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Chapter 9

Discussion

SUMMARY AND RECOMMENDATIONS FOR FUTURE RESEARCH

Functional level

The aim of this thesis is to evaluate determinants of outcome, which will have an effect on overall functionality of the patient with an OBPI. Symptoms of OBPI vary widely over the course of time and from individual to individual and are related to various degrees of denervation, muscle weakness, contractures and bone deformities with their subsequent functional limitations. To date, no universally accepted overall framework is available to assess the outcome of patients with OBPI. At the functional level, the developmental process of outcome measures using the ICF is described (chapter 2). The first step is to conduct four preparatory studies to identify ICF categories important for OBPI: a) a systematic literature review to identify outcome measures, b) a qualitative study using focus groups, c) an expert survey and d) a cross-sectional, multicentre study. The proposed method to develop ICF Core Sets for OBPI yields a practical tool for multiple purposes: for clinicians to systematically assess and evaluate the individual's functioning, for researchers to design and compare studies, and for patients to get more insight into their health problems and their management.

Clinical level

At the clinical level, impaired muscles and joint deformities and their treatment options are addressed. Long-term denervation results in muscle degeneration including muscle atrophy, fatty degeneration and interstitial fibrosis in the muscle. Assessment of contractile CSA might yield valuable insight in pathophysiology and might be used to predict the outcome of conservative and surgical procedures. Volumes of interest were manually drawn on MRI scans by two independent observers to calculate the percentage of muscle fat, the total CSA and the contractile CSA in both the sound and the injured upper extremity in patients with a traumatic BPI (chapter 3). The contractile CSA showed the highest association with active flexion and muscle force compared to fat percentage and total CSA. The mean contractile CSA was lower in the affected biceps brachii 8 cm^2 (SD 5.1) compared to a mean of 19 cm^2 (SD 4.9) in the non-affected biceps brachii ($p < 0.001$) with an excellent inter-observer reliability (ICC 0.88). The contractile CSA of the affected biceps brachii was associated with active elbow flexion with an estimate of 7.1 °, 95 % CI 2.8 to 11.5, $p = 0.003$), i.e. an increase of 1.0 cm^2 of contractile CSA results in an increase of 7.1 ° active elbow flexion. The contractile CSA of the affected biceps brachii was associated with muscle strength in MRC with an odds ratio of 2.6 (95 % CI 1.1 to 6.1, $p = 0.029$). One cm^2 increase in contractile CSA of the affected biceps brachii was associated with an increase of 13 Newton muscle force (95 % CI 8.9 to 17.1, $p < 0.001$).

The effect of serial casting on elbow flexion contractures in OBPI was evaluated (chapter 4). A prospective consecutive cohort study was performed with a median of 5-year follow-up. Forty-one patients with elbow flexion contractures ≥ 30° were treated with serial casting for a maximum of 8 weeks until the flexion contracture was ≤ 10 °. Serial casting improved elbow flexion contractures with an increase of passive extension from a median -40 ° (IQR -50 to -30) before casting to -15 ° (IQR -10 to -20, $p < 0.001$) after casting. Recurrences were frequently observed. Overall, twenty (49 %) patients showed thirty-seven recurrences. The severity of elbow flexion contracture was only a small predictor for recurrent elbow flexion contracture with a hazard ratio of 0.93 (95 % CI 0.89 to 0.96, $p < 0.001$).

The effect of botulinum toxin A (BTX-A) injection in the subscapular muscle in patients with internal rotation contracture was evaluated using the external rotation and the need for tendon transfer for external rotation as outcome (chapter 5). A prospective comparative study was performed including 15 consecutive patients treated with BTX-A (2 IU/kg body weight) under general anaesthesia and a historic control group of 67 patients with mean age 30 months (SD 10). BTX-A injection in the subscapular muscle increased the passive external rotation in adduction from -1 ° (95 % CI -10 to 8) to 32 ° (95 % CI 17 to 46) at 3 months. BTX-A injection also reduced the need for tendon transfer surgery as 6 patients were indicated for surgery in the BTX-A group compared to 66 in the control group. At 5 years follow-up, 10 patients in the BTX-A group were indicated for surgery with a hazard ratio of 4.0 (95 % CI 1.9 to 8.4).

Cellular level

Finally at the cellular level, muscle degeneration is characterized in both inflammation (rheumatoid-RA) and osteoarthritis (OA) as well as in denervated muscles. In the latter group, also cell therapy is explored as a treatment option. The effect of chronic inflammation compared to non-inflammatory muscles around the knee joint on the regenerative potential of satellite cells in human muscle was studied (chapter 6, 7). As a model for chronic inflammation, muscle biopsies form 16 patients suffering from osteoarthritis were compared to 11 patients suffering from rheumatoid arthritis. Histological characteristics showed no significant differences in type II muscle fiber atrophy, lipofuscin accumulation, or satellite cell number in RA compared to OA patients. After mononuclear cell explantation, myogenic purity, viability, proliferation index, number of colonies, myogenic colonies, growth speed, maximum number of population doublings and fusion index were not different between RA and OA patients. Furthermore, the expression of proteins involved in replicative and stress-induced premature senescence and apoptosis, including p16, p21, p53, hTERT and cleaved caspase-3, was not different

between OA and RA patients. Mean telomere length was shorter in the RA group compared to the OA group. In conclusion, chronic inflammation in RA does not affect the *in vitro* regenerative potential of human satellite cells.

A pilot study is described to assess the safety and regenerative potential of autologous bone marrow-derived mononuclear cell injection in a partially denervated biceps muscle of BPI patients (chapter 8). Nine adult traumatic BPI patients with insufficient active elbow flexion received intramuscular escalating doses of autologous bone marrow-derived mononuclear cells, combined with an elbow flexorpronator group transfer (Steindler procedure). Mononuclear cell injection in a partially denervated biceps muscle of these brachial plexus patients was safe and showed no adverse effects on vital signs, bone marrow aspiration sites, injection sites, or surgical wound. Results suggest enhanced muscle regeneration with a 52 % decrease in muscle fibrosis ($p = 0.01$), an 80 % increase in myofiber diameter ($p = 0.007$), a 50 % increase in satellite cells ($p = 0.045$) and an 83 % increase in capillary-to-myofiber ratio ($p < 0.001$) was shown. CT analysis demonstrated a 48 % decrease in mean muscle density ($p = 0.009$). Motor unit analysis showed a mean increase of 36 % in motor unit amplitude ($p = 0.045$), 22 % increase in duration ($p = 0.005$) and 29 % increase in number of phases ($p = 0.002$).

Recommendations for future research

At the functional level, studies on the evaluation of OBPI show high variability between the used outcome variables. Children with OBPI experience difficulties in all areas of functioning, as well as in both environmental and personal factors [1]. These results underscore the need for the development and use of outcome variables representing all domains of health status in these patients. Future research should include the evaluation of functionality problems in OBPI patients with an expert survey and a cross-sectional, multicentre study. The latter was recently done at our institution in 1000 Patients (ZAP-Plexus www.zenuwcentrum.org). As for the definition of valid functionality outcome scores for OBPI, a first version of ICF Core Sets should be defined at a Delphi conference to integrate the evidence from the preparatory studies. In a second step, field-testing among patients should validate this first version of Core Sets for OBPI. In the future, standardised ICF Core Sets will not only be useful for research, but also in the important shared decision making process between patient and physician. Eventually these ICF data can be used to quantify the severity of OBPI and compare them between patient groups and even medical centers, to improve decision making in the clinical settings.

A result of muscle degeneration includes the development of contractures including elbow flexion contractures and internal rotation contractures around the shoulder, both affecting functionality. Future research should gain more

insight into the underlying factors of contractures including muscle imbalance, reduced longitudinal muscle growth, capsular fibrosis and posture which could reveal possible treatment strategies [2-6]. To unravel the impaired movement, the combination of a haptic manipulator and surface EMG could be use to discriminate neural (active and reflexive) and non-neural contributors (passive muscle and connective tissue properties) [7]. Muscle degeneration as reflected by both muscle atrophy and fatty degeneration can be quantified using three-point Dixon MRI with an excellent reproducibility. Contractile CSA was significantly associated with active muscle flexion force. Future research should determine whether quantitative measurement of muscle degeneration could predict the outcome of conservative and surgical procedures. Case reports on posterior shoulder dislocation at young age have been described before, suggesting direct trauma at birth as a cause of the dislocation [8-11], which is contradictory to observations at successive MRI's in our clinic [12]. However, at outdoor clinics the awareness of the occurrence of potential contractures should be recognised at the shoulder (internal rotation and abduction contractures) and at the elbow (flexion and supination contractures). Therefore, specialised multidisciplinary clinics (the Dutch model), involving neurosurgeons, orthopaedic surgeons, rehabilitation physicians as well as physiotherapists and ergo therapists are necessary for optimal care of the patients and their family.

At the cellular level, muscle regeneration has potential despite the partial denervation [13, 14]. Cell therapy can be a therapeutic option to replenish the exhausted satellite cell pool. Future research should focus on the identification of mechanisms influencing muscle regeneration by modulation of its microenvironment to improve strategies for muscle regeneration. Furthermore, future research should determine whether a combination of nerve repair en muscle regeneration could be effective. Animal models are available to identify mechanisms for nerve repair and muscle regeneration in BPI [5, 15, 16].

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