

Transplantation of muscle-derived stem cell plus fibrin glue restores urethral function in a pudendal nerve-transected rat model.

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Abstract:

Hypothesis / aims of study: Most muscle-derived cell(MDC) regenerative approaches can restore injured urethral rhabdosphincter. In this study, we investigated if fibrin glue(FG) could improve muscle-derived stem cells(MDSCs) restore urethral function in a pudendal nervetransected rat model. Study design, materials and methods: The pudendal nerve-transected adult female SPF Wistar rats were used to make stress urinary incontinence models. The gastrocnemius muscles of normal three-week-old female SPF Wistar rats were used for the purification of the muscle-derived stem cells. The animals were randomized into five recipient groups: normal (N),denervated (D), denervated+Fibrin Glueinjected rats(F), denervated +MDSCs-injected rats(M),.and denervated +MDSCs+FibrinGlue-injected rats(FM). Each group (n = 10) was also split into two subgroups according to the time; 1 week (n = 5) and 4 weeks (n = 5). In the F, M, FM groups injection of FG and/ or MDSCs was made into the proximal urethra two weeks after pudendal nerve transection. One and four weeks after transplantation , leak point pressure (LPP) and closing pressure(CP) were used to assess urethral rhabdosphincter function. PGC-FU-GFP-Lentivirus was performed to infect MDSCs to track the implantation and immunohistochemical staining was used to detect the neovasculature formation at four week after transplantation. Results: Both LPP and CP were lower in D group at each time compared with those of N, F, M and FM groups ($P<0.05$).Both LPP and CP in the F group were slightly higher than those of D group after one week ($P<0.05$) but no difference between the two groups after four weeks($P>0.05$). Both LPP and CP in FM as well as M groups were slightly higher than those of D group at one week($P<0.05$) and significantly at four

weeks($P<0.001$) but no difference compared with those of N group at each time ($P>0.05$). Both LPP and CP in FM group were slightly higher than M group but no difference between the two groups at each time ($P>0.05$). After four weeks, pathological examination indicated that transplanted MDSCs in FM group survived better than those in M group and neovasculature density increased significantly in FM group and slightly in F and M group. Interpretation of results: In this study, it was seen that LPP and CP in the F group increased slightly at one week but decreased at 4 weeks. The reduction in volume of Fibrin glue (FG) which acted as a bulking agent induced the declining tendency of LPP and CP. It was found that both the LPP and CP in FM as well as M groups were shown increasing tendency with the time and even equalled to those of N group. Both the LPP and CP in the D group decreased significantly with time. It was also seen that there were more survival transplanted MDSCs and higher neovasculature density in injected area in FM group as compared to those in M group. To explain the results, FG, a composite of fibrinogen and thrombin, is a potentially suitable biological vehicle for cell transplantation because it has proven biocompatibility, biodegradability and binding capacity to cells. Fibrin-stabilizing factor XIII contained in fibrin glue favors migration of undifferentiated stem cells on the highly cross-linked structure of the glue, and it enhances the proliferation of these cells¹. This keeps the cells in place, increases cell survival, and improves the immediate mechanical properties of the implant. The fibrin extracellular matrix remains in situ while the cells proliferate and differentiate into new tissue, before the scaffold is completely resorbed. Most important of all, the fibrin glue promotes angiogenesis via chemotactic and mitogenic stimuli that promote cell migration, proliferation and matrix synthesis^{2, 3}. Concluding message: Fibrin glue can improve transplanted muscle-derived stem cell survival in the injected area, induce neovasculature formation and improve urethral rhabdosphincter function greatly in SUI rat models.