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Bioretec R&D:
BIOABSORBABLE INTRAMEDULLARY NAIL FIXATION OF FOREARM FRACTURES IN CHILDREN

Prospective, randomized, clinical trial (RCT) compared Bioretec Activa IM-Nail™ and elastic stable intramedullary nailing (ESIN) in the treatment of children's forearm shaft fractures. The investigation was a two-center study, performed in Oulu University Hospital, Oulu, Finland, and the Central Hospital of Päijät-Häme, Lahti, Finland in 2010-2017[i].

Altogether 35 patients were randomized. Bioabsorbable intramedullary nailing was used in 19 (54.3%) and ESIN in 16 cases. The patients were evaluated at four weeks, three months, six months, and two years postoperatively and contacted by phone one year postoperatively. ESINs were removed six months postoperatively. In the literature, it is recommended that nail removal should not be performed before 4 to 6 months after insertion and not before complete consolidation of the fracture occurred. [1, 2]. Patients between 5 and 15 years with single- or double-bone forearm shaft fractures requiring surgical fixation were invited. Patients with open fractures, significant soft-tissue injury, pathological fractures, or previous fracture or infection in the forearm were excluded. Also, patients with metabolic bone diseases, systemic disease or medication affecting bone quality or resistance to infection, or fractures older than seven days were excluded. All information was collected via standardized questionnaires.

An operative treatment by surgical fixation is mandatory to avoid complications such as residual deformity with permanent loss of forearm rotation. Also, fracture remodeling will not correct rotational deformities of the forearm, and therefore, the intramedullary nailing is used as a fixation method to avoid residual functional deficiency. [3] In former days, fully corrected rotational restriction was not as necessary, as the shoulder could compensate for the dysfunction. However, nowadays, complete forearm rotation, especially pronation, is required, primarily

because it is necessary for working with the computer. Therefore, the primary outcome variables for evaluating the new surgical technique's feasibility and efficacy were range of motion (ROM) in the forearm, wrist and elbow (e.g. measuring supination/protonation and flexion-extension movements). Also, subjective pain was assessed during the recovery and measured by Visual Analogue Scale (VAS, 0–100 mm) in mm ± SD.

Overall recovery at the final follow-up was interpreted by using the Price's classification system of forearm shaft fractures (<15 degrees of change in motion range is excellent clinical outcome), and Flynn's criteria for upper extremity assessment (<10 degrees of change in ROM justifies satisfactory outcomes). ROM is a widely used measurement to determine the healing efficacy of the IM-nailing of pediatric patients. [4, 5]

The study's secondary objectives were to compare the radiographic outcome of the forearm fracture treatment between the patients treated using the study method and the patients treated by the reference method. The key variables in the assessment of the secondary objectives were fracture reduction and angular deformity in radiographs, the formation of bridging callus and consolidation of the fracture line (union, delayed union, non-union and malunion). These were studied in each follow-up visit to assess the bone-healing process and to record treatment-related complications (e.g. implant-related osteolysis and intramedullary nail failure). A possible soft-tissue reaction against the biodegradable implant was also studied by Magnetic Resonance Imaging (MRI) for a randomly selected sub-group of 13 patients.

Other outcome variables included operation time, length of hospitalization, and complaints in daily living. All surgery-related infections, intra-operative complications related to fixation hardware, osteolysis, bio-incompatibility reactions, and mechanical implant failure (loss of reduction) were registered to ensure the device's safety.

The study implant was found to be a feasible solution to the study purpose, and there were no biological or biochemical adverse events. MRI showed no soft-tissue

reactions such as osteolysis in any patient. The clinical and radiographical findings were comparable with the reference method. Following assessments were made to evaluate whether the primary objective for the clinical investigation was reached:

Table 1 Assessment of the primary objectives.

Range of motion (ROM)	**Forearm:**	Data: BIN (study group) 162° / ESIN (reference group) 151° (P=0.201) Result: No statistical difference between the study and reference groups
	Wrist:	Data: BIN 150° / ESIN 150° (P=0.872) Result: No statistical difference between the study and reference groups
	Elbow:	Data: BIN 154° / ESIN 148° (P=0.233) Result: No statistical difference between the study and reference groups
Pain assessment		The pain seemed to be greater postoperatively in the ESIN group: VAS 62.2 mm than in the BIN group VAS 40.9 mm (P=0.050). At two years, some pain at the fracture site (VAS) was reported in 3/16 cases in ESIN group compared to none (0/16 cases) in BIN group (P=0.998). Result: No statistical difference in pain between the study and reference groups. Postoperative pain seemed to be greater in the ESIN group, compared to BIN, but the statistical significance was intermediate (P=0.005).
Conclusion concerning the primary objective of the clinical investigation:		There was no difference between the BIN and ESIN in forearm fracture treatment in keeping the level of reduction and alignment that were appropriate to the age of the child.

Following assessments were made to evaluate whether the secondary objective set for the clinical investigation was reached:

Table 2 Assessment of the secondary objectives.

- Fracture reduction and angular deformity (alignment) in radiographs **- Formation of bridging callus and consolidation of the fracture line** **- Soft-tissue and bone-tissue (interface between bone and tissue) reactions**	Result: Every patient presented complete bone union at two years with invisible fracture line and completely remodeled bone. There were no abnormal soft-tissue reactions nor osteolysis in the stabilized bone in the two-year's MRI (N=13). The biodegradable implants were partially (N=3) or almost completely (N=10) resorbed.
Conclusion concerning the secondary objective of the clinical investigation:	There were no differences in the clinical or radiographic or MRI outcomes between the patients treated by BIN and by ESIN.

The of Activa IM-Nail™ with the appropriate immobilization during the healing period provides reduction of the bone fragments and maintains appropriate bone-to-bone contact. The cast immobilisation compensates mechanical property differences between the ESIN and the Activa IM-Nail™.

Activa IM-Nail™ has a load-carrying capacity for at least 8 weeks supporting the tissue healing until it has achieved its original strength. Hence, Activa IM-Nail™ continues to support the healing after the cast removal at week four or later.

Table 3 contains ultimate bending strengths and elastic modulus of the bone and Activa IM-Nail™. The Activa IM-Nail™ bending properties resemble the properties of the bone. This prevents stress shielding and enables stimulus for continued remodeling required to maintain bone mass.

Table 3 Bending Ultimate Strength and Elastic Modulus of bone and Activa IM-Nail™.

	Bending Ultimate Strength (MPa)	**Elastic modulus, 3-point-bending (GPa)**
Femur (2-17 years, mid-diaphysis) [6]	180	11
Rib (0-9 years whole bone) [7]	87	5
Activa IM-Nail (wet) [8]	200	5-7

Two patients with a complete bone union in radiographs and MRI suffered a new high-energy injury in the same anatomical location during the follow-up and consequently, were excluded from the two-year follow-up. They were found to have excellent clinical outcomes and complete union in radiographs and MRI, before their re-fractures. The first was a 10-year old girl who fell 8 months postoperatively and the other a 9-year old boy, who injured on a trampoline 10 months after the surgery. Both patients were reoperated using ESIN and the latter patient got one more fracture (distal radius) in the same forearm 2 months after the re-fracture. These re-injuries were not related to the product safety in any way. Similar re-fractures have been reported in the published literature in connection to ESIN as well, which concludes that the new external accidents with the reasonable trauma-energy were not related to the implants used in these cases.

In addition, two adolescent patients (13 years and 14 years) in the BIN group had inadequate bone healing resulting to the decision to re-operate. Nonetheless, there were no statistical differences in the rate of reoperation (excluding ESIN removal operations) between the BIN and ESIN groups (P=0.245). The 14-year old patient was obese (BMI 29.8 kg/m^2, nearly reaching the exclusion criteria >30 kg/m^2) and was operated without any technical issues. Four weeks postoperatively he complained of pain and malalignment of the forearm was observed in radiograph. The cast was found to be broken at the out-hospital visit in the pediatric trauma unit. The proper postoperative cast immobilization is obligatory with BIN; thus, his postoperative treatment was not following the instructions.

The other patient (13 years old) had delayed bone healing in the ulna, and no callus formation was seen during the first 12 weeks. However, moderate callus formation was seen in radius. Delayed healing in ulna was taken to be due to the massive invasive surgery (open reduction, muscle interposition release), which is a known risk for disrupted bone healing. [8, 9, 10] Further, moderate swelling postoperatively resulted in need of removing the cast, which did not provide the necessary support anymore. 13 year old adolescent female and 14 year old male may refer to too mature skeleton, resulting in disadvantageous outcomes. Therefore, based on the all available information of the new implant and the previous knowledge concerning the forearm shaft fractures and growing bone, an extra precaution has been introduced by limiting the use of the product to patients below 13 years of age and emphasizing the need of external cast immobilization with Activa IM-Nail™ to hold the alignment.

In conclusion, there were no differences in two-year outcome between the BIN and the ESIN groups regarding the primary and secondary objectives with children below 13 years of age. All the known benefits of the intramedullary nailing for children's forearm shaft fractures are available with BIN. Also, due to the ESIN's non-absorbable nature and mandatory removal operation the patients with the ESIN must have part of the implant sticking out from the bone during five to six months causing unnecessary pain and discomfort.

As a conclusion, the use of the BIN in treating forearm shaft fractures in children was a feasible and safe method. It resulted in good clinical and radiographic outcomes in all patients at the two-year mark.

References

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[i] Investigation was performed according to ISO 14155:2011. The study plan was approved by the Medical Ethics Committee and the Hospital Ethics Committee of Tampere Hospital District, Tampere, Finland (§R09231/2009) and recorded in the annals of the Northern Finland Hospital District, Oulu, Finland. The study is registered in Clinical Trials.gov (NCT03474900) and the National Supervisory Authority for Welfare and Health (Valvira) approved the implant for use in this study.