MUSCLE DAMAGE CAN BE REDUCED BY APPLICATION OF GROWTH HORMONE IN LIMB LENGTHENING

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Introduction:
The successful outcome of distraction osteogenesis depends in part on the adequate adaptation of the surrounding soft tissue, particularly the muscle, to stretching. Shen et al. reported in a rat callotasis that initial muscleia, the lengthening of more than 20% caused acute stiffness of the gastrocnemius muscle, presumably due to an increase in endomysial and perimysial fibrosis. Growth hormone (GH) increases skeletal muscle synthesis either by direct action on receptors of muscle tissue or by indirect mediation of somatomedins or insulin-like growth factors (IGF). IGF-I, a peptide produced by the liver and other tissues, including skeletal muscle, is responsible for increased protein and mRNA synthesis, amino acid uptake and growth of cartilage and muscle. The purpose of this study was to verify the hypothesis that muscle damage can be minimized or prevented by application of the growth hormone during extensive limb lengthening.

Materials and Methods:
A rat model of tibial lengthening (forty male Sprague-Dawley rats) was used with a protocol divided into a latency period of 5 days, a distraction period that lasted 30 days with a daily distraction rate of 0.5 mm in two steps, and a consolidation period of 28 days. Forty rats had approximately 30% lengthening of the left tibiae. Right tibiae were left intact and were used as control. Twenty rats were administered daily with 100 μg/kg of recombinant human GH, and the remaining twenty with same amount of normal saline, from operation to sacrifice. Histologic (hematoxylin and eosin staining), immunohistochemical (proliferating cell nuclear antigen), desmin, and vimentin stainings1), and electrophysiologic studies were performed, on the tibialis anterior, to compare the muscle responses between the GH treated lengthened limbs (GL group) and other control limbs (CL group, saline treated lengthened limbs; CN group, saline treated non-lengthened limbs; and GN group, growth hormone treated non-lengthened limbs) at postoperative days 34 (at the completion of lengthening) and 61 (after 4 week rest for recovery of muscle function). The sum of the histologic scores, positively stained fibers to PCNA, desmin and vimentin stainings were compared among the groups by the general linear model ANOVA test. For comparison of the electrophysiologic changes of the muscle, the Kurskal-Wallis test and the Wilcoxon rank-sum test were used. The level of significance was determined at p<0.05.

Results:
When the sum of the histologic score was compared, CL group had significantly higher score than other groups. There was no statistically significant difference among the proximal, middle, and distal regions of the tibialis anterior, or in the scores between day 34 and day 61. On day 34, PCNA positively stained cells were most frequently and significantly found in the GL group. There was no significant difference in scores according to the regions. On day 61, however, there was no significant difference in the proportion of PCNA positive cells among the groups. Similar patterns were found in the desmin staining. The proportion of vimentin positive cells, suggestive of degenerative fibrosis, was significantly higher in the CL group than any other groups on both day 34 and day 61 (Fig. 1). There was no significant difference in scores among the regions. There was a significant difference in the maximum tetanic force among the groups (p=0.0003). The force was highest in the GN group, followed by CN, GL and CL groups in order. However, there was a significant difference in maximum tetanic force between the GL group and CL group on both day 34 and day 61 (Fig. 2). There was no significant difference in single twitch force, time to peak twitch tension and twitch one-half relaxation time.

Conclusion:
Our data clearly suggests that application of growth hormone was beneficial in extensive bone lengthening in terms of increasing the adaptive response to stretching by promoting muscle neo-genesis and by decreasing endo/perimysial fibrosis in the lengthened muscle. Raschke et al. reported systemic administration of recombinant homologous growth hormone also significantly accelerates ossification of bone regenerate in distraction osteogenesis. Final regenerate torsional failure load was 131% higher and ultimate torsional stiffness was 231% higher in the GH treatment group than in the control group. When considering the beneficial effects of growth hormone on acceleration of regenerate bone consolidation and minimizing muscle damage, the use of growth hormone may be justified in the clinical practice dealing with an extensive lengthening or congenital limb shortening with inherent fibrosis.

References:

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