

group applied with high-dose EPO, fibrosis was seen at significantly low rates and in 3 of the 10 rats, no fibrosis was seen in normal urethral tissue at the end of 15 days. In the samples of both groups where EPO was used, fibrosis and inflammation were significantly less than in the control group. However, no statistically significant difference was determined between high-dose EPO and low-dose EPO in respect of fibrosis and inflammation. The stimulating effect of EPO on angiogenesis, which is one of the most important markers of wound healing and regarded as congestion of lamina propria in the histopathologic analysis, was clearly observed. In both EPO groups, congestion of vessels was observed at a significant rate in the lamina propria of almost all the samples. Although a significant difference was determined between the two EPO groups and the control group in respect of congestion, no statistically significant difference was determined between high-dose EPO and low-dose EPO.

In addition to being the main regulator of hematopoiesis, EPO is used as an important cytoprotective agent in organs such as the brain,⁵⁻⁷ heart,⁸ skin,¹⁹ and upper urinary tract system.²³ However, there are no data showing the effect of the cytoprotective property of EPO in urethral trauma. The current study is the first in this field to show this effect. The main limitation of this study was that there were no long-term results as it was an animal experimental study.

A ready-to-use injector will make it easy to inject EPO into the urethral stricture area in future clinical trials. Local use will inhibit the systemic side-effects of EPO such as hemoglobin increase. A cost-effect analysis of medical treatment vs surgery management of urethral stricture can be debated in the future.

CONCLUSION

Erythropoietin can be considered a promising agent which could prevent fibrosis forming after urethral trauma and could accelerate urethral healing. There is therefore a clear need for further clinical studies with long-term results to be able to better evaluate this effect.

References

1. McCammon KA, Zuckerman JM, Jordan GH. Surgery of the penis and urethra. In: Wein AJ, Kavoussi LR, Partin AW, Peters CA, eds. *Campbell-Walsh Urology 11th ed*. Philadelphia: Elsevier; 2016;40:907-945. e4.
2. Santucci R, Eisenberg L. Urethrotomy has a much lower success rate than previously reported. *J Urol*. 2010;183:1859-1862.
3. Hofer MD, Cheng EY, Bury MI, et al. Analysis of primary urethral wound healing in the rat. *Urology*. 2014 Jul;84:246.e1. <http://dx.doi.org/10.1016/j.urology.2014.04.012>.
4. Elliott S, Sinclair AM. The effect of erythropoietin on normal and neoplastic cells. *Biologics*. 2012;6:163-189.
5. Wenker SD, Chamorro ME, Vittori DC, et al. Protective action of erythropoietin on neuronal damage induced by activated microglia. *FEBS J*. 2013;280:1630-1642.
6. Tugyan K, Ozbal S, Cilaker S, et al. Neuroprotective effect of erythropoietin on nandrolone decanoate-induced brain injury in rats. *Neurosci Lett*. 2013;533:28-33.

7. Undén J, Sjölund C, Länsberg JK, et al. Post-ischemic continuous infusion of erythropoietin enhances recovery of lost memory function after global cerebral ischemia in the rat. *BMC Neurosci*. 2013;14:27.
8. Cariou A, Claessens YE, Pène F, et al. Early high-dose erythropoietin therapy and hypothermia after out-of-hospital cardiac arrest: a matched control study. *Resuscitation*. 2008;76:397-404. <http://dx.doi.org/10.1016/j.resuscitation.2007.10.003>.
9. Mandhani A, Chaudhury H, Kapoor R, et al. Can outcome of internal urethrotomy for short segment bulbar urethral stricture be predicted? *J Urol*. 2005;173:1595-1597.
10. Greenwell TJ, Castle C, Andrich DE, et al. Repeat urethrotomy and dilation for the treatment of urethral stricture are neither clinically effective nor cost-effective. *J Urol*. 2004;172:275-277.
11. Sahinkanat T, Ozkan KU, Ciralik H, et al. Botulinum toxin-A to improve urethral wound healing: an experimental study in a rat model. *Urology*. 2009;73:405-409.
12. Da-Silva EA, Sampaio FJB, Dornas MC, et al. Extracellular matrix changes in urethral stricture disease. *J Urol*. 2002;168:805-807.
13. Hebert PW. The treatment of urethral stricture: transurethral injection of triamcinolone. *J Urol*. 1972;108:745-747.
14. Shirazi M, Khezri A, Samani SM, et al. Effect of intraurethral captopril gel on the recurrence of urethral stricture after direct vision internal urethrotomy: phase II clinical trial. *Int J Urol*. 2007;14:203-208.
15. Nagler A, Gofrit O, Ohana M, et al. The effect of halofuginone, an inhibitor of collagen type I synthesis, on urethral stricture formation: In vivo and in vitro study in a rat model. *J Urol*. 2000;164:1776-1780.
16. Mazdak H, Meshki I, Ghassami F. Effect of mitomycin C on anterior urethral stricture recurrence after internal urethrotomy. *Eur Urol*. 2007;51:1089-1092.
17. Yardimci I, Karakan T, Resorlu B, et al. The effect of intraurethral dexpanthenol on healing and fibrosis in rats with experimentally induced urethral trauma. *Urology*. 2015;85:274.e9-13. <http://dx.doi.org/10.1016/j.urology.2014.09.038>.
18. Chung JH, Kang DH, Choi HY, et al. The effects of hyaluronic acid and carboxymethylcellulose in preventing recurrence of urethral stricture after endoscopic internal urethrotomy: a multicenter, randomized controlled, single-blinded study. *J Endourol*. 2013;27:756-762.
19. Lu H, Wu X, Wang Z, et al. Erythropoietin-activated mesenchymal stem cells promote healing ulcers by improving microenvironment. *J Surg Res*. 2016;205:464-473. <http://dx.doi.org/10.1016/j.jss.2016.06.086>.
20. Tavukcu HH, Aytac Ö, Atug F, et al. Protective effect of platelet-rich plasma on urethral injury model of male rats. *Neurol Urodyn* 2017. <http://dx.doi.org/10.1002/nau.23460>. [Epub ahead of print].
21. Wang K, Guan Y, Liu Y, et al. Fibrin glue with autogenic bone marrow mesenchymal stem cells for urethral injury repair in rabbit model. *Tissue Eng Part A*. 2012;18:2507-2517. <http://dx.doi.org/10.1089/ten.TEA.2011.0359>. Epub. 2012 Aug 30.
22. Kilinc MF, Doluoglu OG, Karakan T, et al. Evaluation of results of diagnostic ureteroscopy in chronic hemodialysis patients. *J Endourol*. 2016;30:371-374. <http://dx.doi.org/10.1089/end.2015.0675>.
23. Janssen C, Jäger W, Moskalev I, et al. Erythropoietin accelerates the regeneration of ureteral function in a murine model of obstructive uropathy. *J Urol*. 2015;193:714-721.

EDITORIAL COMMENT

This is a nice contribution to the limited basic science knowledge we have in regards to urethral injury and urethral stricture disease. However, it is vital to understand the animal model



utilized in this study before any conclusions about clinical applicability in humans can be drawn.

The analogous clinical scenario in humans to the benchtop one depicted here in rats would be for a clinician to inject erythropoietin into the urethra immediately after a known (likely iatrogenic?) urethral injury so to prevent a possible urethral stricture. When is a urethra knowingly injured in a manner in which this scenario could be possible or even advisable? Almost never.

What researchers and clinicians alike are really looking for is a substance that can be injected into the urethra after urethrotomy for urethral stricture disease that will hasten scar reformation, keeping the urethral lumen open (>14F) and prevent the need for a urethroplasty.

There are a few candidates that have been investigated whose reported recurrence preventing mechanism is to modify (or prevent) collagen deposition after urethrotomy including, but not limited to, mitomycin,¹ triamcinolone,² and collagenase.³ More recently, injectables that aim prevent recurrence by hastening endothelial and urethral regeneration, including Fat-derived Stem Cells,⁴ platelet rich plasma⁵ and even liquid buccal mucosa grafts⁶ have also been described.

What do all of these injectables have in common? All of them are reported to provide clinical benefit. Why, then, are none of them being utilized routinely? – why are we still doing urethroplasties at all if they work so well? Most obvious is the need to follow these patients longer – and without well-designed RCTs, we'll never know to what degree the success can be attributed to the stricture characteristics, the urethrotomy or the injectable itself. Or perhaps these injectables just delay the recurrence (hence the initial enthusiasm) but don't prevent them (hence the lack of follow-up data or widespread adoption)?

However, more fundamentally, we likely don't have a winner yet because we don't understand how any of them work – and without an understanding of urethral stricture pathophysiology – how they form (nearly 60% of strictures are still labeled idiopathic!!), why they recur, and how they are related to other local and systemic disease processes⁷ – we never will.

Add erythropoietin to the more recent amementarium of injectables that are hypothesized to help with local regeneration of tissue after urethrotomy for stricture disease. Though I believe regenerative injectables will be the key to eliminating the need for (most) urethroplasties, a specific modifiable target for the injectable within the stricture will need to be found first.

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References

1. Mazdak H, Meshki I, Ghassami F. Effect of mitomycin C on anterior urethral stricture recurrence after internal urethrotomy. *Eur Urol.* 2007;51:1089.
2. Gucuk A, Tuygun C, Burgu B, et al. The short-term efficacy of dilatation therapy combined with steroid after internal urethrotomy in the management of urethral stenoses. *J Endourol.* 2010;24:1017.
3. Sangkum P, Yafi FA, Kim H, et al. Collagenase Clostridium histolyticum (Xiaflex) for the Treatment of Urethral Stricture Disease in a Rat Model of Urethral Fibrosis. *Urology.* 2015;86:647 e1.

4. Sangkum P, Yafi FA, Kim H, et al. Effect of adipose tissue-derived stem cell injection in a rat model of urethral fibrosis. *Can Urol Assoc J.* 2016;10:E175.
5. Tavukcu HH, Aytac O, Atug F, et al. Protective effect of platelet-rich plasma on urethral injury model of male rats. *Neurourol Urodyn.* 2018;37:1286.
6. Nikolavsky D, Manwaring J, Bratslavsky G, et al. Novel Concept and Method of Endoscopic Urethral Stricture Treatment Using Liquid Buccal Mucosal Graft. *J Urol.* 1788;196:2016.
7. Erickson BA, Elliott SP, Myers JB, et al. Understanding the Relationship between Chronic Systemic Disease and Lichen Sclerosus Urethral Strictures. *J Urol.* 2016;195:363.

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AUTHOR REPLY



The most important problem of urethral wound healing is an increase in abnormal fibrosis because of imbalances in the healing processes. Healing of traumatic or idiopathic wounds in the urethra is known to be complicated and a longer process than dermal healing with sequential yet overlapping phases of hemostasis, inflammation, proliferation, and remodeling.¹

The history of wound healing is old as the history of humankind. The oldest known medical record is a clay tablet that was written around 2200 BC.² To ensure that a wound healed properly and quickly, a wide range of practices and materials have been used throughout history. Furthermore, the ability to heal wounds quickly is among the most appealing of all technologies imagined by science fiction movies such as *Transcendence* (Pfister W, 2014) and *Star Trek* episodes. Such advanced technology is mostly based on the use of nanotechnology or nanomedicine.³ Current research investigating ways of hastening the wound healing process continues to increase with advances in technology. The development of complex materials on a nanoscale (1–100 nm) provides a means capable of facilitating migration and proliferation through the controlled release of cytokines and growth factors such as endothelial growth factor, insulin-like growth factor, transforming growth factor and fibroblast growth factor, which form the complex signalling network that alters the growth, differentiation, and metabolism of targeted cells and prevents excessive abnormal collagen formation.^{4,5}

Although the present study has some limitations as it was an animal study, it offers a window to the potential consequences of preventing excessive and abnormal fibrosis after urethral trauma. As stated in the editorial comments, longitudinal, larger, well-designed randomized controlled trials certainly need to be conducted, but it can be clearly stated that the present study is the spark, having secured a tipping point, because of the similarity of nano-technology methodology for the wound healing process. Many of the most significant developments begin with small imperfect steps that become strides towards improvement.

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