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The convergence effect of medical industry through stem cell implant treatment

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줄기 세포 이식 치료를 통한 의료 산업적 융합효과

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Abstract Our experiment studied that grafted stem cells reduced behavioral deficiency in rodent animal models of clip compressive surgery inducing spinal cord infarction. Our research proved the effect of embryonic stem cells to the spinal cord infarction caused by compressing T9-10 with an aneurysm clip, focusing the application of grafted stem cells for reduction of infarction and regeneration of spinal cord nervous injury. Therefore, our research suggests manifest results that implantation of mouse embryonic stem cell could show behavioral improvement after severe spinal cord damage. Therefore, mouse embryonic stem cell (mESC) could be useful application for the method in neurological injury. Conclusively, stem cell implant therapy may enhance the effectiveness of stem cell implant for central nervous system injury.

Key Words : Clip-compression surgery, Spinal cord, Infarction, Implantation, Embryonic stem cell

요 약 본 연구는 이식된 줄기세포들이 혈관용 클립압박으로 유도된 척수경색 동물들에서 행동학적 결핍을 감소시키는 연구를 진행하였다. 흉수신경 9번과 10번에 척수 손상후 5일후에 배아줄기세포 이식을 통해서 배아줄기세포가 경색부위를 채워지게 되므로 이식후 손상부위의 조직학적 감소와 신경세포군의 조직학적 재생을 증명하는데 중점을 두었다. 본 연구를 통해 마우스 배아줄기세포의 이식이 중증 척수 손상후 행동학적 발달을 보여주는 명백한 결과들을 도출하였음을 보여주고 있다. 이러한 마우스 배아줄기세포는 신경학적 손상에 대한 치료로서 사용될 수 있는 처치법이다. 결론적으로, 줄기세포 적용은 손상조직을 재생시켜서 기능적, 행동적 향상에 기여할 수 있기에 다양한 줄기세포 치료법을 통해 임상적 적용을 위한 중요한 치료법이 될 수 있다.

주제어 : 클립압박수술, 척수, 경색, 이식, 배아줄기세포

1. INTRODUCTION

It had been reported that damaged nerve applied as grafted cell insertion into an infarction area inducing from a clip compression damage of the spinal cord, enhances motor & behavioral function in injured rats[1,2]. Various trial of cell transplant has been showed to enhance after spinal cord damage. Previous studies in animal models of Spinal cord injury have been studied that implanted stem cell could survive well in the damaged spinal cord, reduce the cavitation formation and combined with the host spinal cord[3,4].

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It has been revealed that grafted stem cell enhances functional motor ability and activates the excitability of motor nervous system[5]. Following Central nervous system damages, many molecules such as inflammatory factors, specific cell signal pathway, and growth factors could be related to strongly cell regeneration in central nervous system[6]. It has been reported that spinal cord injuries, many molecular factors such as inflammatory cytokines, immune related proteins, and growth factors may contribute strongly to influence stem cell regeneration[7]. A current clinical application has been developing to successful stem cell transplant and positive neurological condition. Many studies suggest being a particularly clinical method to enhancing motor function after spinal cord injury[8,9]. The present study examines whether mESC survive and integrate into the host tissues of the injured spinal cord and whether mESC ameliorate neurological deficits in rats with ischemic spinal cord injury. mESC transplant induced suppression of cavity formation and improved motor function.

2. MATERIALS AND METHODS

2.1 Spinal cord injury experiment

Male SD rats were tested for this research (150-220 g, n=30). This experiment was approved by the animal committee with policies of Namseoul university. We safely anesthetized with an i.p. insertion of pentobarbital sodium solution (30 mg/kg of total body weight). The animal surgery was treated under sterile conditions with safe experimental environment. The clip compression damage was applied to the site of the 9th to 10th thoracic spinal cord by exposing lamina. The vascular clip was been applied to spinal region in animal models. Swelling urinary bladder was emptied by abdominal region pressure at three times daily. The animals were separated into a non-transplant group and a cell-transplant group. The transplant group was administrated with mouse embryonic stem cell(mESC) at 5-day post injury.

2.2 Implantation methods

The non-transplanted group (n=10) was tested to evaluate if solution amount (20 μl) or implantation processing triggered specific locomotor differences in spinal cord injury rats. Non-transplanted control group was applied to spinal cord injury and administration of PBS (20 μl). There was no motor damage in injured rats caused by the insertion processing. Animals were injected with mESC implantation at the 5th day after injured surgery (n=20). Transplantation group was fully tested in animals (n=20) with Basso-Beattie-Breshahan (BBB) test of below 2 score (0 through 20) s at the 5th day after damage. The rest animals with BBB scores below 2, non-implant group (n=10), had occurred spontaneous rehabilitation in locomotor testing for 5 weeks period. A micro-injection was applied to graft intra-cellular amount (1 x 107cells) of cell solution (20μl) using a 40-gauge needle on a 30 μl syringe linked on a micormanipulator. The 20 μl volume of cell suspension was injected into the injury site or near the damage lesion.

2.3 Behavioral characteristics

Experimental animals were trained to have an adjustment of the environment for one week before the trial onset of locomotor testing. The experimental day before & after the injury, motor assessment was maintained using the generalized locomotor testing rating scale[10]. Motor function testing was evaluated by a 30-min acclimation time daily for the 36-day period of the experiment.

2.4 Histological difference

All group rats have given intra-transcardially perfusion. Serial longitudinal sections (10 μm thick) were separated and each spinal cord section was treated with hematoxylin & eosin staining. Sections were also used for toluidine blue-stained, 10-μm thick plastic sections. The entire region of infarction was

examined virtually and stained to distinguish the correct region of the infarction. The each section in the rostral and caudal positions of the infarction region was prepared under at 40x, 100x and 200x image through electron microscopy with H-E staining for a visual difference of cavitation.

2.5 Statistical analyses

All histological values were used to determine the overall comparison both control and experimental group at each point following injury.

3. RESULTS

3.1 Cavity differences

Control group rats with locomotor testing score less than 8 point showed the type of large cavitation morphology in Fig. 1 The infarction size of cell-grafted group animals had cavities much smaller than the cavitation of control group animals in Fig. 1 The morphological characteristics postulated that cell-grafting could reduce the size of cavities after damage in the infarction rodent models.

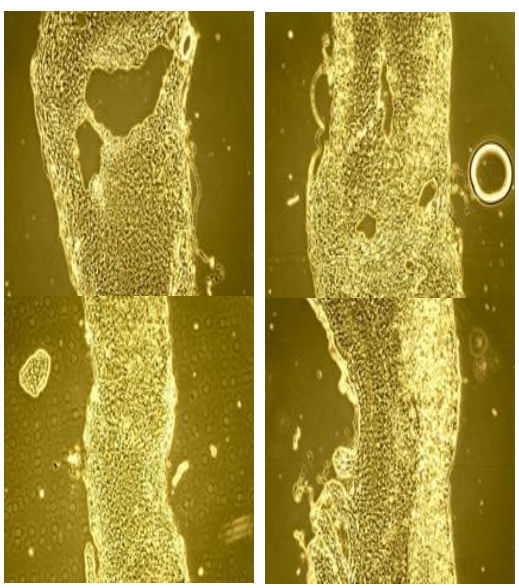

Fig. 1. Non-implant animals with BBB test scores less than 8 showed the formation of large cavities & disconnection. The spinal cord of transplant animals had cavities much smaller than the cavity situation of non-implant animals.
(Upper: non-transplant animal, Lower: transplant animal)

3.2 Transplanted cell survival

The injury site was characterized by a large injured area of cavitation with a rim of preserved white matter. Fig. 2 contained numerous regeneration axons as well as many degenerating cells, and glia including Schwann cells. Electron microscopy showed the presence of various cell types.

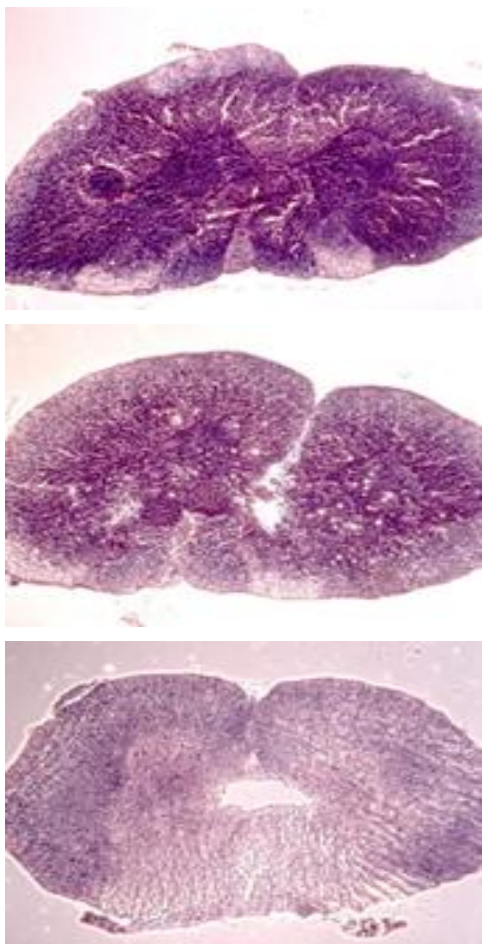

Fig. 2. Schwann cell & glia cell contain numerous myelinated axons in the middle of the graft. All sections show toluidine blue-stained, 10-μm thick plastic sections. (100X magnification)

4. DISCUSSION

Our research has demonstrated that the result of intra-cellular implantation in the damaged animal spinal cord site is proved to an effective & significant enhancement in the BBB scale scores. Functional locomotive movement of the implanted group animals could be proved by a greater survival of regenerative axonal formation in the injured site. Previous studies strongly suggested that implanted cell survival resulted by significant reduction of neuronal cavitation tissue may facilitate motor and functional recovery[5]. The various present studies have demonstrated that the effect of cell transplant in the injured rat spinal cord is evidenced by significant improvement in the locomotive function[10]. Alternatively, local axonal regeneration accompanied by significant reduction of necrotic cavitation may facilitate functional recovery[11]. It has been reported that reduction of cavity formation after spinal cord injury has been also experimented by graft of bone marrow stromal cells and neural progenitor cells (NPCs)/neural stem cells (NSCs) [12,13]. The functional benefits observed in the transplant rats may not be due to the differentiation of stem cell in the injured tissue, but due to the production of trophic factors beneficial to the nervous tissue including neurons and astrocytes[14,15].

5. CONCLUSION

The motor functional benefit was revealed in stem cell implant treatment, showing better functional performance than control group. Long term research may be demanded to prove the maintenance of the histological and locomotive effect of stem cell implant. This experimental study of the treatment of central nervous system damage by broadening the scope of existing stem cell therapies can bring about the future development of the medical industry and the improvement of treatment methods. Stem cell therapy is used for close collaboration with biology, biochemistry, medicine, bioengineering, and biomedical fields in the aspect of industrial convergence of all related medical areas. It can be actively applied to breakthrough clinical patient treatment and medical development. The result in this study suggested that grated stem cell method may be strongly recommended to apply to clinical patients that have the neurological spinal damage.

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