Autologous Bone Marrow Transplantation for Muscle Improvement in Brachial Plexus Patients. Preliminary Results of a Phase-1 Clinical Study

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Introduction: Traumatic brachial plexus (BP) injuries can cause severe loss of elbow flexion (C6) [1]. After nerve surgery, partial muscle reinnervation is possible, but active elbow flexion often remains insufficient. For these patients, muscle strength improvement via cell therapy would represent a tremendous improvement in their treatment and could avoid extensive secondary muscle transfer surgery. Long-term denervation causes irreversible muscle atrophy, interstitial fibrosis and fattening of the muscle. In addition, a decline in number of myogenic precursor cells (satellite cells) is seen [2]. Transplantation of satellite cells has been shown to increase muscle force in rabbits [3]. In humans, transplantation of the mononuclear cell (MNC) fraction of the adult bone marrow (BM) has increased muscle function in peripheral artery disease [4]. The goal of the study was to improve muscle quality of partially reinnervated biceps muscles by autologous BM-derived MNC transplantation.

Materials and Methods: Fifteen adult BP patients with insufficient force recovery of the biceps muscle (MRC 1, 2, 3) are included. The amount of aspirated BM and injected MNC dose per patients group is presented in Table 1. The transplantation was combined with or without a Steindler flexorplasty (tendon transfer surgery). MNCs were transplanted percutaneously into the biceps muscle. Prior to and 3 months after transplantation, a biopsy of the biceps muscle was taken. Muscle morphology was assessed (e.g. fibrosis, fatty degeneration) on at least 10 microscopic images. The diameters of at least 200 myofibers were measured (ImageJ, version 1.37).

Results: Up till now, 8 patients have been treated. In none of the patients adverse effects were noted. Postoperatively, the mean decrease in hemoglobin (Hb) concentration was 0.3 (group A), 1.6 (group B) and 2.8 (group C) g/dl. Six months after transplantation, the Hb concentration normalized in all patients. As compared to the preoperative muscle biopsy, no signs of increased interstitial fibrosis or muscle fattening were noted. The distribution of myofiber diameters of biceps muscles is presented in Figure 1. The preoperative biopsy of patient 2 had insufficient myofibers and was excluded. A significant difference was found between the mean myofiber diameter before and after transplantation in group B (p = 0.03, paired-t-test). In contrast, no difference in the mean myofiber diameter before and after transplantation could be detected in group A and C. Figure 2 shows an example of a hematoxylin-and-eosin staining of a muscle biopsy in group B (patient 6). Prior to the transplantation, a difference in the diameters of the individual myofibers was noted. Three months after the transplantation, the diameters of the myofibers were more equally distributed (Figure 2).

Discussion: This is the first study to use autologous BM-derived MNC transplantation for muscle improvement in orthopaedic patients. No negative side effects were noted. A decrease in Hb concentration was anticipated, but had no negative side effects. Long-term denervated muscles demonstrated a decrease in myofiber diameter [2]. In our study, a significant increase in the myofiber diameter following transplantation was observed in group B. In contrast, an increase could not be detected in group A and C. The MNC dose applied in group B could represent the optimal cell dose to ameliorate muscle atrophy. Whether the transplantation increased the number of satellite cells, or paracrine effects of the injected BM cells are responsible for the increase in myofiber diameter is currently under investigation. Our data suggest that autologous BM-derived MNC transplantation may help treat muscle atrophy in partially denervated muscle of BP patients.