologous adult live cultured buccal epithelial cells (AALBEC) in the treatment of bulbar urethral stricture

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Abstract

Purpose To evaluate the safety and efficacy of autologous adult live cultured buccal epithelial cells (AALBEC) in treatment and management of bulbar urethral stricture in men.

Methods This was a prospective, multi-center, open-label, single-arm phase 2b study. A total of 18 male patients with bulbar urethral stricture of at least 1 − 4 cm in length were enrolled in the study. All 16 patients had AALBEC implanted and were included in the safety set. Change in total American Urology Association (AUA) symptom score, urinary flow rates assessed by uroflowmetry and a requirement for surgery after 24 weeks from baseline were determined in patients. Data of treatment efficacy were analyzed.

Results The AUA score at baseline was 21 (3.9) that showed a statistically significant reduction starting from week 2 [8 (4.4), $p = 0.0001$] which sustained until week 24 [2 (1.2), $p = 0.0005$]. Overall mean total AUA symptom score was reduced by 90.5% after the treatment. Significant reductions from baseline at week-24 were also observed in voiding time (92.5 (47.3) vs. 51.9 (17.4) s, $p = 0.0046$) and flow time [86.9 (48.2) vs. 47.9 (19.6) s, $p = 0.0052$]. All patients showed absence of any significant adverse events.

Conclusion Significant improvement was seen in the AUA symptom score and uroflowmetry parameters and no patients required surgery during 24 weeks post-treatment. It can be concluded that AALBEC is a safe and effective treatment for bulbar urethral stricture of 1 − 4 cm length to improve the quality of life and the physiological function of urethra.

Keywords Bulbar urethral stricture · Buccal epithelial cell therapy · American urology association score · Uroflowmetry · Epithelial regeneration

Introduction

Urethral stricture as described by the International Consultation on Urological Diseases/Société Internationale d'Urologie (ICUD/SIU) is the abnormal narrowing of the urethra. Their common origins are idiopathic, inflammatory, traumatic, or iatrogenic; latter accounting for most cases [1, 2]. Penile and bulbar strictures are most common and are of idiopathic origin followed by iatrogenic and traumatic origin [3–5]. Their incidence is 229–627 per 100,000 males and significantly increases after 65 years [6, 7]. Treatment options include simple dilatation, urethrotomy, and urethroplasty, and choosing a treatment is complex and depends on multiple factors such as stricture site, length, etiology, and surgical history [8].

Direct visual internal urethrotomy (DVIU) and urethral dilatation are preferred for short-length strictures (1–4 cm in

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length) as they are feasible and relatively simple [9, 10] but have lowest rates of long-term success (0–9%) and chances of stricture recurrence, with single or multiple urethrotomy irrespective of the etiology, are high [11]. Moreover, its adverse effects including perineal hematoma, urethral hemorrhage, extravasation of irrigation fluid into perispongiosal tissue, protracted bleeding (6%), and urinary tract infection (UTI, 10%) can potentially reduce quality of life [12, 13]. Urethroplasty has significantly higher success rate compared with urethrotomy and urethral dilatation. However, it has marginal benefits over established techniques for short-length strictures [2, 10], and is recommended for complex strictures (> 4 cm in length) [3, 13]. It is highly invasive with long procedural time and extended stay in hospital. Patients also experience erectile dysfunction, wound infection, neuropraxia and incontinence [13]. It also causes post-stricture repair lower urinary tract (LUT) symptoms. Around 40% of men reported urgency and 12% reported urge incontinence, following anterior urethroplasty [14].

Urethrotomy or dilatations widen strictures but do not address the underlying cause (like a damaged or injured epithelium), and urethroplasty is highly morbid. Given high stricture recurrence rate following urethrotomy and dilatation and resultant reduction in quality of life [13, 15], novel treatments are needed to address structural and functional dysfunction of short-length strictures. Medical devices/biological drugs leading to regeneration of epithelium without further restenosis/fibrosis can potentially fulfill treatment need. Research in tissue engineering for urethral reconstruction has progressed significantly in the past decade [7, 16, 17]. Oral buccal mucosal tissue displays greater benefit over bladder mucosa and scrotal skin owing to lower morbidity rate, better adaptability to a wet environment, similarity in cell type, and promising results [2, 16, 17]. Efficacy and safety of tissue-engineered oral buccal mucosa graft raised the possibility of using autologous buccal cell implantation for managing urethral stricture. Here, we evaluate safety and efficacy of autologous adult live cultured buccal epithelial cells (AALBEC) in treating and managing urethral stricture in men.

Methods

Study design and patient population

This prospective, multi-center, open-label, single-arm phase 2b study enrolled men (18–65 years) with a BMI < 35 kg/m^2 diagnosed with retrograde urethrography with bulbar urethral stricture (1–4 cm in length) with/without prior DVIU. Patients presenting with strictures > 4 cm, previously failed urethroplasty, unhealthy buccal mucosa, gonorrheal infection, HIV, syphilis, tuberculosis, hepatitis, enlarged prostate, hypospadias, phimosis or other urethral malignancies, were excluded. Also, patients with history of cardiac, renal and hepatic dysfunctions or diabetes according to specific laboratory criteria mentioned in protocol were excluded. Patients with a history of using smokeless tobacco or sub-mucosal fibrosis were also excluded after the visual inspection of their oral cavity. This study was conducted in accordance with Schedule Y (amended version, 2013), Indian Council of Medical Research guidelines (2017), International Council of Harmonization E6 (R2) 'Guidelines on Good Clinical Practice' (2016), Declaration of Helsinki (Version 2013), and other applicable regulatory authorities. The study was monitored by an independent organization. Study documents were approved by respective local institutional ethics committees at all centers. All patients provided informed consent prior to study commencement. The complete protocol is provided as supplementary material (online resource 1).

Study treatment and procedure

At screening, recording of medical history, assessment of vital signs, and physical examination were performed. Laboratory tests including hematology, biochemistry, urine analysis, urine culture test, chest X-ray, electrocardiogram, screening tests for HIV, Hepatitis B and C, Syphilis were performed. In addition, all patients underwent kidney, ureter and bladder ultrasonography prior to their enrollment in the study. AALBEC, available as Uregrow® manufactured by Regrow Biosciences Private Limited, India, is a suspension of not less than (NLT) 2.5 million cells/0.4 mL Dulbecco's modified Eagle's medium (DMEM) culture per vial. All manufacturing procedures were GMP certified and the product was tested for microbial sterility (absence), endotoxin (< 3 EU/ml), mycoplasma (absence), non-viable impurities (< 1 g/dl), cell characterization (> 80% CK14 + expression), karyotyping analysis (no chromosomal abnormalities). Uregrow® treatment comprised of the following.

Step 1

Approximately 1 × 1.5 cm of oral buccal mucosa tissue was harvested from patient's inner cheek under local anesthesia and placed in DMEM culture using sterile procedure, and sent to the GMP certified laboratory. All principal investigators involved in the trial were provided with a standardized procedure for harvesting the buccal mucosa tissue. Buccal mucosa healing was assessed by the investigator during the implantation visit, and as it is a small size harvest, no donor site morbidity was seen in any patients.

Step 2

AALBEC were isolated by enzymatic digestion of buccal mucosa tissue and separation of epithelial layer from the sub mucosal tissue. Cells were cultured, expanded ex vivo, tested and formulated as a suspension of NLT 2.5 million cells/0.4 mL DMEM culture per vial. Stability of AALBEC was 72 h when stored at 2–8 °C.

Step 3

During implantation, defect site was accessed by a cystoscope with sheath and a small incision was made to the urethral stricture endoscopically to open it. After suspending cells in the vial, they were injected into the stricture site. Each patient was implanted with two vials of Uregrow® via cystoscopic implantation slowly 21 ± 7 days after cell harvesting. Patients were discharged after 48 h of hospitalization. The Silicone Foley's catheter was removed within 2 weeks post-implantation. The study involved seven study visits: screening, cell harvesting, AALBEC implantation, and five follow-up visits at weeks 2, 4, 12, 24 after the day of implantation.

Study outcomes

Primary outcome was change in total American Urology Association (AUA) symptom score and secondary outcomes were change in urinary flow rates assessed by uroflowmetry and a requirement for surgery after 24 weeks from baseline. The AUA symptom index includes eight questions on frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying, and urgency accounting for most obstructive and irritating symptoms. A score of 7 or less is mildly symptomatic, 8–19, moderately symptomatic, and 20–35 is severely symptomatic [18, 19]. The AUA symptom score and uroflowmetry are commonly used diagnostic methods to identify stricture recurrence [20, 21]. Safety assessments included AEs, clinical laboratory parameters, vital signs, physical examinations and concomitant medications, and were graded per the investigator's clinical judgment as mild, moderate, severe.

Statistical analysis

Efficacy assessments were based on the per-protocol (PP) population. For continuous variables, the summary statistics were presented as number of observations, mean, standard deviation, median, minimum and maximum values. Paired-test or non-parametric alternative Wilcoxon signed-rank test were used, as applicable. Categorical values were summarized using frequencies and percentages and analyzed by Chi-square tests. All statistical analyses were carried out using SAS® Version 9.4.

The p value of < 0.05 was considered statistically significant. Considering a 15% dropout, 16 male subjects with short bulbar urethral stricture in length were enrolled to achieve a minimum of 12 evaluable subjects.

Results

Patient disposition and demographics

Between 18 April 2017 and 07 August 2018, 18 male patients were enrolled in the trial (Fig. 1) and 16 patients had AALBEC implanted and were included in the safety set. All 16 patients completed the trial and 2 patients had major protocol violation (denied undergoing kidney, ureter and bladder ultrasonography) and were excluded from the efficacy analysis resulting in analysis of 14 patients in the PP population (Online resource 2). Mean ± SD age was 43.0 ± 12.1 and mean BMI was 24.7 ± 3.8 kg/m^2. The bulbar region stricture had a mean ± SD length of 1.3 ± 0.4 cm. Of 16 patients, 6 (37.5%) had stricture length of 1 cm; 6 (37.5%), between 1 and 1.5 cm, and 4 patients (25%) had stricture length of 2 cm. A total of 5 (35.71%) patients had previous DVIU and 2 (14.29%) had previous dilation performed. Etiology of the urethral stricture was reported to be majorly idiopathic (50%) followed by iatrogenic (21.43%), trauma (21.43%), and Lichen sclerosis (7.14%).

Efficacy analysis

Baseline AUA score was 21 (3.9) showed significant decrease starting from week 2 [8 (4.4), $p = 0.0001$] that remained so until week 24 [2 (1.2), $p = 0.0005$]. Overall, mean total AUA symptom score reduced by 90.48% post-treatment and total AUA score was < 5 for all (100%) patients (Table 1).

Void volume increased from 322 (98.6) ml at baseline to 478 (255.4) ml at 24 weeks demonstrating 48.5% (approx.) increase ($p > 0.05$) despite showing a trend towards improvement. Significant reductions from baseline at week-24 were observed in voiding time (92.5 [47.3] vs. 51.9 [17.4] s, $p = 0.0046$) and flow time [86.9 (48.2) vs. 47.9 (19.6) s, $p = 0.0052$] corresponding to 40.2% and 44.9% reductions from baseline in voiding time and flow time, respectively. Maximum flow rate was 10.0 (11.8) mL/sec at baseline and started to increase immediately at 2 weeks [29.0 (10.1)], remained constant for 4 weeks [25.5 (8.6)] but decreased from week 12 resulting in no difference from baseline at week 24, 18.6 (12.6). Overall, maximum flow rate increased by 72% post-treatment and remained higher than 15 mL/sec

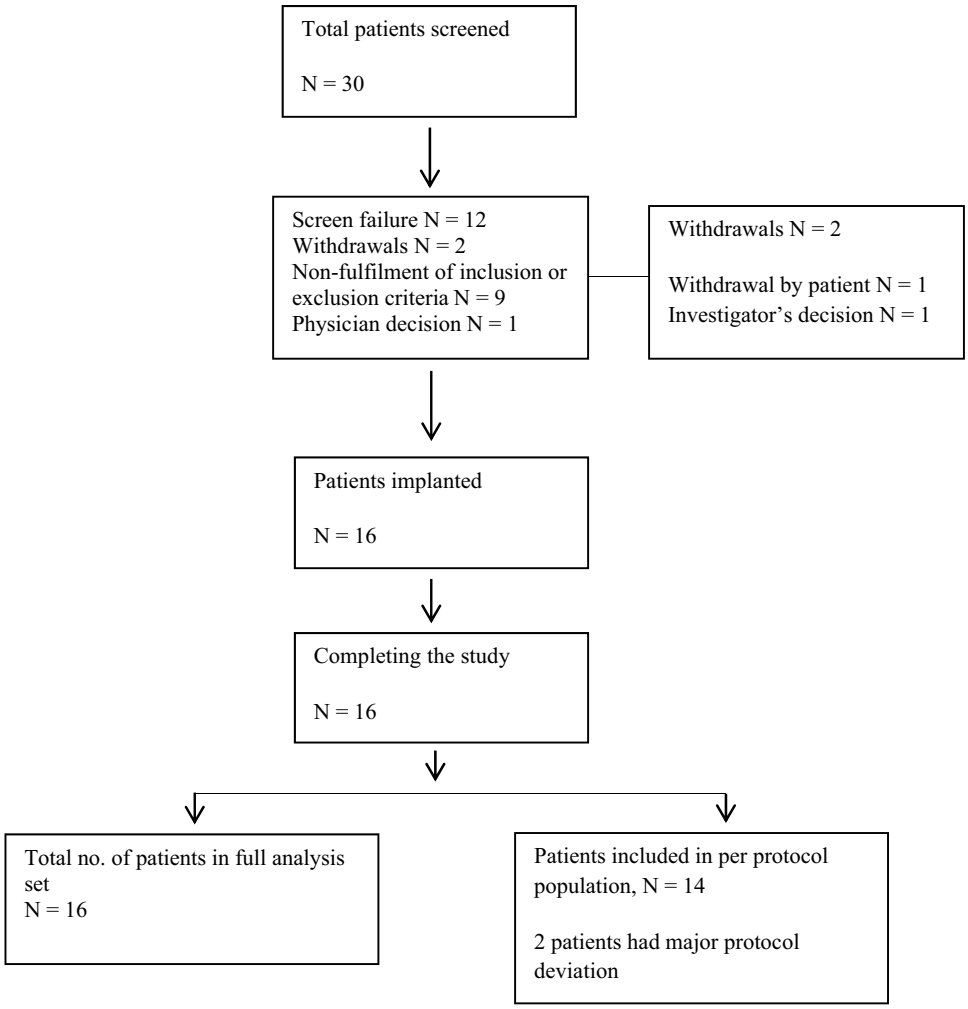

Fig. 1 Participant flow

in seven patients (53.8%) at 24 weeks. A similar trend was observed in average flow rate and time to maximum flow. Overall, average flow rate was increased by 76.9% post-treatment at 24 weeks (Table 1).

A subgroup analysis was carried out where participant age criteria changed to include patients between 18 and 56 years per recommendations of Central Drug Standard Control Organization (CDSCO). Results of this subgroup analysis ($N=13$) remained comparable to the overall population (Online resource 2). In an additional subgroup analysis, younger patients showed significantly improved outcome compared with older patients. The improvement in the AUA symptom score was similar in patients with or without previous DVIU or dilatation (Online resource 2).

Safety analysis

Nine treatment emergent adverse events (TEAEs) were reported in six patients during study duration. Of these, seven were moderate, and two were mild and not related to study treatment (Table 2). The most frequently reported AE was urinary tract infection (UTI) (five patients, 31.3%), and the urine culture test was positive as the catheter was intact after 14 days. No undesired effects were reported at oral harvest site. There were no deaths, serious or significant AEs during the study duration.

Discussion

We evaluated efficacy and safety of AALBEC in treatment and management of urethral stricture using AUA symptom index, uroflowmetry, requirement of surgery post treatment at 24 weeks, and AEs, respectively. After AALBEC, decreased AUA symptom score, void time, and flow time at 24 weeks ($p<0.05$). Mean AUA symptom index reduced by 90.5% and showed improvement in 100% of patients post-treatment after 24 weeks, a direct measure improved quality of life. Mean flow rate increased from 10.1 to 18.3 mL/s, a 72.8% increase from baseline.

Urethrotomy has lower success rate for treating short urethral strictures [22]. Stricture recurrence in 37% of

Table 1 Change in uroflowmetry parameters and American Urology Association (AUA) symptom score

Parameter	Baseline	Week 2	Week 4	Week 12	Week 24
Voided volume (ml)	322.0 (98.6)	398.0 (243.8)	382.0 (209.2)	484.0 (226.2)	478.0 (255.4)
Change from baseline	–	76.0 (278.4)	60.0 (261.6)	58.0 (292.8)	156.0 (291.7)
p value	–	0.3253	0.4052	0.0977	0.0668
Maximum flow rate (mL/sec)	10.0 (11.8)	29.0 (10.1)	25.5 (8.6)	19.4 (10.3)	18.6 (12.6)
Change from baseline	–	18.9 (11.5)	15.5 (15.0)	5.2 (15.8)	8.5 (17.0)
p value	–	< .0001	0.0020	0.1559	0.0828
Average flow rate (mL/sec)	6.4 (8.2)	15.4 (5.1)	13.7 (5.2)	11.5 (4.9)	11.3 (6.9)
Change from baseline	–	9.0 (9.)	7.3 (9.9)	2.6 (9.9)	4.9 (11.4)
p value	–	0.0025	0.0162	0.2405	0.1279
Voiding time (sec)	92.5 (47.3)	32.0 (25.7)	37.9 (23.1)	57.9 (32.1)	51.9 (17.4)
Change from baseline	–	− 60.5 (58.2)	− 54.6 (47.9)	− 47.0 (71.3)	− 40.6 (44.4)
p value	–	0.0019	0.0009	0.2294	0.0046
Flow time (sec)	86.9 (48.2)	32.0 (24.7)	32.9 (21.6)	46.9 (23.5)	47.9 (19.6)
Change from baseline	–	− 54.9 (50.7)	− 54.1 (48.4)	− 50.0 (64.2)	− 39.0 (43.6)
p value	–	0.0014	0.0011	0.0940	0.0052
Time to max flow (sec)	39.1 (44.7)	12.1 (12.0)	12.3 (8.2)	11.4 (9.5)	21.3 (13.2)
Change from baseline	–	− 26.9 (40.5)	− 26.8 (37.6)	-30.1 (48.9)	− 17.8 (49.5)
p value	–	0.0273	0.0195	0.0221	0.2020
Hesitancy[a]	7.0 (9.6)	5.0 (6.9)	10.0 (17.2)	5.0 (5.2)	6.0 (7.3)
Change from baseline	–	− 3.0 (6.4)	3.0 (9.5)	− 3.0 (6.4)	− 2.0 (4.7)
p value	–	0.3527	0.4745	0.2882	0.3800
AUA score	21.0 (3.9)	8.0 (4.4)	5.0 (3.2)	3.0 (2.7)	2.0 (1.2)
Change from baseline	–	− 14.0 (4.5)	− 16.0 (3.2)	− 18.0 (3.1)	− 19.0 (3.3)
p value	–	0.0001	0.0002	0.0010	0.0005

Data mean (SD) or number (%), [a]$n = 6$

Table 2 Summary of treatment-emergent adverse events by severity grade and system organ class and preferred term (safety population)

AEs	Number of patients ($N = 16$)	Number of events
Patients with at least 1 TEAE	6 (37.5%)a	9
Mild		
Infections and infestations	1 (6.3%)	1
Urinary tract infection	1 (6.3%)	1
Investigations	1 (6.3%)	1
Lymphocyte count decreased	1 (6.3%)	1
Moderate		
Blood and lymphatic system disorders	1 (6.3%)	2
Leukopenia	1 (6.3%)	1
Neutropenia	1 (6.3%)	1
Infections and infestations	4 (25.0%)	4
Urinary tract infection	4 (25.0%)	4
Renal and urinary disorders	1 (6.3%)	1
Urinary tract pain	1 (6.3%)	1

AEs are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0

AEs adverse events, *TEAE* treatment emergent adverse event

[a]Percentages are calculated based on total number of patients in safety population

cases within median time to recurrence as 4.5 months in addition to poor uroflowmetry is reported after optical urethrotomy [23]. Treatment with AALBEC improved AUA symptom score, increased maximum flow rate in all patients and no requirement of consecutive procedures or surgery during 24 weeks, indicated a 100% success rate in terms of need for additional treatment at 24 weeks.

Age, BMI, stricture length and etiology, and prior treatments are predictors of stricture recurrence as reported in several studies [24, 25]. Younger patients showed increased improvement in AUA and maximum flow rate in our study. Any chances of recurrence at old age can be associated with decline in chances with aging and consequent deposition of collagen and elastic tissues [26]. Patients with previous dilatation or urethrotomy have higher risk of recurrence as reported in several studies [23, 25]. However, patients with or without previous DVIU or dilatation showed similar improvement in our study. It was found that recurrence occurs in 75–100% of strictures of length > 1 cm after urethrotomy, whereas 29–50% strictures, < 1 cm recurred [26, 27]. Most importantly, our treatment was successful in 100% of patients with stricture length of 1 – 4 cm, without needing surgical intervention during 24 weeks of follow-up.

Urethroplasty is a better alternative to urethrotomy; however it is expensive and associated with excessive fibrosis at graft site [20]. Moreover, for stricture > 4 cm [3, 13] and after using tissue-engineered buccal mucosal graft in 15.8% of patients, stricture recurrence was observed. Using AALBEC in patients with shorter stricture length, study outcomes evaluating urethroplasty should be cautiously interpreted and not directly compared.

In summary, using AALBEC for treating short strictures can improve patient outcomes compared to urethrotomy and dilatation. This investigational study lacks benefits of a large population set. Therefore, large-scale, well-designed studies are required to substantiate results of this phase 2b study.

Conclusion

This study proves safety and efficacy of AALBEC implantation for bulbar urethral strictures of 1 − 4 cm as AUA symptom score and uroflowmetry parameters significantly improved, and no patients required surgery during 24 weeks of post-treatment follow-up. It improved quality of life and restored physiological function of urethra, and could be an effective alternative to urethrotomy and dilatation, and can be a futuristic treatment option for urethral reconstruction. However, results need to be further substantiated in large, well-designed studies.

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Author contributions SBK: protocol management, data collection/analysis; HP: protocol management, data collection/analysis; SK: clinical trial patient recruitment; SC: protocol management, data collection. All authors have equally contributed in writing and editing of the manuscript and have read and approved the final manuscript.

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Availability of data and material This manuscript has data included as supplementary material.

Code availability Not applicable.

Compliance with ethical standards

Conflict of interest The authors declare that they do not have any conflicts of interest.

Ethics approval All procedures performed in studies involving human subjects were according to Schedule Y (amended version, 2013), ICMR guidelines (2017), ICH E6 (R2) 'Guidelines on Good Clinical Practice' (2016), Declaration of Helsinki (Version 2013), and other applicable regulatory authorities.

Consent to participate Informed consent was obtained from all individual participants included in the study.

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