



# Bladder wall injection of mesenchymal stem cells ameliorates bladder inflammation, overactivity and nociception in a chemically induced interstitial cystitis-like rat model

Dina El-Hamamsy<sup>1</sup>

Received: 1 February 2018 / Accepted: 5 March 2018 / Published online: 29 March 2018  
© The International Urogynecological Association 2018

This study set out to accomplish two goals: one was to evaluate a chemically induced interstitial cystitis (IC) model in rats, and the other was to determine if mesenchymal stem cells (MSCs) injected into the bladder wall of rats with chemically induced IC would have a clinically beneficial effect.

The hydrochloric acid (HCl)-induced cystitis rat model was developed using weekly bladder instillation of HCl (or phosphate buffered saline [PBS] in the control group) for 2 weeks, after which the histological and immuno-histochemical bladder changes were examined at weekly intervals for 4 weeks. These included markers for inflammation (mast cells, tumour necrosis factor alpha [TNF $\alpha$ ], transforming growth factor beta [TGF- $\beta$ ]), neovascularisation (vascular endothelial growth factor [VEGF]), mucosal denudation (E-cadherin) and fibrosis (collagen).

Simultaneously, the authors set out to examine the effects of bladder wall injection of adipose-derived MSCs on bladder inflammation, nociceptive (pain) behaviour and bladder function in their cystitis rat model. To examine these, the bladder walls of the rats were injected with either MSC suspension or PBS (sham procedure) at the time of the second HCl instillation. Two rats were also injected with green fluorescent protein (GFP)-MSCs. The study outcome measures were then evaluated 2 weeks later. The nociceptive response to capsaicin bladder instillation was measured using the number of freezing events (motionless head turning to lower abdomen), indicating bladder pain. Conscious cystometry was used to evaluate bladder function.

Following HCl bladder instillation, markers of inflammation increased in the first 2 weeks and that for fibrosis in weeks 2–4, hence the authors' decision to examine MSC effects 2 weeks after HCl (and MSC) injection. The GFP-MSCs were detected within the bladder muscle layer 2 weeks after injection.

There was a significant increase in mast cell infiltration, TNF- $\alpha$  and TGF- $\beta$  expression, collagen fibres and nociceptive behaviour in the HCl/sham rats (cystitis model) compared with controls. All of these outcome measures also significantly decreased in the HCl/MSC rats (treatment model) compared with the HCl/sham group, suggesting a potentially therapeutic role for MSCs in the cystitis model described. Compared with the PBS/sham group (completely neutral, control group), this group (HCl/MSCs) also demonstrated an increase in mast cells, collagen and nociceptive behaviour, but not TNF- $\alpha$  or TGF- $\beta$ .

Bladder capacity and voiding threshold pressures were significantly reduced in HCl/sham (cystitis model) rats compared with controls (PBS/sham), although other cystometric parameters were not different. There were no cystometric differences between the HCl/MSC (treatment model) and HCl/sham (cystitis model) groups.

Overall, this study's cystitis rat model showed an increase in some, but not all cystitis markers measured, including those of inflammation (mast cells, TNF- $\alpha$ , TGF- $\beta$ ) and fibrosis (collagen), but not neovascularisation (VEGF) or mucosal denudation (E-cadherin). It also demonstrated an increase in nociceptive behaviour and a decrease in bladder capacity and voiding threshold, although other cystometric parameters in the cystitis model and the control group were not significantly different. This presents a potentially useful cystitis rat model that could be used to study bladder pain syndrome/IC.

The potential therapeutic role of MSCs in this condition was also explored in this study. The GFP-MSCs were detected

✉ Dina El-Hamamsy  
deh15@le.ac.uk

<sup>1</sup> Leicester General Hospital, University Hospitals of Leicester NHS Trust, Gwendolen Road, Leicester LE5 4PW, UK

within the bladder muscle layer 2 weeks after injection. The authors suggest further studies exploring different routes of administration of MSCs to determine the most effective one for therapeutic uses.

Compared with the cystitis model, the rat treatment model showed some markers of improvement in their condition.

These included reductions in inflammatory and fibrosis markers and nociceptive/pain behaviour. However, there were no differences in cystometric parameters between the two groups and the study authors suggest further exploration of this point in larger studies.