Sustained anal pressure improvement after anal sphincter injury and serial IV infusions suggests homing of mesenchymal stem cells.

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Introduction

Damage to the anal sphincter during delivery of children can lead to fecal incontinence, a condition that is devastating to quality of life. Stem cells have the potential to facilitate recovery from this damage and treat or prevent fecal incontinence. Intravenous (IV) delivery of stem cells may provide a less invasive delivery route if they home to areas of injury and facilitate recovery. The hypothesis of this study was that mesenchymal stem cells (MSC) will home to the injured anal sphincter and facilitate restoration of continence. We tested the hypothesis by comparing functional and anatomic outcomes of intramuscular (IM) (direct injection-single dose) and IV administration of MSC’s in an animal model of anal sphincter injury.

Method

Forty five virgin rats were divided into injury (n=35) and no injury (NI<n=10) groups. The injury group was divided into saline PBS or MSC treatment and a control group (n=5) which received no treatment. Each treatment group was further divided into IM and serial IV (n=5) group. The MSC: IM and IV (n=5) and control groups were followed up for 5 weeks. The injury was a partial anal sphincter excision (PSE) of 25% of the anal sphincter (both internal and external). Anal pressures were recorded prior to, 10 days and 5 weeks after treatment with a balloon connected to a digital recorder as per our previous model[1]. 24 hours after injury[2], the animals received 5x10^6 labeled MSC or 0.2ml saline into the anal sphincter for IM treatment, while IV treatment group received the same dose daily for 6 consecutive days via the tail vein. Anal sphincters were harvested and submitted for Masson’s staining.

Results

Direct injection (IM) treatment group

10 Ten days after IM treatment, significant increase in resting (P<0.001) and peak pressures (P<0.001) was seen compared to PBS after injury. (9.78±0.84, 13.13±1.2, respectively) vs. (6.23±0.48, 8.32±0.64, respectively). When compared with the NI group and MSC treatment, recovery of the anal pressures did not reach pre-injury levels (resting (P=0.04) and peak pressures (P=0.02).

IV infusion treatment group

The IV infusion group showed significantly increased resting (P<0.001) and peak pressures (P<0.001) in MSC treated animals compared with PBS (11.03±0.71, 16.68±1.33, respectively) vs. (6.94±0.28, 8.56±0.34, respectively) after injury. However recovery was complete (reaching pre-injury levels) and no significant difference was seen in the resting pressures when compared to NI group.

Results at 5 weeks

At 5 weeks after IM treatment significant peak pressures (P=<0.001) after MSC treatment were seen compared to NI group. However, after IV treatment significant resting (P=0.01) and peak pressures (P=<0.001) were seen compared to NI group. Marked decrease in fibrosis and scar tissue was seen in the MSC treated group.

Interpretation of Results

Anal sphincter pressures declined after PSE with PBS treatment. Ten days after treatment with MSC via either IM or IV routes, anal pressures increased significantly with a greater increase after IV infusion. Five weeks after PSE and MSC IV treatment, anal pressures remained significantly high compared to a PSE group that received no treatment. Histology demonstrated that the process of healing is by fibrosis, which is markedly reduced in the IV infusion group that received MSC.

Conclusion

Although direct injection (IM) of MSC into the anal sphincter muscle after injury facilitates an increase in anal pressures, it is not sustained 5 weeks later to the same extent as after treatment with IV infusion. Healing is by fibrosis in the PBS treated animals while the MSC treated groups showed less scarring, particularly after IV infusion of MSC. IV infusion appeared to confer more benefit than a single IM injection of MSC in the anal sphincter muscle. This may be due to the greater number of cells utilized and greater duration of treatment in the IV infused group. This study suggests the potential effectiveness of a clinical study utilizing multiple IV infusions of MSC after anal sphincter injury.

Reference
