Plasma Factor XIII Accelerates Bone Formation in the Treatment of Bone Defects

INTRODUCTION:
Callus distraction is a well-accepted method for treating large bone defects. Unfortunately, the time for the maturation of a newly formed regenerate is long and can lead to complications. A method which would allow the acceleration of the maturation process would shorten the treatment time, reduce the costs and would be a great benefit for the patients.

Plasma factor XIII has demonstrated an enhancing effect on the proliferation of osteoblasts [1] and fibroblast [2], and for the healing of diaphyseal fractures [3]. Therefore, the hypothesis should be tested whether plasma factor XIII can also accelerate bone formation after callus distraction.

METHODS:
A 15 mm bone defect was created in the distal third of the right metatarsal of 18 female sheep. A 25 mm long diaphyseal segment was osteotomized and all fragments were stabilized by a custom-made ring fixator. After a latency period of 4 days the segment was transported to close the 15 mm defect and to stimulate callus formation by tissue strain. After the distraction length had been reached the sheep were divided into two groups: a control group which was sacrificed 84 days after the operation (n=8) and a factor XIII group (n=10) which additionally received Fibrogammin HS intravenously the first day after distraction (2500 IU) followed by 1250 IU on days 22, 24, 26 and 28 after the operation. To study the dynamics of bone formation, fluorescent labeling was performed with calcein green on day 19 in both groups and with Tetracycline on day 39 in the FXIII group and on day 49 in the control group.

At the end of the study all animals are sacrificed, the fixator removed and the metatarsal excised. A longitudinal section of the bone was taken for undecalcified histology. After embedding in methacrylate, a 70 µm slice was prepared and its surface stained with Paragon. This slice was investigated by quantitative histomorphological analysis of the tissue composition and for fluorescent-labelled bone in the former bone defect area (Fig.1).

RESULTS:
There was significantly more new bone formation in the FXIII group (47.3%) in the middle of the callus distraction area than in the control group (29.5%) (Fig.2).

DISCUSSION:
The results demonstrate that systemic application of plasma factor XIII can stimulate bone formation and maturation of newly formed distraction callus, and is able to reduce the long treatment time. These results are in accordance with previous studies, which showed an enhancement of callus healing in diaphyseal fractures under FXIII treatment [3].

Whereas up to the end of the distraction phase the bone-building rate was the same in both groups, during the maturation phase the FXIII treatment caused a significant acceleration of the bone formation rate. One possible reason for these effects is the higher proliferation rates of osteoblasts and fibroblasts [1, 2] under increased FXIII levels. Taking into consideration the relatively high rates of complications in the treatment of large bony defects with external fixators and the high costs for the long treatment time, the application of plasma factor XIII might be an additional treatment option.

SIGNIFICANCE:
This histomorphological study demonstrated for the first time that Factor XIII can significantly reduce the time for the treatment of large bone defects by callus distraction.

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REFERENCES: