

Increased safety in treatment of urethra strictures, thanks to tissue engineering

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Biotechnology saves patients from excision of large pieces of native oral mucosa transplants for the plastic reconstruction of morbidly constricted urethras.

About one percent of the male population is affected by urethra strictures, with increasing incidence in elderly people. Patients are chronically ill with a severely diminished quality of life, suffering from low urinary flow, pain, chronic urinary infections, urinary stones, urinary reflux and urinary damage and failure. If untreated, life-threatening urinary retention can occur.

In the vast majority of cases, urethral stricture is treated by urethrotomy, an endoscopic procedure in which the urethra at the narrowed site is dilated by a longitudinal incision. This usually leads to an improvement of the clinical picture in the short term, but success is often only temporary. If urethrotomy is repeated, the success rate and duration to relapse will be reduced to zero after the third surgery.

Improved prospects: plastic reconstruction

A therapeutic option with much better prospects is the plastic reconstruction of the urethra with native oral mucosa from the patient. This technique was developed some twenty years ago. Unfortunately, it requires the excision of large segments of mucosa from the mouth of the patients, causing multiple short- and long-term injuries with a significant impact on patients' quality of life. These include:

- Intraoral pain;
- Bleeding and swelling;
- Sensory loss and oral numbness;
- Compromised oral health and dental hygiene;
- Oral scarring and chronic oral ulcers, due to repeated bites on scar bulges;
- Impaired lip mobility;
- Permanent salivation;
- Oral stenosis;
- Facial deformities and diminished facial expressions;
- Impaired mouth opening and impaired drinking, eating and speaking;
- Increased periodontal disease and loss of teeth, implants and ill-fitting dentures; and
- Due to chronic irritation and inflammation, the risk of oral cancer development.

Prolonged duration of anaesthesia required by two surgeries and nasal intubation, which has to be used in oral surgery, increases risk of intraoperative fatal bleeding and ruptures in the nasopharynx. Due to this, urethroplasty is not a standard but a niche therapy. Only a minority of operative urologists carry out this procedure. The removal of the native oral mucosa is a non-specialist operation for the urologist and, frequently, it is performed without training and detailed knowledge of the intraoral anatomy.

MukoCell®: a breakthrough in tissue engineering

MukoCell® is a new therapeutic option and a breakthrough in tissue engineering. The product was developed by UroTiss Europe GmbH to be used as graft for urethroplasty in patients with urethral stricture, while replacing native oral mucosa excision and, with thus, avoiding complications associated with the harvest of native oral mucosa segments.

MukoCell consists of oral mucosa cells obtained from a tiny piece of oral mucosa biopsy from the patient. The biopsy taken by the physician is sent to a laboratory with legal authorisation for production of medicinal products. After aseptic cultivation and

proliferation in designated cleanrooms, the cells are seeded on a resorbable carrier membrane. The whole process has a duration of three weeks and is performed in strict compliance with the pharmaceutical principles of good manufacturing practices. Before product release, each batch is tested to ensure uniformity and high quality of the products. MukoCell is then sent back to the clinic, ready to use as a transplant.

The efficacy and safety of MukoCell has been shown in different non-clinical and clinical studies. UroTiss has performed a prospective multi-centre, non-interventional clinical study with 99 patients suffering from urethral strictures.¹ Patients with comparatively unfavourable therapy prognoses were included. All but one patient had previously had at least one unsuccessful surgical pre-treatment and 77% had at least two. Included were complex penile and longer strictures – factors known to be unfavourable to treatment success. Efficacy of MukoCell showed to be comparable to the efficacy of native oral mucosa, as reported in literature. Safety was distinctively superior to native oral mucosa, especially at the oral harvest site, but also at the site of urethral surgery where the only complications observed were related to the surgical procedure. To date, no adverse events related to MukoCell have been reported.

The MukoCell study has a comparatively high evidence level, due to the prospective design, as well as by data monitoring and evaluations performed independently by a clinical research organisation. In contrast, the efficacy and safety of native oral mucosa used as a transplant for urethroplasty is not nearly matched by today's standards for clinical trials. Until today, there were no controlled clinical trials. Relevant publications are usually based on retrospective evaluations of cases selected from certain points of view in order to optimise the publication result without quality assurance measures and without independent monitoring. The risk of bias in this data is extremely high and the level of evidence is, therefore, very low.

Monitoring the impact MukoCell stands to have

In a long-term assessment at a median 55-month follow-up, the safety, feasibility and efficacy of MukoCell in the urethra reconstruction of 38 patients was satisfactory; 95% of the patients had experienced failed treatments; comparatively, 32 out of 38 patients (84%)

had a successful outcome; and no local or systemic adverse reactions, due to the use of engineered material, were registered.²

Health insurances in many cases do not yet cover this innovative therapy, despite the huge benefits to the patients and that UroTiss Europe GmbH has obtained market approval for MukoCell in Germany. For clinics and health insurance, patient tissue is attractive because it is gratis. In conclusion, from a very basic perspective, an indication which requires patient tissue as graft for treatment represents a high medical need, especially in patients for whom native oral mucosa is either not available or its excision would cause damages, or is unacceptable for the patient in terms of quality of life. These patients are not able or willing to undergo excision of substantial pieces of oral mucosa or where such a procedure would represent a significant risk for complications and disability. These include patients with:

- Long urethral strictures (>4cm), where large oral mucosa pieces would have to be harvested or bilateral, oral, mucosal excision would be required, with increased risk of sustained oral damage;
- Disturbed wound healing due to concomitant diseases, such as diabetes;
- Tendency to increase scar formation, where the excision of oral mucosa is associated with risks of parafunctional bites, chronic irritation and inflammation;
- Existing intraoral inflammatory disease;
- A small oral cavity or limited mouth opening, where access to the oral cavity is limited or excision of larger pieces of oral mucosa is not possible;
- Pre-existing oral mucosal damage, especially after removal of oral mucosa;
- Dentures: where excision may lead to ill-fitting dentures or loss of dental implants;
- Patients who, as a consequence of oral mucosa excision, are at risk of premature tooth loss, due to a worsening of oral hygiene options or of increased tension of the gums, followed by paradontosis;
- Patients in positions where impairment of physiognomy or oral anatomy, or gustatory sensation impacting job or social function, such as teachers, sales people, politicians, amongst others;
- Patients in whom nasal intubation or general anesthesia is associated with unacceptable risks; and
- Patients who principally reject oral mucosal excision.

Financing alternative therapeutics for urethra strictures

To obtain reimbursement from health insurances and in preparation of an application for market authorisation within the EU, UroTiss is planning a pivotal Phase 3 study to compare safety and efficacy of MukoCell with native oral mucosa as a graft in urethral strictures. The study aims to unambiguously show that MukoCell is highly superior to native oral mucosa as a transplant in respect to safety and complication rates at the graft harvest site, and is equivalent in efficacy.

The development and market approval of tissue-engineered products in the EC is a very demanding task. Regulatory challenges in qualitative, preclinical and clinical development are to be mastered.³ UroTiss sees the implementation of this study as the final milestone on this path.

References

1. Ram-Liebig G et al. EBioMedicine 2017; 23: 185–192
2. Barbagli G et al. J Urol 2018;200:448-456
3. Ram-Liebig G et al. Adv Drug Deliv Rev 2015;82-83:181-191

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