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HUMAN MESENCHYMAL STEM CELLS ENCAPSULATED IN A DITYRAMINE CROSS-LINKED HYDROGEL RECONSTITUTE URINARY CONTINENCE IN A PUBOURETHRAL LIGAMENT TRANSECTED RAT MODEL

Hypothesis / aims of study

Stress urinary incontinence (SUI) is the result of connective tissue damage and resultant laxity of the supporting ligaments of the pelvis, much of which can be sustained as a result of birth trauma. The intent of this study was to examine the ability of bone marrow-derived human mesenchymal stem cells (hMSCs) to restore continence in a previously described vaginal distention (VD) rat model of SUI (Lin et al, 2008).

Study design, materials and methods

Female Sprague-Dawley rats (N = 180) underwent serial VD with lubricated bouge dilators of increasing size (from 24F to 32F), followed by a modified 10F Foley catheter. The catheter balloon was gradually inflated with 3cc sterile water and secured in place for four hours, after which the catheter was deflated. Rats received immediate treatment with either periurethral or systemic injection of either 0.1mL hMSCs (10^7 cells/mL) or 0.1 mL normal saline. Either 4, 10, or 14 days after surgery, leak point pressure (LPP) was measured in animals via an implanted suprapubic tube. LPP was also measured in 11 control rats that did not undergo VD or treatment. The mean of 8-11 LPP measurements per rat was calculated, and the level of significance between groups was determined using a two-tailed unpaired t-test assuming equal variance and ANOVA with a post-hoc Tukey test, $P < 0.05$.

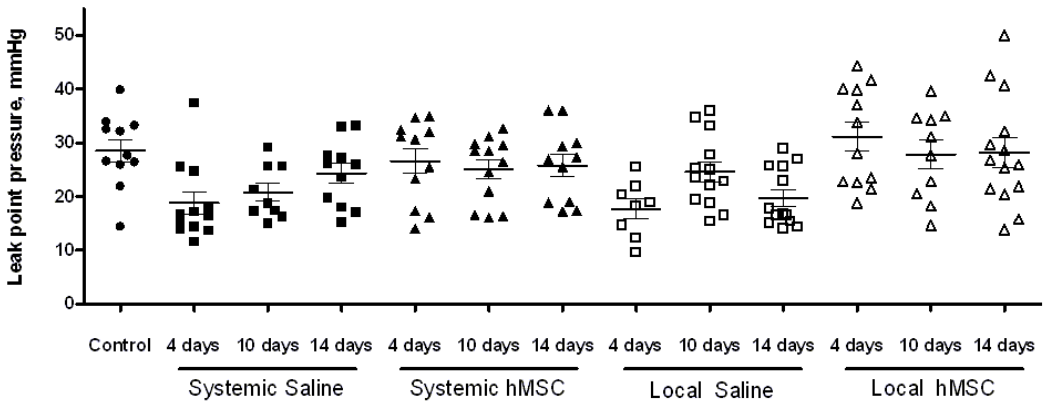
Results

Mean LPP in rats treated systemically with saline (18.82 and 20.77 mmHg; $P \leq 0.01$), but not hMSCs (26.57 and 27.84 mmHg; $P=0.53$ and $P=0.21$), after VD were significantly different compared with controls rats (28.56 mmHg) at 4 and 10 days, respectively. By day 14, LPP in rats treated with systemic saline after VD showed recovery of continence as is expected in VD model ($P=0.14$), and LPP in rats treated with systemic hMSCs remained similar compared with controls ($P=0.36$).

Rats treated with periurethral injection of hMSCs after VD demonstrated mean LPP similar to control rats at 4, 10, and 14 days ($P= 0.46, 0.83, 0.92$). Periurethral injection with saline at 4 and 14 days yielded mean LPP significantly lower than that in control rats ($p<0.01$ at 4 and 14 days). In this group, there was no statistically significant difference in mean LPP vs. control at 10 days ($p=0.17$).

Interpretation of results

Bone marrow-derived hMSCs injected systemically or periurethrally restore the continence mechanism with an immediate and sustained effect in this murine model for SUI. Treatment with saline yields an expected gradual return to continence only with systemic treatment after 14 days, though continent rats were also observed 10 days after periurethral saline injection, perhaps as a result of a local inflammatory response.



Concluding message

Bone marrow-derived hMSCs delivered either systemically or periurethrally demonstrate ability restore the continence mechanism with an immediate and sustained effect in this murine model for SUI and may hold promise for future investigations into clinical treatment of SUI in women.

References
1. Lin AS, Carrier S, Morgan DM, Lue TF: Effect of simulated birth trauma on the urinary continence mechanism in the rat. Urology 52:143-51, 1998.

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What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**IACUC #2010-0120**