Study protocol

Use of the bioabsorbable Activa IM-Nail™ in pediatric diaphyseal forearm fractures: a cohort study of 30 patients

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The Danish Data Protection Agency ID: P-2020-1197

The Danish National Committee On Health Research Ethics ID: H-21004012

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Abstract

Background

Pediatric diaphyseal forearm fractures are common and one of the most frequent reasons for orthopedic care. Fractures in need of surgery are often treated with metal Elastic Stable Intramedullary Nails (ESIN). Nail removal after 6-12 months is generally advocated. Surgical hardware removal has few complications; however, it is a substantial burden on the child, the family and healthcare economy. Bioabsorbable Intramedullary Nails (BIN) have been developed for the same indications as metal ESIN. The use of bioabsorbable implants would deem hardware removal unnecessary and relieve the child of further surgery and reduce healthcare costs.

Methods

We aim to recruit all children in the catchment area of Herlev and Gentofte University Hospital (Copenhagen, Denmark) with acute unstable diaphyseal forearm fractures. Participants will be operated with BIN and followed consecutively for 2 years with interim analysis of data after 6 months. We will report radiological healing using the Radiographic Union Score (RUS) 3 months after surgery together with any adverse events during follow-up.

Discussion

This study will provide important preliminary data and asses the feasibility of using the bioabsorbable Activa IM-Nail™ in pediatric diaphyseal forearm fractures. This study is a pilot study for initiating an RCT comparing BIN to metal ESIN hypothesizing that BIN is not an inferior treatment.

Keywords

Pediatric fracture, bioabsorbable implant, diaphyseal forearm fracture, intramedullary nails, BIN, ESIN

Introduction

Pediatric diaphyseal forearm fractures are common and one of the most frequent reasons for orthopedic care [1]. The fractures are often treated by surgical stabilization with metal Elastic Stable Intramedullary Nails (ESIN) [2]. Nail removal after 6-12 months is generally advocated [3–5]. Surgical hardware removal has few complications; however, it is a substantial burden on the child, the family and healthcare economy [6]. Bioabsorbable Intramedullary Nails (BIN) have been developed for the same indications as metal ESIN. The use of bioabsorbable implants would deem hardware removal unnecessary and relieve the child of further surgery and reduce the healthcare costs [7].

Background

Epidemiology

Fractures constitute 10-25% of all pediatric injuries. During childhood almost 50% of boys and 30% of girls will sustain a fracture. The type, pattern and cause of fracture varies from one country to another [8]. Pediatric diaphyseal fractures of the radius and/or ulna are one of the most common reasons for orthopedic care in children [1]. With an incidence of 6.8 (8.3 for boys and 5.2 for girls)/10.000 this injury accounts for 3-6% of all pediatric fractures [8,9], occurring primarily between the age of 5 and 14 (median 8.5) [10]. The last three decades have shown a dramatic increase in the incidence of these fractures; however, the precise cause is unknown [2,8]. Speculations point to inactivity, obesity and vitamin D deficiency as causes for lowered bone mineral density and increasing numbers of pediatric fractures [11].

Treatment options

Due to the complex relationship between the radius and ulna the prognosis is dependent on fractures healing without excess shortening, rotation or angulation. Historically minimally displaced diaphyseal forearm fractures have been managed successfully with closed reduction and casting [12]. The last two decades has shown a significant increase in the percentage of operatively managed fractures [13]. Non-operative treatment requires less than 10-15° of angulation and less than 5 mm of shortening at the DRUJ. Re-displacement in the cast is seen in about 10% of cases and requires re-reduction or surgical fixation [12].

As with any other fracture, demand for better outcome has developed during the last two decades. There are especially strict demands for movement of the elbow, forearm and wrist. A functional range of movement was in 1981 declared as flexion/extension of 30-130 degrees and forearm rotation of 50-50 degrees [14], but the study did not include children. More recent studies have reported that contemporary tasks such as using a mobile phone, tablet or a computer keyboard requires additional degrees of

movement [15,16]. Functional demand together with parental and socioeconomic pressure is expanding the indication for surgical stabilization of pediatric forearm fractures.

The most common methods for treating unstable pediatric forearm fractures are open reduction and internal fixation (ORIF) using plates and screws or intramedullary (IM) nailing [17]. ORIF with plates and screws yields good reduction and a stable osteosynthesis, but also requires large soft tissue dissection and often also hardware removal.

There is not enough evidence to support one surgical method over another but with the introduction of the minimally invasive ESIN, the proportion of this method has increased significantly [2,13,17,18] making this the preferred operative technique.

Metal Elastic Stable Intramedullary Nailing (ESIN)

The method of ESIN was introduced in the 1970s using Kirschner wires. In the 1990s ESIN specific implants became widely available. ESIN has since shown to produce excellent results with few complications [4,19]. Advantages include closed fracture reduction, minimal soft tissue dissection, early motion, sustained reduction and easy hardware removal. Complications are rare but do exist in the form of soft tissue irritation, superficial radial nerve injury, extensor pollicis longus tendon rupture, delayed union, malunion, refractures and infection [3,20,21].

Several metallic alloys have been used to produce ESIN implants. The most widely used is titanium (Ti6Al14V) which has suitable elastic properties [4]. The Titanium Elastic Nail System (DePuy Synthes, Raynham, Massachusetts, USA) is commonly used and has been used in our institution for several years.

Hardware removal

Removal of metal implants including ESIN after fracture surgery in children is currently the practice in Denmark and is sanctioned by the Danish Health Authority. Implant removal is done because of potential interference with the child's growing skeleton, late tissue reactions, difficulty in late removal and concerns about stress shielding due to metal stiffness [22].

Bioabsorbable implants

It is important to retain a common and unified nomenclature within this research field. Liu et al. [23] suggest that foreign implants or other kinds of biomaterials eventually absorbed by the body be labeled as "absorbable" or with the prefix "bio". The term "absorbable" focuses on the host's metabolism of degraded products of the implanted material. Within this study protocol and the final manuscript, we will adhere to the label "bioabsorbable implants".

Bioabsorbable implants have been known since the 1970s and over the years many different materials have been investigated. The use of bioabsorbable implants is increasing and has proved a safe and feasible method of stabilizing fractures in the growing skeleton [24–26]. By using bioabsorbable implants the need for implant removal is overcome and risks of late tissue reactions, stress shielding and infections are lowered [27].

Implants made from oriented poly L-lactide-co-glycolide (PLGA) copolymers are strong enough to support fractured bones. The monomers of PLGA are L-lactic acid and glycolic acid, which are part of the normal metabolic chemistry of human cells. PLGA implants undergo a controlled degradation through hydrolysis forming lactic acid and glycolic acid which are absorbed by the cells and metabolized into carbon dioxide and water. The implant retains strength and size for at least eight weeks and over the course of approximately two years the implant will be completely absorbed [28]. Medical grade PLGA implants manufactured by Bioretec Ltd. (Hermiankatu 22, Tampere, Finland) are sterilized with gamma radiation. Gamma radiation also reduces molecular weight of oriented PLGA implants. The reliability and safety of the Activa IM-Nail™ has been described in the manufacturer's premarket trials and one RCT [7], the implant is FDA and CE approved for the same purpose as in the present study.

Objectives

Primary objective

The primary objective of this study is to evaluate the amount of radiological healing three months after surgery with the Activa IM-Nail™ for pediatric diaphyseal forearm fractures.

Secondary objectives

The secondary objectives are to report the functional outcome, calculate refracture rate and any other complications up to two years following surgery and to describe MRI findings two years after insertion of Activa IM-Nail™.

Hypothesis

We hypothesize that radiological healing is established three months after surgery with the Activa IM-Nail™.

Methods and materials

Study design

We use a cohort study design [29] conformed to the STROBE Statement [30]. We aim to recruit all children with diaphyseal forearm fractures (cohort) operated with BIN (exposure) and report radiological healing

(outcome). This study design is relevant in reporting radiological healing and calculating absolute risk of adverse events based on the exposure in our cohort.

Selection and withdrawal of participants

Setting

The study will be performed in the Capital Region of Denmark, Europe. Patients in Herlev and Gentofte University Hospital's catchment area (population 700.000 of which 80.000 are children age 3-15) are eligible for recruitment.

Participants

This study investigates the treatment of pediatric forearm fractures; therefore, this study cannot be conducted in consenting adults. Forearm fractures occur in all age groups and thus it is not possible to select only older children for inclusion. This study is believed to have great positive implications for the participants and successive patients with the same condition.

Participants eligible for recruitment are patients from 2 years of age until physeal closure with an acute traumatic diaphyseal forearm fracture of the radius, ulna or both. Fractures need to be complete (not unicortical or green stick) and displaced more than 50% of bone width or angulated more than 10° in any plane or irreducible or unstable after reduction.

We exclude patients

- with fractures that are well managed conservatively (undisplaced or minimally displaced)
- with previous ipsilateral forearm fracture
- with fractures unsuited for intramedullary nailing (e.g. multifragmentary, metaphyseal or epiphyseal)
- with fractures with ipsilateral wrist or elbow involvement (e.g. Monteggia or Galeazzi variants)
- unable to participate in follow-up
- with existing bone pathology (e.g. tumor, osteogenesis imperfecta, degenerative disease)
- in whom internal fixation is otherwise contraindicated (e.g. active or potential infection)

Recruitment

Recruitment starts May 25th, 2021 and is estimated to take 12 months. Patients may be seen primarily in our Emergency Department (ED) or referred by local clinics or another hospital. Patients with displaced forearm fractures are reviewed daily by the department's trauma surgeons. Any patients eligible for recruitment are referred to the PI for evaluation. Eligible patients are contacted by the PI and invited to a

scheduled visit as soon as possible. The parents are informed of the possibility of bringing an assessor. Parents, and when applicable the child, are informed face-to-face about the project. Parents are given both oral and written information. Patients are recruited at Herlev and Gentofte University Hospital by the principal investigator (PI).

Informed consent

Children are not able to give informed consent to participate in a study. Therefore, all legal guardians are asked to consent on behalf of the child. Oral and written information about the study, together with general information about participating in a research project from the Danish National Committee on Health Research Ethics is given face-to-face by the PI prior to asking for consent. Information is given in an undisturbed environment at the pediatric ward. The PI is the head of pediatric orthopedic trauma and is very skilled in communication with both parents and injured children.

Unstable or displaced diaphyseal forearm fractures usually do not require emergent treatment, but we strive to treat fractures as soon as possible. In planning, both surgeons and operating personnel need time to prepare for the specific procedure. Therefore, we ask that consent is given the day before surgery at the latest. Parents will in most cases have at least 24 hours to consider enrollment however, there might be factors (e.g. open fracture or neurovascular compromise) that dictate more emergent treatment requiring consent with less consideration time.

If participation is declined the patient will receive standard treatment with TEN, and standard rehabilitation and follow-up after 2 and 6 weeks and 6 months. TEN will be removed approximately 6 months after insertion during a scheduled outpatient operation under general anesthesia.

Follow-up

Outpatient visits are scheduled at 2 and 6 weeks, 3 and 6 months and 1 and 2 years following surgery.

All participants live in the catchment area of our hospital with short transportation time. Information about the time and place for the follow-up examination is sent via the electronic health record (EHR) and physically by mail to the current address registered in the Civil Registration System. Parents are usually very keen to take their children for follow-up appointments making the risk of missing an appointment low. Any participants who miss an appointment will be contacted by phone to reschedule.

Withdrawal

If a participant chooses to discontinue the follow-up examinations for any reason, the date and reason for drop-out is recorded and the latest examination will be carried forward in the analysis. In case of reoperation, the patients continue with their follow-up examinations and they are included in the 2-year analysis. In case of drop-out before the first follow-up visit the participant will be excluded from the

analysis. The author will record any protocol violations. Participants are only removed from the study if they decline participation.

Surgical technique and post-operative regime

The preoperative investigations are the same as for operations with a conventional metal implant. They consist of clinical history, physical examination and radiographs in anterior-posterior (AP) and medial-lateral (ML) plane. All operations will take place at our hospital and will be carried out by one of five experienced orthopedic trauma surgeons. The surgical procedure is almost identical with that of metal ESIN except the exchange to a bioabsorbable implant after dilation of the medullary canal.

The Activa IM-Nail™ is implanted according to the manufacturer's surgical technique. Operations are performed under general anesthesia together with a peripheral nerve block (PNB) [31]. Prophylactic antibiotics are given in the form of cloxacillin with dose according to the patient's weight. In the case of allergy towards cloxacillin, cefuroxime will be used as an alternative. Patients are in the supine position with the injured arm on a radiolucent arm table. One incision is made over the radial aspect of the distal radius taking care not to harm the dorsal branch of the superficial radial nerve. Another incision is made over the radial aspect of the proximal ulna. The customized instrumentation for the Activa IM-Nail™ is used. The cortical bone is opened using an awl and an appropriate size dilator is used. The dilator is replaced with the appropriate size bioabsorbable nail under image intensification to the desired depth and the implant is cut flush with the cortical surface. Wounds are closed using absorbable sutures and dressed. The injured arm is put in an above elbow posterior splint. Post-operative radiographs are taken. The patient is discharged when the effect of the PNB has worn of and the child is well, either on the same day or day after surgery. No formalized physiotherapy or rehabilitation is given beside oral and written information on exercises.

Risks, side effects and disadvantages

Based on previous studies using the Activa IM-Nail™ [7] we predict that the risk of side effects is comparable or less than those seen with metal ESIN.

Infection

Any surgery caries the risk of infection, however previous studies have shown close to no infection risk [3,32] with the ESIN procedure.

Nerve complications

Studies have shown a 5% risk of nerve injury [32], however all cases had spontaneous recovery of nerve function.

Extra visits to the outpatient clinic

We follow all patients with six visits to the outpatient clinic. This is three more than with standard treatment and might be viewed as a disadvantage.

Radiation

Three extra radiographs are obtained during outpatient visits. A radiograph of an extremity leads to a radiation dose of less than 0.001 mSv and compares to 3 hours of background radiation. Three extra radiographs is far below the threshold of 0.1 mSv.

MRI

Two years after surgery an MRI is performed. We follow a special MRI-protocol without the need for sedation or anesthesia.

Variables

At recruitment baseline data will be collected:

- Demographic data (age, gender, handedness, height and weight)
- Injury data (date and time, left or right arm, location, activity, mechanism, open or closed fracture, diagnosis code, indication for surgery)
- Historical data (metabolic disease, medication, other systemic illness)

After surgery, operative data is collected (date and time of surgery, operative time, closed or open reduction, any complications).

During follow-up in the outpatient clinic data will be collected on:

- Pain (Faces Pain Scale - Revised) or VAS according to child's age
- Use of pain medication
- Wound appearance (visible signs of infection)
- Neurovascular status
- Bilateral elbow and forearm range of motion (ROM) measured in degrees by goniometer
- Forearm radiographs in AP and ML planes (Radiographic Union Score)

2 years following surgery MRI findings (absorption of the nail, activity at fracture site, soft-tissue reactions) will be collected.

Outcomes

The primary objective is quantified using the Radiographic Union Scale (RUS) [33] based on degree of callus formation and visibility of fracture line on AP and ML plain radiographs. We define established healing as a RUS of > 9.

Secondary objectives are described as absolute risk of refracture, time to established healing (weeks), pain (Faces Pain Scale – Revised (FPS-R) or visual analogue scale (VAS)), elbow and forearm range of motion (in degrees), visible signs of infection, neurovascular complications and any reoperation. MRI findings (absorption of the nail, activity at fracture site, soft-tissue reactions) after 2 years are described.

The Radiographic Union Score

Fracture healing based on plain radiographs has largely been a subjective evaluation by the orthopedic surgeon. Whelan et al. developed the Radiographic Union Score (RUS) in order to quantify healing in tibial fractures [33]. RUS is a score derived from assessing AP and lateral radiographs. Each cortex (anterior, posterior, medial and lateral) is assigned a score of 1 to 3. A cortex with a visible fracture line and no callus is given a score of 1, a cortex with callus but a visible fracture line is scored as 2 and a cortex with bridging callus and no visible fracture line is scored as 3 (Table 1). Scores are added to give a minimum score of 4 (not healed) and a maximum of 12 (healed).

Table 1 – The Radiographic Union Score

Score per cortex	**Callus**	**Fracture line**
1	Absent	Visible
2	Present	Visible
3	Present	Not visible

Table 1 - The individual cortical scores (anterior, posterior, medial, and lateral) are added to provide a RUS of 4 (definitely not healed) to 12 (definitely healed).

RUS has since been shown to be a reliable and repeatable outcome measure to assess fracture healing, not only in the tibia [34–36]. RUS has also been shown to correlate well with physical properties of healing and a RUS of > 9 to be equal to established bone healing [37]. We find that the use of RUS is warranted in quantifying healing in our population. The surgeon who sees the patient in the outpatient clinic will calculate RUS.

Faces Pain Scale – Revised (FPS-R)

To measure the outcome of pain in children below 8 years of age we use the Faces Pain Scale – Revised (FPS-R) [38]. It is a self-report measure of pain intensity developed for children. It was adapted from the Faces Pain Scale [39] to make it possible to score the sensation of pain on the widely accepted 0-to-10

metric. The scale shows a close linear relationship with visual analog pain scales (VAS) across the age range of 4-16 years. It is easy to administer and requires no equipment except for the photocopied faces (Figure 1). The child is asked to point to the face that shows how much pain the child is in at that moment. Faces are scored 0-10 so 0 equals no pain and 10 equals very much pain.

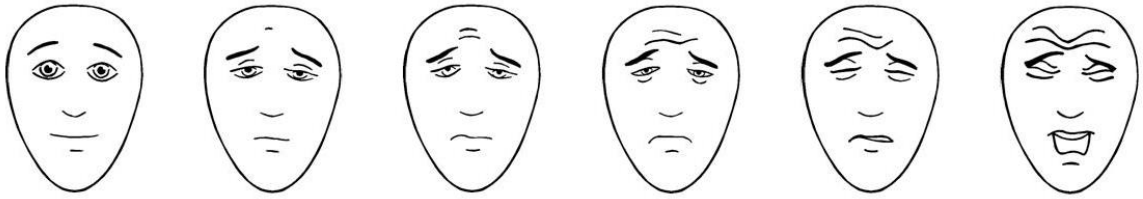

Figure 1 – Faces of the FPS-R. The child is instructed to point to the faces that shows how much pain the child is in at that moment. Faces are scored 0, 2, 4, 6, 8 or 10 from left to right.

Visual analogue scale

To quantify pain in children age 8 and above we will use a visual analogue scale (VAS) (Figure 2). VAS has been extensively investigated in quantifying pain in older children [40,41]. The child is asked to put a mark on the line corresponding to the child's pain at that moment. A mark to the far left equals no pain and a mark to the far right equals worst possible pain. The line is 10 cm long and the child's mark is measured from left to right in cm with one decimal e.g. 3.4 cm equaling a VAS of 3.4. If the child cannot cooperate to using VAS, FPS-R is used instead.

Figure 2 - Visual analogue scale (VAS) for quantifying pain in children age 8 and above.

Bias

We strive to minimize bias in our study. Displaced forearm fractures do not go unnoticed. A strict protocol for referrals for treatment are in place in Denmark. All eligible patients referred to Herlev and Gentofte University Hospital will be asked to participate in the study. We speculate that by enrolling 30 participants the cohort will be representative of the background population. We speculate that these efforts will limit

selection bias. Efforts described in the follow-up section reduce the risk of loss to follow-up. Overall, we find a low risk of bias in our study for the chosen study design and size.

Study size

The surgical procedure for the Activa IM-Nail™ resembles that of TEN very much and performing surgeons are all experienced traumatologists. All surgeons will be thoroughly introduced to the procedure, the instruments and the implants, thereby minimizing learning curve phenomenon. We predict that 30 participants will be sufficient in establishing the basis for planning a randomized trial.

Statistics

Data will be analyzed using SPSS (SPSS, Chicago, IL, USA). Descriptive statistics will be used to present the patient-related data, number of dropouts, radiological outcome and number of complications (categorical variables). Age and functional outcome (continuous variables) are expected to be expressed as medians with interquartile ranges. Changes in functional outcome between measurements are expected to be analyzed using Friedman test for related non-parametric data. A p-value of <0.05 is regarded as being significant.

Discussion

Operative treatment with metal ESIN is the preferred technique for stabilizing pediatric forearm fractures. Removal of the metal nails is generally advocated in many countries including Denmark. By using BIN, a second operation to remove the nails is avoided.

The hypothesis is that satisfactory fracture healing is accomplished 3 months after operation with BIN. The only previous study on BIN used forearm rotation and not fracture healing as primary outcome [7]. The authors describe that all 15 fractures operated with BIN had healed after 2 years.

The cost of one Activa IM-Nail™ ($400) is approximately 4 times higher compared with a traditional TEN ($100). However the cost of implant removal is approximately $1900 [7,42] and the extra implant costs are readily balanced out.

Ethics and security

Ethics

The implant is CE approved for the same indications as the use in this study. Permission from the Danish Data Protection Agency is obtained before the inclusion is initiated. The trial will be conducted in accordance with the Declaration of Helsinki of 1996 and principles of good clinical practice.

As with any treatment in the Danish healthcare system all patients are insured and covered by The Patient Compensation Association (Patienterstatningen).

To quantify any unknown side effects or complications an interim analysis of data will be performed 6 months after recruitment of the last patient. An absolute refracture rate of more than 25% is not tolerated and will be a criterion for stopping the study.

In comparison with the standard follow up of pediatric forearm fractures there are 3 additional visits to the out-patient clinic with radiographs of the forearm in AP and ML view. Collectively, the effective dosage is 0.003 mSv - far below 0.1 mSv and is considered insignificant.

Identification of the implant

The traceability of the device is identified by device name, catalogue number (REF) and batch number (LOT).

Hospital records

No access to the patient's EHR regarding the study is made before informed consent to participate is given.

In order to plan and conduct visits, admission and operation we ask that consent is given to access the patient's EHR. We ask permission to retrieve patient-related data and to read entries regarding visits, admission and operation. We ask permission to access radiographs and MRIs.

We ask that access the patient's EHR is given until the conclusion of the project.

Consent gives the person responsible for the trial and the relevant authorities direct access to obtain information in the patient's medical record for the purpose of carrying out the project as well as for control purposes.

Data security

The patient's hospital records are stored securely in the hospital's EHR (Epic Systems Corporation, Verona, Wisconsin, USA).

The project's Electronic Case Report Form (eCRF) is stored securely using Research Electronic Data Capture (RedCAP, Vanderbilt University, USA).

Radiographs and MRIs are stored in the hospital's Picture archiving and communication system (PACS).

The project complies with the EU's General Data Protection Regulation (GDPR) according to the Danish law on data protection *Databeskyttelsesloven* and *Databeskyttelsesforordningen.*

Publication

The study will be reported to ClinicalTrials.gov before trial initiation.

The results, both positive, negative and inconclusive, will be sent for submission in a peer reviewed international orthopedic journal, and the results will be presented at national and international scientific meetings. Reporting will adhere to the STROBE guidelines for cohort studies [30].

Perspective

If proven safe and effective, the use of BIN would deem hardware removal unnecessary and relieve the child of further surgery and reduce the healthcare costs.

This study is a pilot for a randomized controlled trial comparing the Activa IM-Nail™ (Bioretec Ltd., Hermiankatu 22, Tampere, Finland) to the Titanium Elastic Nail System (TEN) (Depuy Synthes, Raynham, Massachusetts, USA) which is currently used for pediatric forearm fractures in our hospital. This pilot study will diminish any learning curve, evaluate the clinical safety of the implant, and test the recruiting and follow-up of patients before embarking on the RCT.

Disclosures and economy

The initiative for this study has been taken solely by the authors.

The authors and affiliated colleagues have not received any financial payments or other benefits from any commercial entity related to the subject of this study. The authors declare that they have no conflict of interest.

Participants do not receive any economic benefits or gifts from the participation in this project.

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