Efficiency and Safety Assessment of 50 Tissue Engineering Surgeries in Spinal Cord

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Introduction. Different methods have been offered to restore spinal cord (SC) after the injury through tissue engineering (TE) [1, 2, 3, 4, 5]. Our approach is based on neurorestoration of SC by an equivalent of artificial neural tissue (ANT) composed of biodegradable polymer matrix (BDPM) Sphero®Gel™ with autologous progenitor cell systems. The goal of the study was to evaluate efficiency and safety of proposed SC TE in clinic.

Methods. One hundred five patients with severe chronic spinal cord injury (SCI) participated in open randomized longitudinal (7 years) trial. The trial followed IMITE international protocol. Main inclusion criteria: 1) no less than 3 years post injury period; 2) SCI lesion should be over 50% crosswise and no less than 1 SC segment longwise. Two patients with severed SC were included into the trial. The trial consisted of three groups: 1-st (control) group – 25 patients, who received conventional surgical intervention (CSI), i.e. orthopedic correction of spinal injury, decompression of SC, myeloradiculolysis, opening and drainage of SC cyst; 2-nd (main) group – 50 patients, who received CSI with implantation of ANT equivalent into SC lesion; 3-d (additional) group of 30 patients received CSI and intrathecal infusions (ITI) of peripheral blood mobilized hematopoietic (CD34+,CD45-) stem cells (PBHSC) in the dose of $5x10^9$ in 0.5-1 mcl of 0,9% NaCl solution (ITI every 3 months for 3 years). ANT equivalent was received by infusion of autologous cell preparations into BDPM Sphero®Gel™ (biodegradation period: 10-12 months, final biodegradation products are CO_2 and H_2O; approved for clinical application in the Russian Federation). Stem cells of bone marrow were mobilized through standard 4 days stimulation of hematopoiesis by G-CSF followed by leukapheresis, separation of endothelial cell (EnC) and PBHSC and cryopreservation. Olfactory ensheathing cells (OEC) and neural stem cells (NSC) were received from olfactory nasal sheath by culturing [6]. 1ml of BDPM Sphero®Gel™ was infused with cell suspension at a ratio of 1:2:5:500 ($1x10^6$ NSC, $2x10^6$ OEC culture, $5x10^6$ EnC culture with CD34+ marker and $5x10^9$ PBHSC with CD34+CD45- markers). Biopolymer membrane *ElastoPOB*® isolated implanted ANT equivalent from CSF. Main stages of standard TE surgery in SC are shown at Fig. 1.

A B

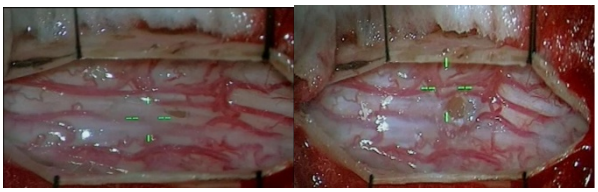

Figure 1. SC TE for patient D., SCI on C5-C6 level: A – the SC cyst is opened and drained; B – SC after ANT equivalent implantation.

Results. Evaluation of clinical manifestations and post-operative assessment by ASIA and FIM as well as long-term follow up showed 64% efficiency rate in the patients of 2-nd group. Efficiency rate in 1-st and 3-d groups was 8% and 36.7%, respectively. Motor function appeared and partially restored in 15 (30%) patients of 2-nd group, various types of sensation restored in 35 (70%) patients, bowel and bladder function restored in 35 (70%) patients, and 3 (14%) began to walk with walkers and crutches. Electroneuromyography with somatosensory evoked potentials showed valid ($p<0.05$) improvement of nerve impulse conductance through SCI site in 2-nd group patients. Complex urodynamic tests confirmed restoration of bowel and bladder functions in 2-nd and 3-d group. No restoration of motor and bowel and bladder functions was registered in 1-st group patients. No objective data confirmed motor functions restoration in 2 patients with severed SC, but one restored bowel and bladder functions. Results manifested mostly 18-36 months post TE surgery and improved after neurorehabilitation. Safety was confirmed by long-term (7 years) follow-up, immunochemical monitoring of neurospecific proteins and their antibodies in CSF and blood, annual CT and MRI of brain and spinal cord.

A B C

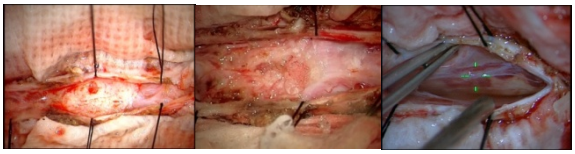

Figure 2. SC of Patient S. during TE surgery, C5-C6, 2007. A) Cicatrical degeneration, calcification; B) SC after calcification removal, meningoradiculolysis and ANT equivalent implantation; C) SC during resurgery in 2009, same level – complete restoration of anatomy, blood supply and nerve conductance.

Discussion and Conclusions. TE of SC is a surgery of choice for severe morphological defects after SCI. All complications resulted from insufficient specific preparation of neurosurgeons, but not from the quality of applied cell and polymer materials. No cases of tumor development in brain, spinal cord or internal organs have been registered. Hence restoration of anatomical structure and neurophysiological properties of SC by TE is proved implementable (Fig.2). Yet, functional restoration after severe SCI present a challenge being often limited by severe concomittant diseases associated with SCI: axonal demyelinating polyneuropathy, gross defects of locomotor system (muscle and joints degeneration), atrophic colitis, organic kidney and bladder dysfunction etc.

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