No influence of ibuprofen on bone healing after Colles' fracture - A randomized controlled clinical trial

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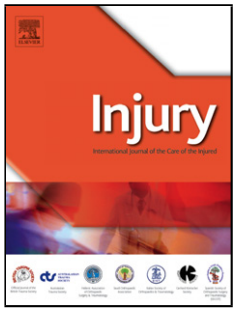

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Revision 1.

No influence of Ibuprofen on bone healing after Colles' fracture - a randomized controlled clinical trial

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HIGHLIGHTS

- Ibuprofen treatment seems not to have any negative influence on radiological outcomes of Colles' fracture.
- Ibuprofen treatment seems not to have any negative influence on functional outcomes of Colles' fracture.
- Ibuprofen treatment has the potential for opioid sparing effect for patients with the Colles' fracture.

ABSTRACT

Introduction: Nonsteroidal anti-inflammatory drugs (NSAIDs) may delay bone healing. This knowledge is mainly derived from retrospective uncontrolled clinical studies and from animal experiments. The purpose of this prospective controlled study was to investigate whether ibuprofen influences pain, function, and bone healing after a Colles' fracture.

Patients and methods: A single center, triple-blind, randomized clinical trial. 95 patients, 80 females and 15 males, with displaced Colles' fracture aged median 65 (range 40-85) years old were included and operated by external fixation from June 2012 through June 2015. 89 participants received interventional medicine and 83 completed the one-year follow-up. The 7-day ibuprofen group received 600mg of ibuprofen three times a day, the 3-day ibuprofen group received ibuprofen for three days and a placebo for the following four days, and finally, the placebo group received a placebo for seven days. All patients received paracetamol 1000 mg four times a day and 50 mg tramadol if needed. The primary outcome were radiological changes in radius tilt, length, and inclination observed during and 6 weeks after the surgery. The analgesic outcome were 14 days experience of pain, and registered use of tramadol. The functional outcomes were the percentage differences in the motion between the injured and non-injured wrist, and the DASH score at 3 and 12 months. All analyses were performed according to the intention to treat.

Results: No clinically relevant difference was observed in the radiological migration between the treatment groups, $0.064 \leq P \leq 0.81$. There was no difference in the pain score between the treatment groups, $P=0.13$. The use of tramadol was lower in the ibuprofen groups than in the placebo group, $P=0.035$. Ibuprofen treatment did not affect the range of motion, $0.148 \leq P \leq 0.963$. Patients in all groups demonstrated DASH score, and wrist motion improvement, close to 90% of normal amplitude. The complication rate was higher in the 7-day ibuprofen group compared to the placebo group, $P=0.043$.

Conclusions: Ibuprofen treatment demonstrated a tramadol-sparing effect during the postoperative period. Neither wrist function nor radiological migration were influenced. The complication rate was higher in the ibuprofen-treated group compared the placebo-treated group.

KEY WORDS: NSAIDs, ibuprofen, fracture healing, Colles' fracture fragment migration, pain, wrist function.

INTRODUCTION

Background

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used analgesics. They are inflammation-reducing medications. Inflammation is also an essential part of the early stage of bone fracture healing. Mechanical damage to bone cell membranes releases arachidonic acid, which is converted by cyclooxygenase-2 into pain-mediating pro-inflammatory prostaglandins. Fracture hematoma occurs immediately after injury due to broken vessels, is characterized by hypoxia and low pH, and contains pro-inflammatory cytokines and cells [1]. Cyclooxygenase-2 (COX-2) levels are increased in fracture hematomas and, besides having pro-inflammatory activity, are also able to promote angiogenesis and the differentiation of mesenchymal cells into osteoblasts [2].

Many animal studies show NSAIDs have an apparent tendency to delay bone healing [3] although the healing delay was not noticeable when NSAIDs were used for a short period of time of seven days [4]. There is still no consensus as to whether short-term NSAID treatment affects bone healing [5], [6].

A distal forearm hand fracture is a common injury with over 1.46 million new cases reported in 1998 in the United States, accounting for 1.5% of all emergency department cases [7]. Many older patients sustain this fracture and may subsequently experience reduced function of the injured wrist, especially if there is secondary dislocation of the bone fragments [8].

Rationale

The question is whether ibuprofen is an effective analgesic after Colles' fracture, without hampering bone healing.

PATIENTS AND METHODS

Study design and consent

Our study was a one-center, randomized, triple-blind, clinical trial in which patients with unstable Colles' fracture were recruited for treatment with ibuprofen or placebo. The study complied with the principles of the Declaration of Helsinki [9], followed Good Clinical Practice requirements [10], and was approved by the Danish National Medicines Agency (Reg. No. ******), the ****** Regional Ethics Committee (Reg. No. **********), and the ***** Data Protection Agency (J. no. *********). The study was registered with the European Clinical Trials Database (EudraCT number **********) and on the clinicaltrials.gov database (**********). None of the sponsors of this study was involved in the design or conduct of the study, data analysis, or writing of the manuscript. The first author takes responsibility for the integrity and accuracy of the reported data and the fidelity of the study to the protocol. We followed the guidelines for reporting parallel group, randomized, controlled trials [11]. Independent monitors assessed the overall performance of the study.

Participants/study subjects

Patients with acute, unstable, Older type III–IV Colles' fractures who needed surgical treatment were selected at **********. Other inclusion criteria was age between 40 and 85 years. Exclusions criteria were age <40 years or >85 years, systematic treatment with NSAIDs, previous fractures of the wrist in question, a lack of mental and physical capacity to follow the study instructions, medical contraindications to the use of NSAIDs, pregnancy, and postoperative dislocation of the fracture.

Description of study treatments

The study was a prospective, randomized, 1:1:1 controlled, triple-blind clinical trial and consisted of three treatment groups. The 7-day ibuprofen group was treated with 600 mg of ibuprofen three times daily for seven days. The 3-day ibuprofen group was treated with 600mg of ibuprofen three times daily for the first three days and then given a placebo three times daily for the remaining four days. The placebo group was treated with a placebo three times daily for seven days. The patients

did not receive prophylactic medication with proton pump inhibitors or other acid neutralizing agents.

The Hospital Pharmaceutical Department performed block randomization 45 + 48 + 3. The patient, the surgeon, the data manager, and the statistician were all blinded.

Participants received a package of dosed analgesics, each of which included 1 g of paracetamol, four times a day for seven days, six 50 mg tablets of tramadol for use at the patient's request, and the specified doses of ibuprofen or placebo.

External fixation bridging using K-wires and a Hoffman II external fixator (Stryker®) was preferred as the standard method of surgery in this study. This operation can be used to treat unstable fractures [12] and remains a viable method of treatment [13]. The same surgeon performed all surgeries in this study to standardize the treatment as best as possible. All patients received an infra-clavicular regional nerve block, either with or without general anesthesia.

For logistical reasons as a result of reduced capacity of the operating department, it was not possible to operate on patients at the same time after injury. The median operation time was two days post injury, with an overall range of 1 – 3 days post injury.

Description of follow-up routine

All patients were invited to outpatient clinic for

- one weeks' control (radiological assessment)
- two weeks control (radiological assessment, collection of pain diary)
- six weeks' control (radiological assessment, removal of external fixation, measurement of range of motion in both wrists)
- three months' control (range of the motion, evaluation of the DASH score)
- one-year control (range of the motion, evaluation of the DASH score).

Outcome measures

The primary outcome were the radiological migration of bone fragments. The degree of displacement with regard to radius tilt, length, and inclination was determined using the EasyViz diagnostic program (Karos Health Incorporated), and calculated as the difference between the result immediately after surgery and the result at six weeks post-operatively. The fractured bone fragments were expected to migrate from the best position immediately after surgery toward a worse position [14, 15, 16]. Three radiological measurements were evaluated. The distal radius inclination: the angle

between the radius' joint surfaces (the ulnar corner and the tip of the radius styloid in the anteroposterior projection). The dorsal tilt of the radius' distal fragment: the angle between the longitudinal radius' axis and the radius' joint surface in the lateral projection. The distal radius length between the ulnar joint surface and the tip of the radius styloid in the anteroposterior projection.

An image intensifier was used during the operations and its pictures saved for documentation and analysis. Length in those pictures was measured in pixels, whereas, standard X-ray pictures from controls used mm as the unit of measurement. A standard 1.4 mm K-wire was used as a calibration device on perioperative pictures to measure thickness in pixels and to calculate an individual pixel value in millimeters, using the formula: pixel value = $\frac{1.4\ mm}{number\ of\ pixels\ between\ edges\ of\ K-wire}$.

The evaluation of ibuprofen's analgesic effect using the daily pain score, measured with the Likert 10-point scale [17], one point for "no pain" and ten for "unbearable pain." The patients were asked to register their pain from inclusion in the study and three times a day for the following 14 days, and to record the use of tramadol. The mean pain score for each of the three groups during the period of 1 – 3 days, 4 – 7 days, and 8 – 14 days was calculated.

As the functional outcomes, we evaluated the analgesic effect of ibuprofen, wrist range of motion, and the DASH score [18].

We measured the motion of the wrist from the neutral position in extension and flexion; supination and pronation; and radial and ulnar deviation. The range of motion was measured at six weeks, three months, and one-year follow-up, and percentage difference in the range of motion between injured and non-injured wrist was calculated.

The DASH survey contained 30 questions with a focus on standard circumstances in everyday life. Each inquiry had a five-point scale, with one point scored for the best function, and five points for the worst. DASH surveys with three or more unanswered inquiries were excluded from the data analysis. The estimation of the DASH result was computed by use of the formula: [((sum of points from n responses)/n) - 1] x 25, where n was the number of questions answered by the patient.

Missing data were multiply inputted in the primary analysis by an independent blinded statistician to increase the precision of the estimates and to avoid potential biases.

Statistical analysis, study size

A detailed statistical analysis plan was made publicly available before the follow-up was completed and the analyses were performed [19]. The sample size calculation was based on changes in radius tilt to test the null hypothesis that NSAID treatment was not inferior to the placebo. The calculation was based on a one SD=9.4° incidence of dorsal tilt [20] and 8° as the limit of reliable measurement [21]. The power was defined to 90%. Therefore, to attain a 90% probability of rejecting null hypothesis using a one-sided 0.05 level test, 66 participants (three equal groups of 22 patients) were required.

To allow for a combined 20% dropout rate and loss to follow-up, and to approximate the normal distribution, 96 participants were recruited in total being three groups with 32 patients in each.

Frequency histograms and Q–Q plots were used to check whether the data from each sample were normally distributed or not. In cases where the data were normally distributed and there was homoscedasticity in all samples, Student's t-tests with a Dunn–Šidák correction ($\alpha = 1 - (1 - 0.05)^{1/k}$, where k is the number of tests, performed) were used to detect significant differences between mean group changes for all outcomes. If the data were not normally distributed, the Kruskal–Wallis nonparametric significance test was used.

Additionally, a Z-test was performed to compare the proportions of side effects and complications between the treatment groups.

MATERIALS

A total of 280 patients were screened between 1 June 2012 and 20 June 2015 (Figure 1, Table 1). Of these patients, 95 were included (an enrolment rate of 33.8%), 121 (43%) were not asked to participate due to time shortages in the emergency department, 45 (16%) were not interested in participating, and 19 (6.8%) fulfilled the exclusion criteria. One pack containing study medication was given to a patient with another type of fracture.

The majority (n=80) of included patients were women, and the median age was 65 years (range: 42–85 years). 89 of the included patients received the allocated treatment while the remaining six patients did not (regret, noncompliance). Four patients retracted their acceptance to participate, three patients lost their pain diary, one patient suffered side effects from the treatment (nausea) and left the study, one patient died before the 1-year follow-up, and one patient was operated on in a different way to that predefined in this study and was subsequently excluded with a secondary dislocation. One patient was excluded from the radiological evaluation due to insufficient quality of

the X-ray pictures. 85 patients, divided into three groups, were analyzed according to the intention to treat.

RESULTS

Radiological outcomes

The changes in radius tilt, length, and inclination followed the same trend in all groups. There were no clinically relevant or statistically significant differences ($0.064 \leq P \leq 0.81$) in radiological migration between the treatment groups (Figure 2).

Pain outcomes

There was no statistically significant difference in the mean pain score between the treatment groups at any time of follow-up, χ^2=3.95, P=0.13. (Figure 3).

Tramadol use was highest in the placebo group with the peak difference at day 2 (Figure 4). During the first 3 days, the median of tramadol consumption was 2 (0-7) tablets in the placebo group and 1 (0-9) tablet in the ibuprofen groups (χ^2=4.43, P=0.035).

Functional outcomes

Patients in all treatment groups demonstrated the same pattern of wrist joint motion improvement during the follow-up period, which corresponded to 87%–95% of the normal range of movement at the 1-year follow-up (Figure 5). No statistically significant differences were observed between the treatment groups at any of the follow-up checks (P=0.148–0.963, Table 5.7).

The placebo group achieved a higher mean DASH score of 19.95 (SD=14.18) than the 3-day (mean DASH score=17.87, SD=14.47) and 7-day groups (mean DASH score=15.07, SD=10.77). The mean DASH scores in treatment groups were not significantly different (χ^2=1.48, *P*=0.47, (Figure 6)).

Complications and adverse events

The most common complication was a gastrointestinal disorder, which was observed in four patients in the placebo group, seven patients in the 3-day group, and eight patients in the 7-day group (Table 2). The number of adverse events in the 7-day ibuprofen and placebo groups were significantly different (Z=1.709, P=0.043). We observed no severe treatment-related complications in any of the groups.

DISCUSSION

Although bridging external fixation with additional pinning of Colles' fracture fragments is recognized as a reliable method of osteosynthesis [22], the stability is not rigid and fragments will migrate even six weeks post-operatively [23]. A systematic search in PubMed and Embase identified two studies [24, 25] that describe the radiological migration of Colles' fractures in relation to NSAID treatment. Both of these studies treated their patients conservatively, and therefore the results cannot be compared with the radiological outcomes of this study.

The results from this study are comparable with other studies that described radiological outcomes after bridging external fixation of the distal radius. In a randomized prospective study comparing different types of osteosynthesis six weeks after external fixation, Wei et al. [20] found a similar radial inclination, volar tilt, and radial length in the external fixation group. Wright et al. [26] compared radiological outcomes in their retrospective study of volar plating and external fixation and found a radial inclination and a volar tilt at 47 months follow-up, comparable to our results. Our study shows the same pattern of fragment migration in all treatment groups and no statistically significant difference was found in the extent of the secondary displacement. Average inclination, tilt, and length of the distal radius in all treatment groups was comparable to normal anatomical form, which is essential for long-term wrist function as described by Dario [27].

This study showed no significant differences in the pain experienced between the groups treated with ibuprofen or the placebo group. All patients received sufficient pain treatment with paracetamol as the primary treatment, with or without ibuprofen as a supplement, and tramadol as an escape medicine. The 3-day ibuprofen group reported increased pain from day 3 to day 4, which corresponded to the time when ibuprofen was replaced with the placebo, and pain remained higher in this group during the 14-day follow-up period.

Tramadol use during the first three days was significantly higher in the placebo group compared to the ibuprofen treatment groups. Our results suggest treatment with ibuprofen in the acute phase may be beneficial and have an opioid-reducing effect, as it is demonstrated by other studies[28]. Patients with shorter-term or no ibuprofen treatment requested more tramadol to maintain their pain at the same acceptable level as patients treated with ibuprofen for seven days.

Davis et al. [25] treated Colles' fracture patients in a prospective randomized, double-blind study using flurbiprofen for 14 days. The authors found significant pain relief and a paracetamol-sparing

effect during the first three days but reported results in categorical units. The varying doses of NSAIDs in the intervention group and a mean age difference of 8.4 years between the treatment groups makes the interpretation of their results difficult.

Adolphson et al. [24] performed a prospective randomized, double-blind study with two treatment groups containing 21 postmenopausal women with Colles' fractures in each. One group was treated with piroxicam and the other was treated with placebo, for eight weeks. Paracetamol was given as a rescue medicine. Pain level was assessed with a 10-point visual analog scale and was found to be 2.1 in the piroxicam group and 3.1 in the placebo group at ten days. Consumption of rescue medication was significantly less in the piroxicam group. This study included a small sample size of severe, comminuted, unstable fractures scheduled for conservative treatment where 14% of the patients subsequently were surgically treated with external fixation. The severity of the fracture and the treatment method may be confounding factors in pain experience and functional outcomes.

Lee et al. [29] performed a prospective, randomized study regarding the effect of transcutaneous electric nerve stimulation (TENS) on acute pain after Colles' fracture. The authors found the mean pain VAS score reduced from 5.5 points on day 1 to 3.5 points on day 4 in subjects that received the TENS treatment. All patients were treated with NSAIDs and were operated on using volar plating. In our study, patients reported less pain during the first days, likely due to the minor surgical intervention. The pain experienced later in Lee's study was comparable to our results.

In our study, wrist joint mobility improved equally in all treatment groups during the first year after injury. A previous prospective study by Davis et al.[25] described the influence of NSAIDs on functional outcomes after Colles' fracture and demonstrated no differences in one-year functional outcomes of displaced fracture, after two weeks of treatment with flurbiprofen. The patients used on demand medication for 14 days (three to six trials tablets daily). The inconsistent dose of NSAIDs in the intervention group and mean age difference of 8.4 years between intervention and placebo groups makes the interpretation difficult.

A prospective, randomized double-blind and placebo-controlled study by Adolphson demonstrated a similar result. [24] There were no differences in functional outcomes at three months follow-up. The intervention group received piroxicam for eight weeks. A small sample size, coupled with severe comminuted Colles' fractures scheduled for conservative treatment and thus subsequent operation, of 14% of the study population, may influence the validity of this trial.

Wright et al.[26] compared functional outcomes in a retrospective study after volar plating and external fixation of Colles' fracture and reported similar DASH results in the external fixation group at 47-months follow-up.

Kamath et al.[30] showed in a cohort study that the mean DASH score and wrist range of motion at 18-months follow-up results were comparable to our study. Aktekin et al.[31], in their retrospective study, described the same DASH results at two-year follow-up. The patients in our study demonstrated DASH scores comparable to patients treated with volar plating in a study by Richard [32].

Treatment with ibuprofen did not demonstrate significant changes in DASH score between treatment groups. On the other hand, ibuprofen seems to may have a dose-dependent improving influence on both 3-month and 1-year DASH outcome. The mechanism still needs clarification but may be explained by edema reduction [33] and tendon adhesions preventing the effects [34].

A study with extended ibuprofen treatment (several weeks or even months) may be more powerful in demonstrating the true influence on functional outcomes.

Prolonged treatment with NSAIDs is related to an increased risk of cardiovascular, gastrointestinal, and nephrological disorders [35]. From a clinical perspective, a lengthy treatment is not necessary for the acute period and the following osteosynthesis of Colles' fracture.

The rate of complications and side effects was significantly higher in the 7-day ibuprofen group compared to the placebo group and gastrointestinal disorders were observed in all three treatment groups. A few patients may have experienced digestive symptoms due to other factors (e.g., stress during the first days after injury or surgery) and this has to be taken into account when determining whether the adverse effects are ibuprofen-related or not. The incidence rates for gastrointestinal disorders in the 3- and 7-day groups were 23.3% and 27.6%, respectively. These rates were higher than in other studies reporting oral treatment with NSAIDs [36]. We did not use prophylactic medication with proton pump inhibitors or other acid neutralizing agents. Given this, the number of side effects attributable to the NSAID use may probably be less.

Our study has several limitations. There are only a few randomized clinical trials regarding NSAID treatment of fracture patients. Patients sustained the fracture at different times of the day, some received analgesics on the morning of day one while others had no fracture and no pain until the evening of day one. This may lead to some uncertainty regarding the first day's pain experience and some variability at the moment when the patient took their last ibuprofen or placebo tablet after the injury. Attempts were made to include all patients during their first visit to the emergency department; however, it was not possible to assure that all patients took the medicine at the same time after the injury.

Some patients also waited a day or more hoping that they only had a sprain or contusion and therefore came to the emergency department on the second or third day. Others were not asked to participate in the study because staff were too busy, and this job was left to the researcher to do 1–2 days later. These logistical reasons meant that it was not possible to assure that ibuprofen was given at the same time point of the fracture inflammation phase.

Shortages in the operation department's capacity also meant that it was not possible to operate on the patients at the same time after injury. This caused that pain symptoms were relieved by regional anesthesia at different periods during the first 3 days, which may explain some irregularities in pain dynamics in the patient's diaries. This limitation is in some degree compensated by equal distribution of the treatment and operation time in our study groups.

Another potential limitation was the lack of exact standardization using X-ray pictures and lateral projections, as these may vary by a few grades in rotation and may influence the subsequent tilt assessment. There was also uncertainty in measuring the radius length in the perioperative pictures due to the blurred contours of the K-wire, zoomed digitally.

The part of the study describing the functional and radiological outcomes had a non-inferiority design. The limitation of the non-inferiority design is whether there was a proper sample size. Treatment groups demonstrated a difference in the range of motion and DASH scores that were less than 30% of the SD within groups and differences in radiological migration that were less than 50% of the SD within groups. With an α significance level of 0.05 (according to recommendations for non-inferiority trials [37]), the sample size in this study was considered to have proper strength.

CONCLUSIONS

The treatment with ibuprofen had an opioid-sparing effect and did not demonstrate any harmful influence on a patient's radiological and functional outcomes. These findings may offer support as an indication for ibuprofen treatment in the acute fracture phase; however, the risks of ibuprofen's side effects need to be considered.

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LIST OF FIGURES AND TABLES

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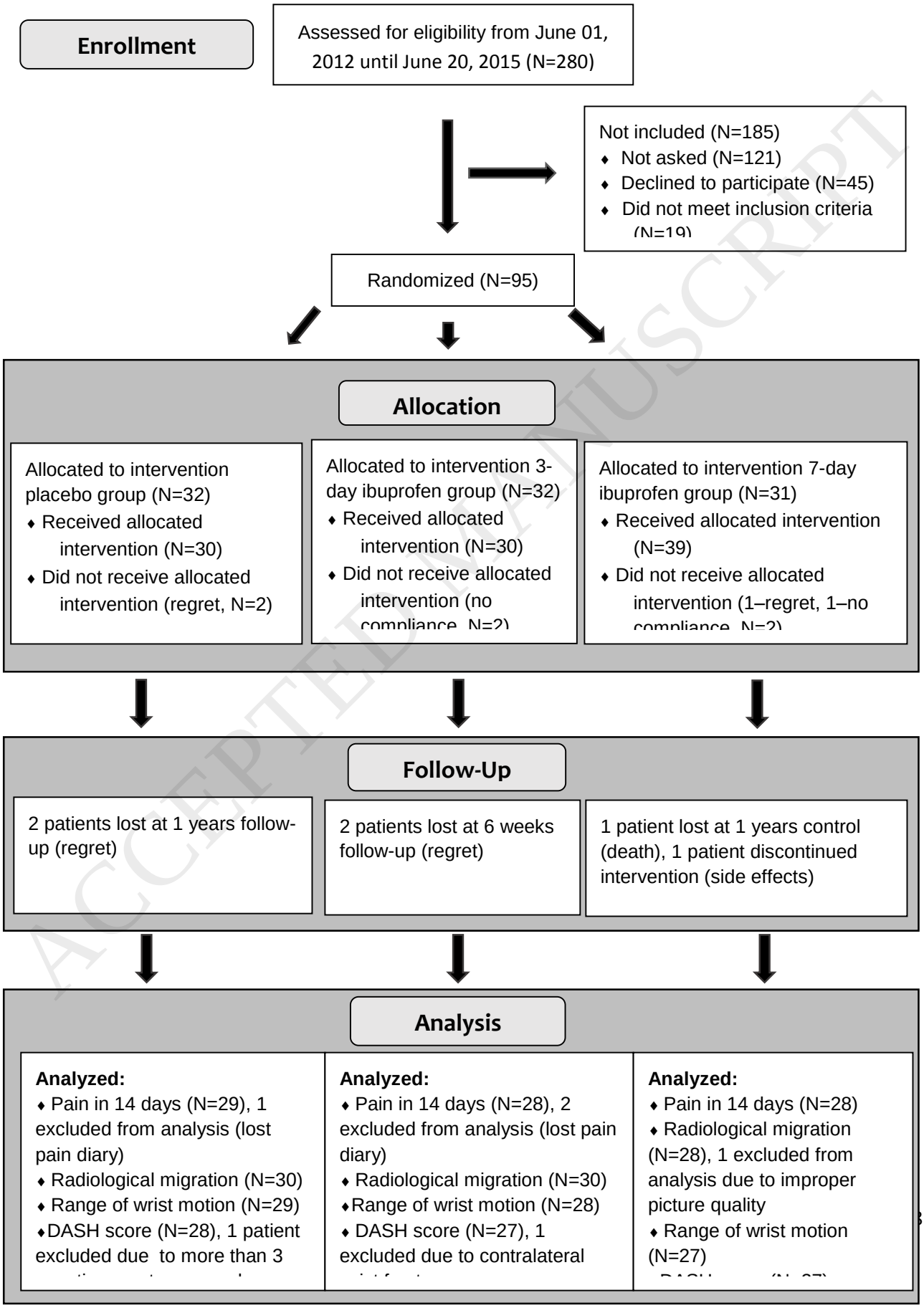

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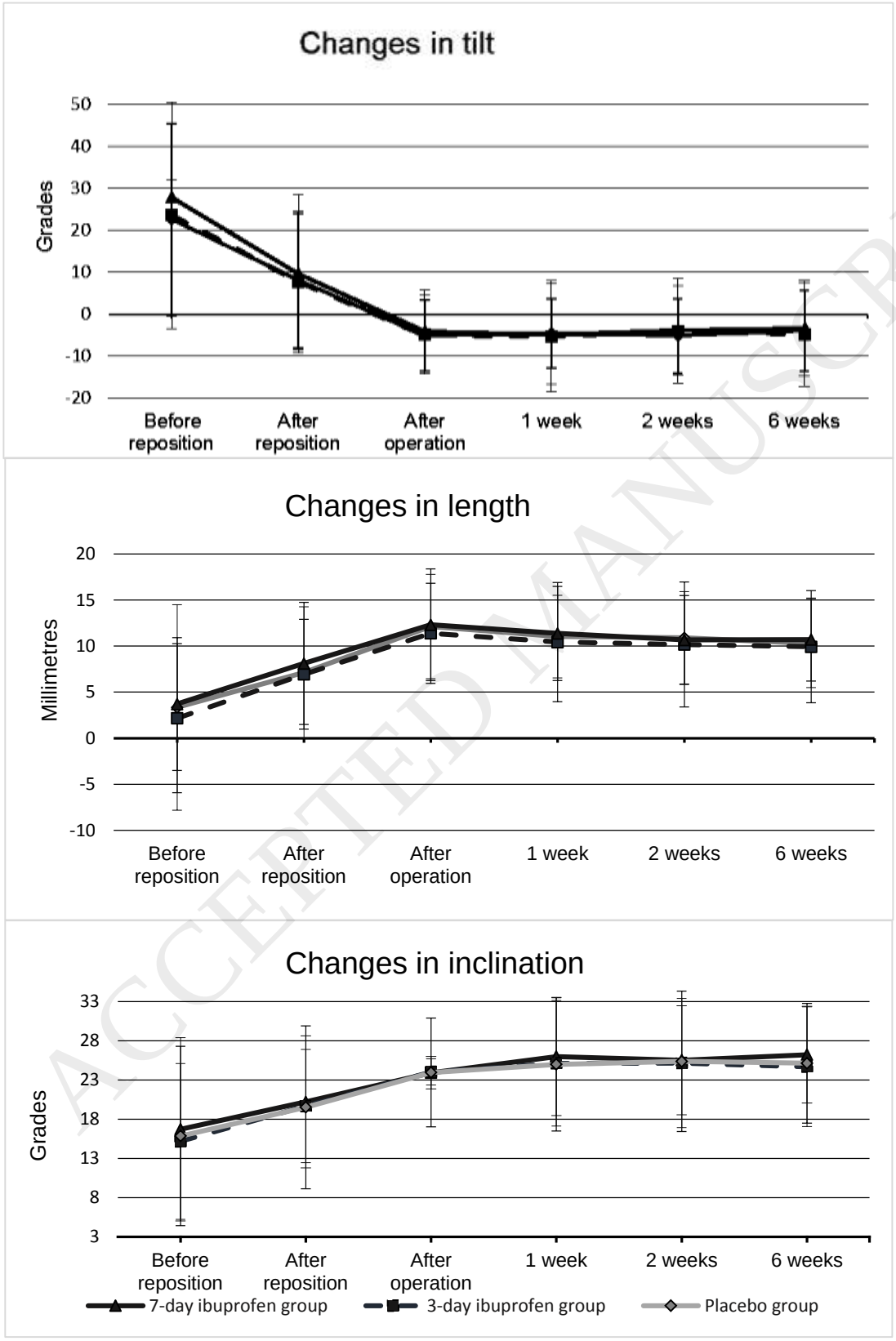
Figure 2. Radiological fragment migration in treatment groups (with 95% CI)



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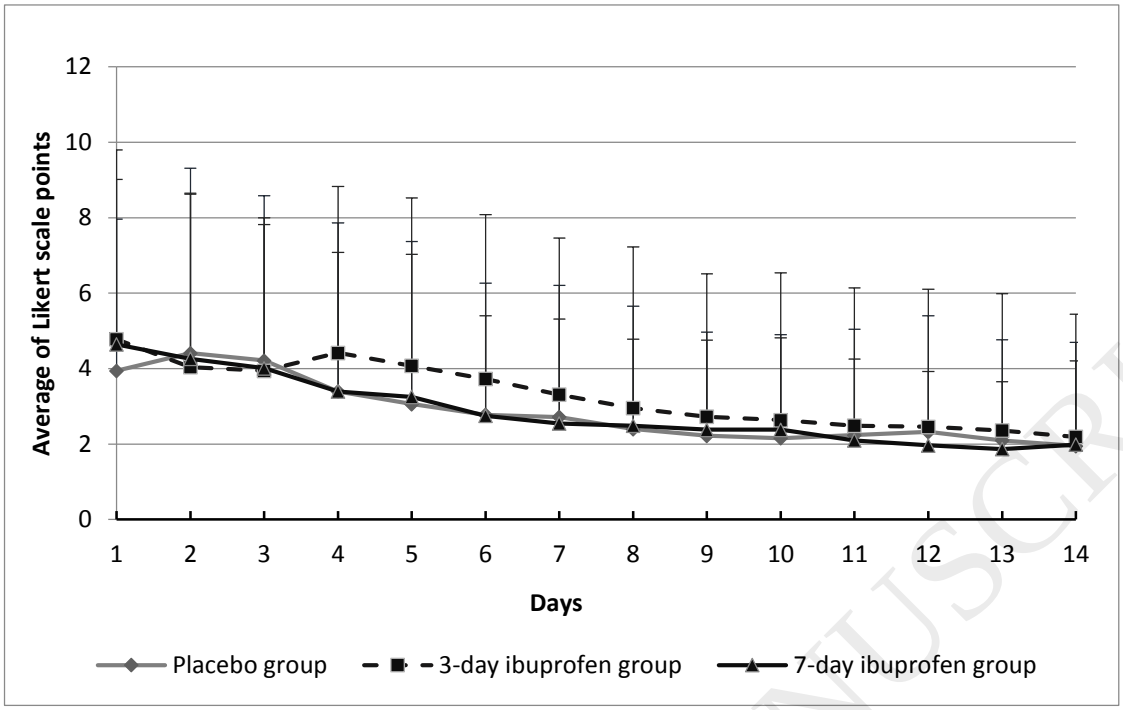

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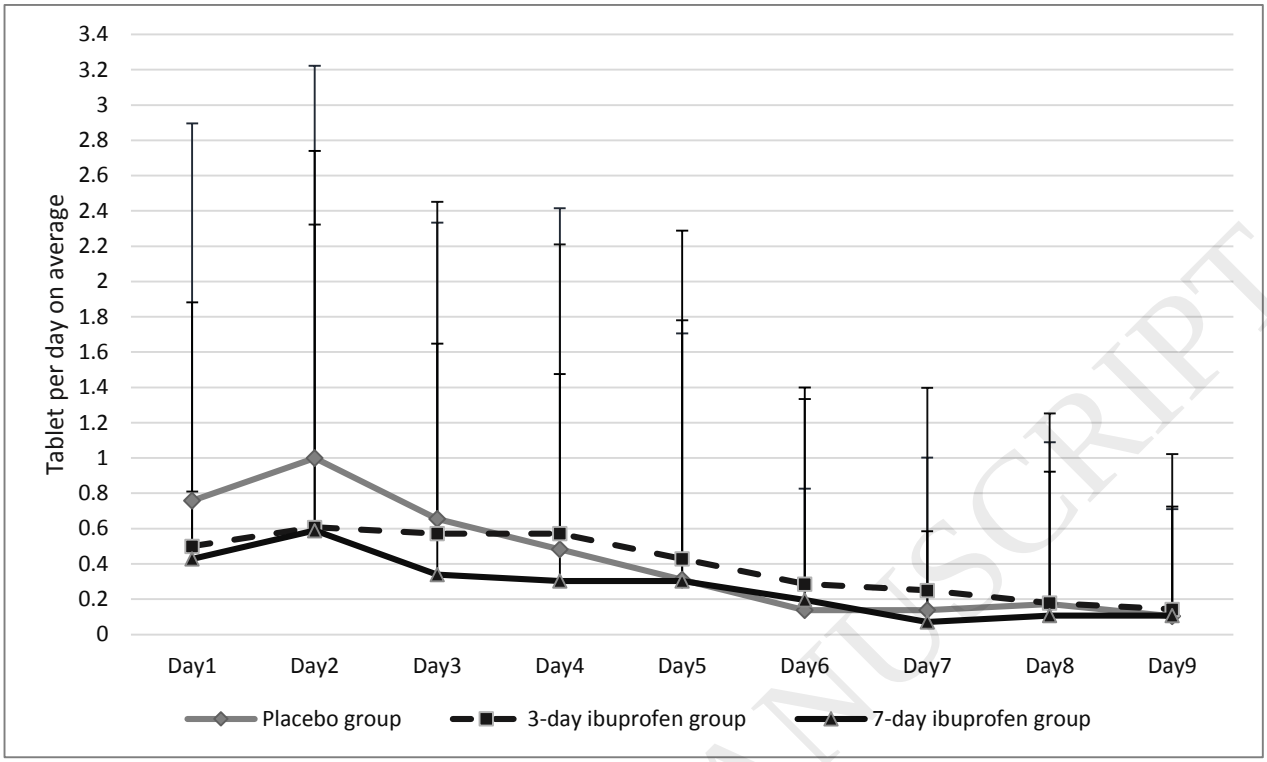

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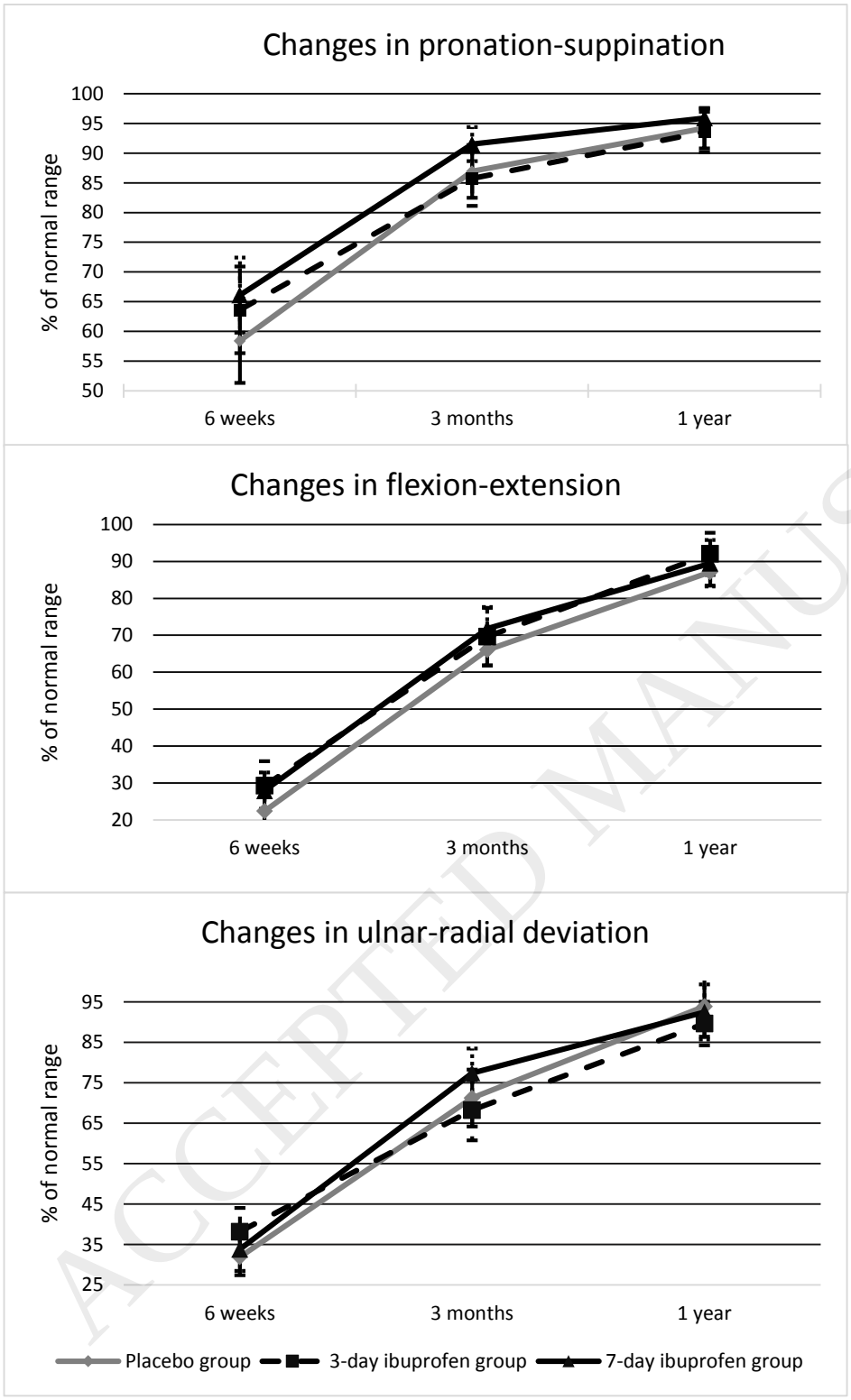
Figure 5. Changes in range of movement in the injured wrist joint (with 95% CI)



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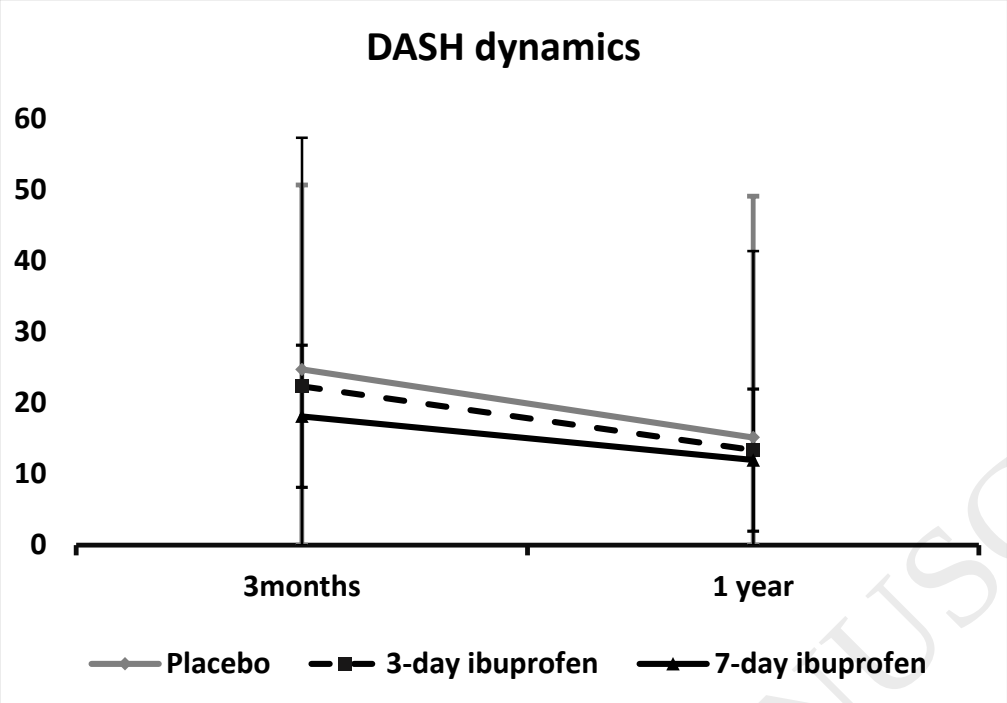

Table 1. Baseline characteristics of the study patients

Table 1. Baseline characteristics of the study patients

Group	Total analyzed	Female\Male	Average age (years)	Dominating\Not
Placebo group	30	25\5	64.3 ± 4.4	15\15
3-day ibuprofen group	30	25\5	67,8 ± 10	13\17
7-day ibuprofen group	29	24\5	65,4 ± 7.9	14\15

Table 2. Adverse events

Table 2. Adverse events **comparison of the placebo group and the 7-day group*

	Placebo group	3-day group	7-day group	Statistics
Overall	**10 of 30**	**12 of 30**	**16 of 29**	**Z* = 1.709, *P* = 0.043**
Gastrointestinal disorders	**4**	**7**	**8**	
Nerve numbness	**6**	**2**	**5**	
Pinholes infection	**0**	**1**	**2**	
Loosening of osteosynthesis material	**0**	**2**	**0**	
Serious secondary dislocation	**0**	**0**	**1**	

Revision 1.