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REVIEW ARTICLE

Current status of tissue engineering applied to bladder reconstruction in humans☆

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Abstract
Context and objective: Bladder reconstruction is performed to replace or expand the bladder. The intestine is used in standard clinical practice for tissue in this procedure. The complications of bladder reconstruction range from those of intestinal resection to those resulting from the continuous contact of urine with tissue not prepared for this contact. In this article, we describe and classify the various biomaterials and cell cultures used in bladder tissue engineering and reviews the studies performed with humans.
Acquisition of evidence: We conducted a review of literature published in the PubMed database between 1950 and 2017, following the principles of the PRISM declaration.
Synthesis of the evidence: Numerous *in vitro* and animal model studies have been conducted, but only 18 experiments have been performed with humans, with a total of 169 patients. ''The current evidence suggests that an acellular matrix OR a synthetic polymer with urothelial and autogenous smooth muscle cells or stem cells would be the most practical approach for experimental bladder reconstruction.''
Conclusions: Bladder replacement or expansion without using intestinal tissue is still a challenge, despite progress in the manufacture of biomaterials and the development of cell therapy. Well-designed studies with large numbers of patients, long follow-up times and standardisation of the check-up functional tests are needed to establish an effective clinical translation.

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PALABRAS CLAVE
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Derivación urinaria artificial

Estado actual de la ingeniería tisular aplicada a la reconstrucción vesical en humanos

Resumen
Contexto y objetivo: La reconstrucción vesical es el procedimiento para sustituir o ampliar la vejiga, siendo el intestino el tejido utilizado en la práctica clínica habitual. Las complicaciones de su uso van desde las propias de una resección intestinal hasta las resultantes del contacto continuo de la orina con un tejido no preparado para ello. En este artículo se describen y clasifican los diferentes biomateriales y cultivos celulares utilizados en la ingeniería tisular vesical y se revisan los estudios realizados en humanos.
Adquisición de la evidencia: Se ha realizado una revisión de la literatura publicada en la base Pubmed entre 1950 y 2017, siguiendo los principios de la declaracion PRISMA.
Síntesis de la evidencia: Se han realizado múltiples estudios *in vitro* y en modelo animal, pero solo se han realizado 18 experimentos en humanos, con un total de 169 pacientes. La pruebas actuales indican que utilizar una matriz acelular o bien un polímero sintético y adherirle *in vitro* células uroteliales y musculares lisas autógenas, o bien células madre, sería la aproximación más realista para realizar una reconstrucción vesical experimental.
Conclusiones: La sustitución o ampliación vesical sin utilizar intestino continúa siendo hoy un reto, a pesar del progreso en la fabricación de biomateriales y del desarrollo de la terapia celular. Para plantear una traslación clínica efectiva será necesario en el futuro realizar estudios bien diseñados, con mayor número de pacientes y tiempo de seguimiento, además de estandarizar las pruebas funcionales de control.

Introduction

Bladder reconstruction is the procedure performed to replace or expand the bladder. Tissue engineering is a set of techniques and knowledge capable of designing and creating a new tissue. Applying this to bladder reconstruction, the tissue generated should offer a good structural function and adapt to preserve the upper urinary tract, maintain urinary continente, and promote adequate urinary emptying. Urinary diversion after radical cistoprostatectomy due to bladder neoplasm is the most frequent indication for reconstruction.[1] The most common causes requiring bladder enlargement are tuberculosis, radiation cystopathy, interstitial cystitis, and some types of neurogenic bladder.

The intestine is the tissue used in clinical practice, since there is no other autogenous or heterogeneous material, natural or artificial, that has shown better results. The complications of bowel use range from those of conventional intestinal resection (paralytic ileus, suture failure, nutritional deficit, diarrhea, steatorrhea) to those resulting from the continuous contact of urine with tissue not prepared for it. The latter can produce electrolyte imbalance (hyperchloremic metabolic acidosis), the appearance of neoplasms (especially in the areas of anastomosis), portal resorption of some drugs eliminated in the urine, which changes the toxicity of these (note methotrexate, phenytoin, and lithium) and the formation of lithiasis. Special mention should be made of the mechanical complications inherent to the reservoir: stromal complications, stenosis of the ureteroenteric or urethroenteric anastomosis, unwanted increase in maximum volume, elevated postvoid residue, nocturnal incontinence (these last 3 in reference to orthotopic neobladders).[2,3] These complications lead to an increase in morbidity.[4]

To prevent the negative effects of the use of intestinal tissue as a substitute for the urinary one and considering that in some reconstructions the use of intestine is not possible (in patients with chronic inflammatory bowel diseases, short bowel syndrome, abdominal-pelvic irradiation, etc.), in the 1950s, experimentation with non-intestinal materials began.[5] Since then, the interest to find a material other than the intestine has been growing, and multiple studies have been made *in vitro* and in animal model (dog, rabbit, rat, and pig), but there are few studies in humans. This review aims to describe and classify the different materials and review the clinical studies conducted in humans until today. With this prior knowledge, the objective is to design new and better studies and not repeat unnecessarily experiments already carried out.

Acquisition of the evidence

A review of the literature published in PubMed was carried out from 1950 to 2017, following the principles of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The terms used in the search were bladder biomaterials, bladder engineering, artificial bladder, artificial urinary conduit, which resulted in 344 articles. Of these, 94 performed experiments that consisted in reconstructing the bladder (both substitutions and extensions); thus, those that included more organs, those that were exclusively *in vitro* studies, or those that were review articles, were ruled out. It should be noted that most of the studies, both in animals and in humans, are small series of cases – prospective – and with short follow-ups. The imaging or functional control tests are not standardized and, sometimes, they are absent. Finally, the *in vivo* studies performed