Chapter 1

Introduction

1

INTRODUCTION

Brachial plexus injury

A brachial plexus injury (BPI) is caused by traction on the brachial plexus during delivery or due to a high-energy road traffic accident in young adults [1, 2]. Multiple synonyms are used for an obstetric brachial plexus injury (OBPI), including neonatal, congenital and perinatal brachial plexus palsy. However OBPI is the most preferred terminology in Europe and is therefore used in this thesis [3]. The incidence of an OBPI during delivery varies between 0.4 and 2.9 per 1000 live births [4-6]. The upper part of the brachial plexus (C5,C6) is most often affected, resulting in variable weakness of active shoulder and elbow flexion movements [7]. Elbow extension, wrist and hand function are additionally impaired when the C7, C8, T1, medial trunk and inferior trunk are involved. An isolated injury of the lower brachial plexus (C8-T1) is rare.

The first focus for therapy is on the type of injury of the peripheral nerve, for that matter, to the severity of the traction injury which may extend from minimal (axonotmesis) to severe (neurotmesis and avulsion) traction, as addressed in previous theses [8, 9]. However, little attention has been paid to the effects on the end organ of the nerve: the muscle and its sequelae on functionality for the patient. A large variety of outcome measures have been used to evaluate the natural history and the effect of treatment, however there is no consensus on which outcome measures are the most appropriate [10, 11]. The International Classification of Functioning, Disability and Health (ICF) is a worldwide accepted model providing a universal language for the description of functioning and includes the domains Body Structures, Body Functions, Activities and Participation as well as Personal and Environmental Factors [12]. ICF Core Sets are generally used to describe the typical spectrum of problems of functioning and health patients with a specific condition (e.g. brachial plexus injury). An important base for the optimal management of OBPI is an in-depth understanding, systematic consideration and sound measurement of the impact of OBPI on health and health-related domains of these patients. To date however, no universally accepted overall framework is available to assess the outcome of patients with (obstetric) BPI.

Muscle degeneration

Long-term denervation results in muscle degeneration including muscle atrophy, fatty degeneration and interstitial fibrosis in the muscle. Current literature on muscle degeneration in the upper extremity of BPI only focuses on total muscle cross sectional area (CSA) and on a qualitative assessment of muscle fatty degeneration including the Goutallier score as a surrogate for contractile CSA, which is the true functional part of the muscle [13-20]. The inter-observer

reliability of the Goutallier score is moderate even in experienced hands [21, 22]. Furthermore, qualitative assessment of fatty degeneration is less sensitive in detecting small differences [23 24, 25]. Quantitative measurements which assess the decrease in contractile CSA compared to the sound extremity could improve insight in the extent of muscle degeneration and would thus facilitate a better treatment strategy.

Muscle denervation and subsequent muscle degeneration results in functional limitations, contractures and osseous deformities. With respect to the elbow, the main complication occurring during follow-up is a flexion contracture, with a prevalence of 50 to 90% [26, 27]. Flexion contractures limited to 10° to 30° can be treated by range of motion exercises and nighttime splinting. In a minority of cases, however, if the contracture exceeds 30°, additional treatment is needed such as serial casting [26, 27]. Although serial casting is frequently applied and globally considered to be the preferred therapy, literature is limited on the effect of stretching by serial casting for elbow contractures. Other clinical consequences of muscle degeneration around the elbow include supination contractures and limited active elbow flexion for which surgical procedures are being performed including forearm osteotomies, biceps rerouting and Steindler elbow flexorplasty [28-33].

Around the shoulder, muscle degeneration often results in internal rotation contractures, with a subsequent posterior humeral subluxation in the growing child, glenoid retroversion and glenoid and humeral head malformation [16, 17, 34]. The prevalence of internal rotation contractures can be as high as 39% depending on the extent and severity of the BPI [35, 36]. Muscle degeneration is most prominent in the subscapular muscle [16, 17]. Treatments of internal rotation contractures include surgical subscapular release combined with transfer of the latissimus dorsi and/or teres major tendon to the rotator cuff to create active external rotation [37-39]. Disadvantages of subscapular release and/or tendon transfer include weaker adduction and potential partial power loss of internal rotation with a subsequent risk for an external rotation contracture of the shoulder. Therefore, coracohumeral ligament releases have been advocated by our group. An even less invasive method to address this internal rotation contracture of the shoulder is the injection of botulinum toxin A (BTX-A) [40, 41]. There have been some reports on BTX-A injections but no clear conclusions could be drawn from these studies since heterogeneity of included patients as well as technique were large (i.e. number and units of BTX-A injections, variety of muscles, combination with tendon transfer surgery etc.) [42-47]. Other surgical procedures to improve shoulder functionality of BPI patients include arthodesis of the shoulder, glenoid anteversion osteotomies and humeral rotation osteotomies [48-51].

1

Muscle regeneration

The regenerative potential of skeletal muscle is determined by muscle stem cells, which are called satellite cells. These are quiescent mononucleated cells that are sequestered between the basal lamina and the plasma membrane of the myofibers and can be identified by the expression of the paired box transcription factor Pax7 [52, 53]. The number of satellite cells in adult human has been shown to range from 7% in young age (20 years old) to 1% of all skeletal muscle nuclei in old age (73 years old) [54]. In response to injury, they become activated, proliferate, differentiate and fuse to existing muscle fibers or fuse together to form new myofibers during regeneration of damaged skeletal muscle [55]. This regenerative potential is influenced by replicative and stress-induced premature senescence and apoptosis of these cells.

Replicative senescence is indicated by exhaustion of the pool of available satellite cells and their proliferative capacity which is limited by the mitotic clock [56-58]. Progressive erosion of telomeres after each cell division leads to critically short telomere length and the activation of replicative senescence through a p53 and p21 dependent pathway [59]. The erosion of telomeres can be prevented by the catalytic subunit of the human telomerase reversed transcriptase (hTERT) leading to extension of replicative life [60]. Furthermore, lack of differentiation may contribute to poor functional recovery of long-term denervated muscle [61, 62]. Up-regulation of the p16 dependent pathway results in proliferative arrest before telomeres reach their critical length known as stress induced premature senescence [63, 64]. The regenerative potential of satellite cells is also limited by the extent of apoptosis. Upon denervation, the susceptibility of satellite cells to apoptosis has been shown to increase [65, 66]. Satellite cell activity can be modulated by a microenvironment inducing inflammatory cytokines, however underlying factors influencing the regenerative potential of satellite cells have not yet been identified [58, 67].

Cell therapy has the goal to repair damaged cells and to replenish the exhausted satellite cell pool by (systemic or local) injection of cells with myoregenerative properties. Transplantation of primairy satellite cells has been shown to improve the properties of reinnervated skeletal muscles [68]. However, poor cellular survival and limited cell dissemination hampers successful satellite cell transplantation. Furthermore, only few transplanted cells fuse with host muscle cell fibers. This suggests that a subpopulation of myogenic cells (i.e. stem cells) may be optimally suited for transplantation [69, 70]. Bone marrow (BM)-derived cells migrate to the site of muscle injury and contribute to the satellite cell pool [71-73]. The injection of autologous BM-derived mononuclear cells (MNCs) has been applied in clinical studies focusing on the muscles of the heart and leg [74-77]. Cell therapy could potentially regenerate partially denervated muscle in BPI by replenishment of the satellite cell pool and re-establishment of vascular and neural connections which are essential for muscle growth and function [78, 79].

AIM OF THIS THESIS

The aim of this thesis is to evaluate determinants of outcome, which will have an effect on overall functionality of the patient with a BPI. Deterioration of functionality will either occur immediate after the injury, but will also occur years after the initial peripheral nerve injury. They are generally, but not exclusively, related to the primary target organ of the nerve: the muscle. Secondary to these impaired muscles with subsequent impaired movement of the extremities, joint development in the growing child will be affected. This will have effect at the functionality level of the patient. To this end, outcome measures of functionality using the ICF model are developed (chapter 2). At the clinical level, muscle and joint deformities and their treatment options are addressed (chapter 3, 4, 5). At the cellular level, a deteriorated muscle is characterized in both inflammatory as well as nerve injury patients (chapter 6, 7). Finally, a possible treatment option with cell therapy for this muscle in nerve injury patients is used (chapter 8). The results of this thesis are summarized and future perspectives of muscle degeneration and regeneration for patients with BPI are considered in the discussion (chapter 9).

1

REFERENCES

1. Midha R. Epidemiology of brachial plexus injuries in a multitrauma population. Neurosurgery 1997; 40:1182-1188.
2. Asplund M, Nilsson M, Jacobsson A, von HH. Incidence of Traumatic Peripheral Nerve Injuries and Amputations in Sweden between 1998 and 2006. Neuroepidemiology 2009; 32:217-228.
3. Phua PD, Al-Samkari HT, Borschel GH. Is the term "obstetrical brachial plexus palsy" obsolete? An international survey to assess consensus among peripheral nerve surgeons. J Plast Reconstr Aesthet Surg 2012; 65:1227-1232.
4. Evans-Jones G, Kay SP, Weindling AM, Cranny G, Ward A, Bradshaw A, Hernon C. Congenital brachial palsy: incidence, causes, and outcome in the United Kingdom and Republic of Ireland. Arch Dis Child Fetal Neonatal Ed 2003; 88:F185-F189.
5. Dawodu A, Sankaran-Kutty M, Rajan TV. Risk factors and prognosis for brachial plexus injury and clavicular fracture in neonates: a prospective analysis from the United Arab Emirates. Ann Trop Paediatr 1997; 17:195-200.
6. Bager B. Perinatally acquired brachial plexus palsy--a persisting challenge. Acta Paediatr 1997; 86:1214-1219.
7. Waters PM. Update on management of pediatric brachial plexus palsy. J Pediatr Orthop B 2005; 14:233-244.
8. MJA Malessy. Brachial plexus surgery; factors affecting functional recovery. Thesis 10-6-1999.
9. W Pondaag. Obstetric brachial plexus lesions; a framework for therapy. Thesis 15-2-2012.
10. Bae DS, Waters PM, Zurakowski D. Correlation of pediatric outcomes data collection instrument with measures of active movement in children with brachial plexus birth palsy. J Pediatr Orthop 2008; 28:584-592.
11. Al-Qattan MM. Assessment of the motor power in older children with obstetric brachial plexus palsy. J Hand Surg [Br] 2003; 28:46-49.
12. World Health Organisation. International Classification of Functioning, Disability and Health: ICF. 22-5-2001. Geneva, WHO.
13. Poyhia TH, Nietosvaara YA, Remes VM, Kirjavainen MO, Peltonen JI, Lamminen AE. MRI of rotator cuff muscle atrophy in relation to glenohumeral joint incongruence in brachial plexus birth injury. Pediatr Radiol 2005; 35:402-409.
14. Poyhia TH, Koivikko MP, Peltonen JI, Kirjavainen MO, Lamminen AE, Nietosvaara AY. Muscle changes in brachial plexus birth injury with elbow flexion contracture: an MRI study. Pediatr Radiol 2007; 37:173-179.
15. Waters PM, Monica JT, Earp BE, Zurakowski D, Bae DS. Correlation of radiographic muscle cross-sectional area with glenohumeral deformity in children with brachial plexus birth palsy. J Bone Joint Surg Am 2009; 91:2367-2375.
16. VAN Gelein Vitringa VM, Jaspers R, Mullender M, Ouwerkerk WJ, van der Sluijs JA. Early effects of muscle atrophy on shoulder joint development in infants with unilateral birth brachial plexus injury. Dev Med Child Neurol 2010.
17. Hogendoorn S, van Overvest KL, Watt I, Duijsens AH, Nelissen RG. Structural changes in muscle and glenohumeral joint deformity in neonatal brachial plexus palsy. J Bone Joint Surg Am 2010; 92:935-942.
18. Ruoff JM, van der Sluijs JA, van Ouwerkerk WJ, Jaspers RT. Musculoskeletal growth in the upper arm in infants after obstetric brachial plexus lesions and its relation with residual muscle function. Dev Med Child Neurol 2012; 54:1050-1056.

19. Hogendoorn S, Duijnisveld BJ, van Duinen SG, Stoel BC, van Dijk JG, Fibbe WE, Nelissen RG. Local injection of autologous bone marrow cells to regenerate muscle in patients with traumatic brachial plexus injury: a pilot study. Bone Joint Res 2014; 3:38-47.
20. Eismann EA, Little KJ, Laor T, Cornwall R. Glenohumeral abduction contracture in children with unresolved neonatal brachial plexus palsy. J Bone Joint Surg Am 2015; 97:112-118.
21. Slabaugh MA, Friel NA, Karas V, Romeo AA, Verma NN, Cole BJ. Interobserver and intraobserver reliability of the Goutallier classification using magnetic resonance imaging: proposal of a simplified classification system to increase reliability. Am J Sports Med 2012; 40:1728-1734.
22. Jain NB, Collins J, Newman JS, Katz JN, Losina E, Higgins LD. Reliability of Magnetic Resonance Imaging Assessment of Rotator Cuff: The ROW Study. PM R 2015; 7:245-254.
23. Fischmann A, Hafner P, Fasler S, Gloor M, Bieri O, Studler U, Fischer D. Quantitative MRI can detect subclinical disease progression in muscular dystrophy. J Neurol 2012; 259:1648-1654.
24. Willis TA, Hollingsworth KG, Coombs A, Sveen ML, Andersen S, Stojkovic T, Eagle M, Mayhew A, de Sousa PL, Dewar L, Morrow JM, Sinclair CD, Thornton JS, Bushby K, Lochmuller H, Hanna MG, Hogrel JY, Carlier PG, Vissing J, Straub V. Quantitative muscle MRI as an assessment tool for monitoring disease progression in LGMD2I: a multicentre longitudinal study. PLoS One 2013; 8:e70993.
25. Willis TA, Hollingsworth KG, Coombs A, Sveen ML, Andersen S, Stojkovic T, Eagle M, Mayhew A, de Sousa PL, Dewar L, Morrow JM, Sinclair CD, Thornton JS, Bushby K, Lochmuller H, Hanna MG, Hogrel JY, Carlier PG, Vissing J, Straub V. Quantitative magnetic resonance imaging in limb-girdle muscular dystrophy 2I: a multinational cross-sectional study. PLoS One 2014; 9:e90377.
26. Ballinger SG, Hoffer MM. Elbow flexion contracture in Erb's palsy. J Child Neurol 1994; 9:209-210.
27. Sheffler LC, Lattanza L, Hagar Y, Bagley A, James MA. The prevalence, rate of progression, and treatment of elbow flexion contracture in children with brachial plexus birth palsy. J Bone Joint Surg Am 2012; 94:403-409.
28. Mayer L, Green W. Experiences with the Steindler flexorplasty at the elbow. J Bone Joint Surg Am 1954; 36-A:775-789.
29. Bahm J, Gilbert A. Surgical correction of supination deformity in children with obstetric brachial plexus palsy. J Hand Surg Br 2002; 27:20-23.
30. Yam A, Fullilove S, Sinisi M, Fox M. The supination deformity and associated deformities of the upper limb in severe birth lesions of the brachial plexus. J Bone Joint Surg Br 2009; 91:511-516.
31. Rolfe KW, Green TA, Lawrence JF. Corrective osteotomies and osteosynthesis for supination contracture of the forearm in children. J Pediatr Orthop 2009; 29:406-410.
32. Gilbert A, Valbuena S, Posso C. Obstetrical brachial plexus injuries: late functional results of the Steindler procedure. J Hand Surg Eur Vol 2014; 39:868-875.
33. Metsaars WP, Nagels J, Pijls BG, Langenhoff JM, Nelissen RG. Treatment of supination deformity for obstetric brachial plexus injury: a systematic review and meta-analysis. J Hand Surg Am 2014; 39:1948-1958.
34. Waters PM, Smith GR, Jaramillo D. Glenohumeral deformity secondary to brachial plexus birth palsy. J Bone Joint Surg Am 1998; 80:668-677.

35. Pondaag W, de Boer R, van Wijlen-Hempel MS, Hofstede-Buitenhuis SM, Malessy MJ. External rotation as a result of suprascapular nerve neurotization in obstetric brachial plexus lesions. Neurosurgery 2005; 57:530-537.
36. Hoeksma AF, ter Steeg AM, Dijkstra P, Nelissen RG, Beelen A, de Jong BA. Shoulder contracture and osseous deformity in obstetrical brachial plexus injuries. J Bone Joint Surg Am 2003; 85-A:316-322.
37. Pearl ML, Edgerton BW, Kazimiroff PA, Burchette RJ, Wong K. Arthroscopic release and latissimus dorsi transfer for shoulder internal rotation contractures and glenohumeral deformity secondary to brachial plexus birth palsy. J Bone Joint Surg Am 2006; 88:564-574.
38. Waters PM, Bae DS. The early effects of tendon transfers and open capsulorrhaphy on glenohumeral deformity in brachial plexus birth palsy. J Bone Joint Surg Am 2008; 90:2171-2179.
39. Van der Holst M, Vlieland TP, Meesters JJ, Bekkering WP, Nagels J, Nelissen RG. Evaluation of shoulder function after secondary surgery in children with Neonatal Brachial Plexus Palsy. J Pediatr Rehabil Med 2015; 8:187-196.
40. Pascual-Pascual SI, Pascual-Castroviejo I. Safety of botulinum toxin type A in children younger than 2 years. Eur J Paediatr Neurol 2008.
41. O'Flaherty SJ, Janakan V, Morrow AM, Scheinberg AM, Waugh MC. Adverse events and health status following botulinum toxin type A injections in children with cerebral palsy. Dev Med Child Neurol 2011; 53:125-130.
42. Desiato MT, Risina B. The role of botulinum toxin in the neuro-rehabilitation of young patients with brachial plexus birth palsy. Pediatr Rehabil 2001; 4:29-36.
43. DeMatteo C, Bain JR, Galea V, Gjertsen D. Botulinum toxin as an adjunct to motor learning therapy and surgery for obstetrical brachial plexus injury. Dev Med Child Neurol 2006; 48:245-252.
44. Price AE, Ditaranto P, Yaylali I, Tidwell MA, Grossman JA. Botulinum toxin type A as an adjunct to the surgical treatment of the medial rotation deformity of the shoulder in birth injuries of the brachial plexus. J Bone Joint Surg Br 2007; 89:327-329.
45. Ezaki M, Malungpaishrope K, Harrison RJ, Mills JK, Oishi SN, Delgado M, Bush PA, Browne RH. Onabotulinum toxinA injection as an adjunct in the treatment of posterior shoulder subluxation in neonatal brachial plexus palsy. J Bone Joint Surg Am 2010; 92:2171-2177.
46. Gobets D, Beckerman H, Groot VD, VAN Doorn-Loogman MH, Becher JG. Indications and effects of botulinum toxin A for obstetric brachial plexus injury: a systematic literature review. Dev Med Child Neurol 2010.
47. Michaud LJ, Louden EJ, Lippert WC, Allgier AJ, Foad SL, Mehlman CT. Use of Botulinum Toxin Type A in the Management of Neonatal Brachial Plexus Palsy. PM R 2014.
48. Chammas M, Goubier JN, Coulet B, Reckendorf GM, Picot MC, Allieu Y. Glenohumeral arthrodesis in upper and total brachial plexus palsy. A comparison of functional results. J Bone Joint Surg Br 2004; 86:692-695.
49. Dodwell E, O'Callaghan J, Anthony A, Jellicoe P, Shah M, Curtis C, Clarke H, Hopyan S. Combined glenoid anteversion osteotomy and tendon transfers for brachial plexus birth palsy: early outcomes. J Bone Joint Surg Am 2012; 94:2145-2152.
50. Atlan F, Durand S, Fox M, Levy P, Belkheyar Z, Oberlin C. Functional outcome of glenohumeral fusion in brachial plexus palsy: a report of 54 cases. J Hand Surg Am 2012; 37:683-688.

51. Hultgren T, Jonsson K, Roos F, Jarnbert-Pettersson H, Hammarberg H. Surgical correction of shoulder rotation deformity in brachial plexus birth palsy: long-term results in 118 patients. Bone Joint J 2014; 96-B:1411-1418.
52. Mauro A. Satellite cell of skeletal muscle fibers. J Biophys Biochem Cytol 1961; 9:493-495.
53. Seale P, Sabourin LA, Girgis-Gabardo A, Mansouri A, Gruss P, Rudnicki MA. Pax7 is required for the specification of myogenic satellite cells. Cell 2000; 102:777-786.
54. Schmalbruch H, Hellhammer U. The number of satellite cells in normal human muscle. Anat Rec 1976; 185:279-287.
55. Hawke TJ, Garry DJ. Myogenic satellite cells: physiology to molecular biology. J Appl Physiol 2001; 91:534-551.
56. Viguie CA, Lu DX, Huang SK, Rengen H, Carlson BM. Quantitative study of the effects of long-term denervation on the extensor digitorum longus muscle of the rat. Anat Rec 1997; 248:346-354.
57. Renault V, Piron-Hamelin G, Forestier C, DiDonna S, Decary S, Hentati F, Saillant G, Butler-Browne GS, Mouly V. Skeletal muscle regeneration and the mitotic clock. Exp Gerontol 2000; 35:711-719.
58. Renault V, Thornell LE, Eriksson PO, Butler-Browne G, Mouly V. Regenerative potential of human skeletal muscle during aging. Aging Cell 2002; 1:132-139.
59. Vaziri H, West MD, Allsopp RC, Davison TS, Wu YS, Arrowsmith CH, Poirier GG, Benchimol S. ATM-dependent telomere loss in aging human diploid fibroblasts and DNA damage lead to the post-translational activation of p53 protein involving poly(ADP-ribose) polymerase. EMBO J 1997; 16:6018-6033.
60. Di DS, Mamchaoui K, Cooper RN, Seigneurin-Venin S, Tremblay J, Butler-Browne GS, Mouly V. Telomerase can extend the proliferative capacity of human myoblasts, but does not lead to their immortalization. Mol Cancer Res 2003; 1:643-653.
61. Dedkov EI, Kostrominova TY, Borisov AB, Carlson BM. Reparative myogenesis in long-term denervated skeletal muscles of adult rats results in a reduction of the satellite cell population. Anat Rec 2001; 263:139-154.
62. Borisov AB, Dedkov EI, Carlson BM. Abortive myogenesis in denervated skeletal muscle: differentiative properties of satellite cells, their migration, and block of terminal differentiation. Anat Embryol (Berl) 2005; 209:269-279.
63. Janzen V, Forkert R, Fleming HE, Saito Y, Waring MT, Dombkowski DM, Cheng T, DePinho RA, Sharpless NE, Scadden DT. Stem-cell ageing modified by the cyclin-dependent kinase inhibitor p16INK4a. Nature 2006; 443:421-426.
64. Bigot A, Klein AF, Gasnier E, Jacquemin V, Ravassard P, Butler-Browne G, Mouly V, Furling D. Large CTG repeats trigger p16-dependent premature senescence in myotonic dystrophy type 1 muscle precursor cells. Am J Pathol 2009; 174:1435-1442.
65. Jin H, Wu Z, Tian T, Gu Y. Apoptosis in atrophic skeletal muscle induced by brachial plexus injury in rats. J Trauma 2001; 50:31-35.
66. Jejurikar SS, Marcelo CL, Kuzon WM, Jr. Skeletal muscle denervation increases satellite cell susceptibility to apoptosis. Plast Reconstr Surg 2002; 110:160-168.
67. Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, Sevini F, Panourgia MP, Invidia L, Celani L, Scurti M, Cevenini E, Castellani GC, Salvioli S. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mech Ageing Dev 2007; 128:92-105.

68. Lazerges C, Daussin PA, Coulet B, Boubaker el AR, Micallef JP, Chammas M, Reyne Y, Bacou F. Transplantation of primary satellite cells improves properties of reinnervated skeletal muscles. Muscle Nerve 2004; 29:218-226.
69. Skuk D. Myoblast transplantation for inherited myopathies: a clinical approach. Expert Opin Biol Ther 2004; 4:1871-1885.
70. Beauchamp JR, Morgan JE, Pagel CN, Partridge TA. Dynamics of myoblast transplantation reveal a discrete minority of precursors with stem cell-like properties as the myogenic source. J Cell Biol 1999; 144:1113-1122.
71. Matziolis G, Winkler T, Schaser K, Wiemann M, Krocker D, Tuischer J, Perka C, Duda GN. Autologous bone marrow-derived cells enhance muscle strength following skeletal muscle crush injury in rats. Tissue Eng 2006; 12:361-367.
72. Ferrari G, Cusella-De AG, Coletta M, Paolucci E, Stornaiuolo A, Cossu G, Mavilio F. Muscle regeneration by bone marrow-derived myogenic progenitors. Science 1998; 279:1528-1530.
73. Abedi M, Greer DA, Colvin GA, Demers DA, Dooner MS, Harpel JA, Weier HU, Lambert JF, Quesenberry PJ. Robust conversion of marrow cells to skeletal muscle with formation of marrow-derived muscle cell colonies: a multifactorial process. Exp Hematol 2004; 32:426-434.
74. Van Tongeren RB, Hamming JF, Fibbe WE, Van W, V, Frerichs SJ, Stiggelbout AM, Van Bockel JH, Lindeman JH. Intramuscular or combined intramuscular/intra-arterial administration of bone marrow mononuclear cells: a clinical trial in patients with advanced limb ischemia. J Cardiovasc Surg (Torino) 2008; 49:51-58.
75. Tateishi-Yuyama E, Matsubara H, Murohara T, Ikeda U, Shintani S, Masaki H, Amano K, Kishimoto Y, Yoshimoto K, Akashi H, Shimada K, Iwasaka T, Imaizumi T. Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial. Lancet 2002; 360:427-435.
76. Kamihata H, Matsubara H, Nishiue T, Fujiyama S, Tsutsumi Y, Ozono R, Masaki H, Mori Y, Iba O, Tateishi E, Kosaki A, Shintani S, Murohara T, Imaizumi T, Iwasaka T. Implantation of bone marrow mononuclear cells into ischemic myocardium enhances collateral perfusion and regional function via side supply of angioblasts, angiogenic ligands, and cytokines. Circulation 2001; 104:1046-1052.
77. Beeres SL, Bax JJ, bbets-Schneider P, Stokkel MP, Fibbe WE, van der Wall EE, Schalij MJ, Atsma DE. Intramyocardial injection of autologous bone marrow mononuclear cells in patients with chronic myocardial infarction and severe left ventricular dysfunction. Am J Cardiol 2007; 100:1094-1098.
78. Borisov AB, Dedkov EI, Carlson BM. Differentiation of activated satellite cells in denervated muscle following single fusions in situ and in cell culture. Histochem Cell Biol 2005; 124:13-23.
79. Gayraud-Morel B, Chretien F, Tajbakhsh S. Skeletal muscle as a paradigm for regenerative biology and medicine. Regen Med 2009; 4:293-319.