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A Randomized Controlled Clinical Trial

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Influence of ibuprofen on bone healing after Colles' fracture - a randomised controlled clinical trial

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Author contributions statement

Marius Aliuskevicius contributed in research design, patient enrolment, sample collection, acquisition, analysis and interpretation of data, drafting of the paper. Svend Erik Østgaard contributed in revising of the paper. Ellen Margrethe Hauge contributed in analysis of bone biopsies and revising of the paper. Peter Vestergaard contributed in analysis of DXA scanning and revising of the paper. Sten Rasmussen contributed in research design and revising of the paper.

All authors have read and approved the submitted manuscript.

ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) may delay bone healing. The purpose of this prospective controlled study was to investigate whether ibuprofen affects bone

mineral density, turnover biomarkers, and histomorphometric characteristics of the callus after a Colles' fracture.

This study was a single centre, triple-blinded, randomised clinical trial. Ninety-five patients (eighty females) with displaced Colles' fracture, median age 65 (range 40–85) years were included in the study and operated on by external fixation from June 2012 through to June 2015. 89 patients received interventional medicine and 83 completed the one-year follow-up. The 7-days ibuprofen group received 600 mg of ibuprofen three times a day (N=29), the 3-days ibuprofen group received ibuprofen for three days (N=30) and a placebo for the following four days, and finally, the placebo group received a placebo for seven days (N=30). The primary outcome was the difference in bone mineral density between the ultra-distal region of the injured and non-injured radius at three months after surgery. The histomorphometric outcomes included assessment of callus tissue volume- and surface fractions at six weeks postoperatively. The biomarkers Osteocalcin and CrossLaps were measured at baseline, one week, two weeks, six weeks, three months, and one year. We included the results of the dropped-out patients in the intention to treat analysis. There was no difference between treatment groups in bone mineral density, histomorphometric estimations and changes in bone biomarkers. These findings may offer an indication of ibuprofen as a bone-safe analgesic treatment in the acute fracture phase.

KEYWORDS: ibuprofen, fracture, DXA scanning, bone biomarkers, callus histomorphometry.

INTRODUCTION

The distal forearm fracture is a common injury in the elderly population. Nonsteroidal

anti-inflammatory drugs (NSAIDs) are one of the most used analgesics. There is still no consensus as to whether short-term NSAID treatment affects bone healing.[1,2] Despite this, it is a general recommendation to use caution when treating pain with NSAIDs for fracture patients, [2] and further prospective clinical studies are warranted.[3]

More than 1.46 million new cases of Colles' fractures were reported in 1998 in the United States, accounting for 1.5% of all emergency department cases.[4] Many older patients sustain this fracture and may subsequently experience the reduced function of the injured wrist, especially if there is secondary dislocation of the bone fragments.[5]

Inflammation is an essential part of the early stage of bone fracture healing.[6] Mechanical damage to the bone cell membranes releases arachidonic acid, which is converted by cyclooxygenase-2 into pain-mediating pro-inflammatory prostaglandins. Fracture haematoma, occurring immediately after injury due to broken vessels, is characterised by hypoxia and low pH and contains pro-inflammatory cytokines and cells.[6] Cyclooxygenase-2 (COX-2) levels are increased in fracture haematomas and, besides having pro-inflammatory activity, are also able to promote angiogenesis and the differentiation of mesenchymal cells into osteoblasts.[7]

Many animal studies show that NSAIDs have an apparent tendency to delay bone healing [8], although the healing delay was not noticeable when NSAIDs were used for a short period of seven days.[9] The prospective human studies report clinical outcomes such as dental pocket depth [10], pain, joint motion, and implant migration [11] with no adverse effects of NSAIDs reported.

The randomized, controlled clinical trial, investigating clinical outcomes of Colles' fracture found no influence of ibuprofen on fragment migration, and wrist function.[12] In

addition to clinical outcomes, described in our previous study, ”DXA, histo, and sero” exist in helping to understand the physiological aspects of fracture healing.

A dual-energy X-ray absorptiometry (DXA scanning) is a non-invasive method for determining bone mineral density (BMD) and is widely used in diagnosis of osteoporosis. Evaluation of traditional radiographs of healing fractures is highly subjective and can have as much as 20–25% inter-physician variability.[13] DXA scanning allows quantified evaluation of the mineralisation process in the maturing callus. Although this method is not the standard tool in orthopaedic surgery, it wins more popularity in experimental studies. A high correlation between BMD and mechanical rigidity of the callus has been previously reported.[14] This method was used for the evaluation of the NSAID effect on fracture healing in animal models,[15] and has the potential for a more accurate fracture repair assessment in humans.[13]

Quantitative analysis of bone callus (histomorphometry) is a potential tool for investigating bone repair.[16] It provides counting and quantification of qualitatively assessed bone structures, as bone (lamellar and woven) volume, fibrous tissue, osteoid volume, compared with total tissue volume. It also allows evaluation of bone resorption, regeneration, and repair process by estimation of bone surface fractions.[17] Bone surface, covered by osteoid, and/or osteoblasts, represents bone regeneration. On the contrary, surfaces, covered by osteoclasts, are the sign of bone destruction/resorption in the process of fracture healing.[18]

Serological bone biomarkers are another tool with the potential to detect any disturbances in the physiology of bone healing. The bony destruction is followed by synthesis of the new bone matrix.[19] Type I collagen accounts for more than 90% of the organic matrix of

bone and is synthesised primarily in bone.[20] C-terminal telopeptide (CrossLaps) is released after bony breakdown [21], and small peptide fragments are secreted into the bloodstream, to be eliminated later by renal excretion. These fragments can be measured using immunoassays. During the later fracture healing process, the increased activity of osteoblasts can be quantified by measuring serum levels of osteocalcin, the product of osteoblasts [22], and thus monitoring the process of bone formation.[23] In consideration of the non-invasive, dynamic picture of the healing process of the fracture [24], bone markers are used for investigative purposes. Their serum levels may vary highly between individuals, fracture severity, performed surgery [25], and circadian variation.[21]

The research objective is, whether short-term treatment with Ibuprofen in the acute phase of Colles' fracture hampers bone healing and callus maturation in terms of densitometric, histomorphometric, and biochemical outcomes in elderly patients.

MATERIALS AND METHODS

Study Design and Consent

Our study was a one-centre, randomised, triple-blinded, clinical trial in which patients with unstable Colles' fracture were recruited for treatment with ibuprofen or placebo (Level 1 of Evidence). The study complied with the principles of the Declaration of Helsinki [26], followed Good Clinical Practice requirements [27], and was approved by the Danish National Medicines Agency (Reg. No. 1253599), the Danish Regional Ethics Committee (Reg. No. N-20100015), and the Danish Data Protection Agency (J. no. 2008-58-155 0028). The study was registered with the European Clinical Trials Database (EudraCT number 2010-018543-34) and on the clinicaltrials.gov database (NCT01567072). 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, randomised, controlled trials.[28] Independent monitors assessed the overall performance of the study.

Patients Patients with acute, unstable (Older classification type III–IV) Colles' fractures, requiring surgical treatment, were selected at the Aalborg University Hospital, Denmark. Another inclusion criterion was to be aged between 40 and 85 years. Exclusions' criteria was 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 displacement of the fracture, if re-operation was indicated.

Description of Study Treatments

The study was a prospective, randomised, 1:1:1 controlled, triple-blinded clinical trial and consisted of three treatment groups. The 7-days ibuprofen group was treated with 600 mg of ibuprofen three times daily for seven days. The 3-days ibuprofen group was treated with 600 mg 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 neutralising agents.

The Hospital Pharmaceutical Department performed block randomisation of 5×9 + 8×6 + 1×3. 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.

We preferred a bridging external fixation using 1.4mm K-wires and a Hoffman II external fixator (Stryker®) as the standard method of surgery for all patients in this study.

This operation can be used to treat unstable fractures [29], and remains a viable method of treatment.[30] The same surgeon performed all surgeries in this study so as to standardise the treatment as best as possible. All patients received an infra-clavicular regional nerve block, either with or without general anaesthesia.

For logistical reasons, because of the 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.

Outcome Measures

The primary outcome was the change in BMD in the injured wrist compared with the contra-lateral non-injured wrist. Study participants were scanned at three months after injury using a Discovery A DXA-scanner (Hologic Inc., MA, USA). For lumbo-sacral bone mineral density (LS-BMD) the in vivo precision (CV%) at our facility is 0.90%, for total hip 1.00% and for the femoral neck 1.79%.

The region of interest was determined as the 30 mm wide ultra-distal zone UD, starting at the distal ulnar edge of the radius. The outcome was the percentage of injured wrists' BMD compared with the healthy contralateral wrists' BMD as the reference.

We used the Cobas e 411 ECLIA immunoassay analyser (Roche Diagnostics®) to determine our secondary outcome–levels of serum CrossLaps and osteocalcin. To avoid circadian level variation, all blood samples were collected from fasting patients at 9.00 a.m. by a medical laboratory technologist from the Department of Laboratory Medicine. We took the blood samples before surgery, at one-week, two-weeks, three-months, and one-year follow-up visit for each patient. Blood sampling tubes were filled with a K_3-EDTA and Li-heparin plasma. All blood samples were stored at 5 ºC temperature and analysed after the last follow-up visit of the last patient. After two points' calibration and generation of the master-curve, the immunoassay analysis was performed by using monoclonal anti-ß-CrossLaps and anti-N-MID osteocalcin antibodies (mouse-derived).

We took the biopsy from the callus at 6-weeks follow-up visit after surgery at the time of external fixation removal in the outpatient clinic. The biopsy location; central dorsal over the fracture site, was determined by using an image intensifier and marked on the skin. We injected 5 ml of 0.55 Lidocaine for local anaesthesia and used a T-Lok™ Bone Marrow Biopsy Needle of 13 G (Product No. DBMNJ1304, ARGON® Medical devices) to obtain a 5–7 mm long bone callus biopsy. The material was placed in a plastic tube with a 70% alcohol solution and stored at 8 ºC temperature. The biopsies were embedded undecalcified in methylmethacrylate (MMA). 7 µm sections were cut using a Jung microtome model K (R.Jung GmbH, Heidelberg, Germany), equipped with a tungsten knife. The biopsies were cut into the middle in order to get the largest possible area. Four levels with three sections on each level were cut with a distance of 175 µm. The sections were stained with Goldner Trichrome.

We compared histomorphometric characteristics of the volume and surface in the callus between treatment groups: bone volume/tissue volume (BV/TV %), woven bone volume/tissue volume (WBV/TV %), lamellar bone volume/tissue volume (LBW/TV %), fibrous tissue volume/tissue volume (FV/TV %), osteoid volume/tissue volume (OV/TV %), osteoid surface/bone surface (OS/BS %), osteoblast surface/bone surface (ObS/BS %), and osteoclast surface/bone surface (OcS/BS %).[17]

The same observer performed all the analyses using an Olympus BH microscope with 200 times magnification and polarized light (used for differentiation between lamellar and woven bone). All sections of each biopsy were analysed with five sight fields in each biopsy. We used a 10 ×10 point ocular-grid was used for volume estimations (with a total 100 volume points of reference) and ten line-grids for surface estimations (the reference was the number of all tissue surface-grid line crossings). The line-grid was rotated randomly for each area. Randomly collected biopsies (10%) were evaluated after three months to calculate the observers' repeatability in terms of the coefficient of variation (CV%) with 95% of confidence intervals.

Statistical Analysis, Study size

The sample size calculation was based on the difference in radius BMD between injured and non-injured wrists to test the null hypothesis that NSAID treatment was not inferior to the placebo. The calculation was based on a one standard deviation of 4.35% difference between the baseline BMD and BMD after injury at three months follow-up visit [31] and 3.35% as the non-inferiority limit after 1% error of precision [32] was subtracted. The power was defined to 90%. Therefore, to attain a 90% probability of rejecting the null hypothesis using a one-sided 0.05 level test, 93 participants (three equal

groups of 31 patients) were required. Thus, we recruited 96 participants with 32 patients in each treatment group.

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, the ANOVA test with post hoc Tukey test was 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.

Intra-observer repeatability of histomorphometric estimations was calculated as the coefficient of variance (CV) of all characteristics. We used the formula: CV = $\sqrt{\frac{\sum(d/m)^2}{2n}}$, where d—the difference between two observations, m—the mean of two observations, and n—the number of observations.

Missing values were multiply inputted and included in statistical analysis.

RESULTS

Study Patients

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 lack of time in the emergency department, 45 (16%) were not interested in joining, 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). Eighty-nine of the included patients received the allocated treatment while the remaining six patients did not (regret, non-compliance). 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. Two patients were excluded from the histomorphometric evaluation due to insufficient quality of the biopsy material. For one patient, DXA scanning was not performed due to logistical reasons. Eighty-seven patients, divided into three groups, were analysed according to the intention to treat. We also included registered outcomes of the dropped-out patients in the data analysis.

DXA Scanning

The injured radius demonstrated a higher mean BMD value in the ultra-distal region of interest (Figure 2) compared to the non-injured contra-lateral radius. There was no significant difference between treatment groups, P=0.69 (Figure 3).

Histomorphometric Outcomes

No significant differences between treatment groups in both volume and surface estimations (Figure 4) have been detected, $0.38 \leq P \leq 0.99$ (Table 2). Median intra-observer coefficient of variance was 4.7%, range 0-36.9%. There was a trend of less woven bone, and more quiet bone (with no formation/remodeling or resorption activities) surface in the second evaluation. *Bone Biomarkers* Our study demonstrated no difference in plasma Osteocalcin ($0.43 \leq P \leq 0.99$) and CrossLaps

($0.37 \leq P \leq 0.95$) levels at any time in repeated measurements (Figure 5).

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-days group, and eight patients in the 7-days group (Table 3). The number of adverse events in the 7-days ibuprofen and placebo groups was significantly different ($Z=1.709$, $P=0.043$). We observed no severe treatment-related complications in any of the groups.

DISCUSSION

Our study has demonstrated no influence of short-term ibuprofen treatment on the healing of Colles' fracture in terms of bone mineral density in the distal radius, histomorphometric estimations of the callus, and bone biomarkers.

To our knowledge, there is only one study that previously looked at the effects of NSAID on BMD of the fractured and non-fractured distal radius, performed by Adolphson et al.[33] This prospective, randomised, double-blinded, and placebo-controlled study showed no difference between piroxicam and placebo-treated groups in changes of bone mineral content at eight weeks follow-up visit. A direct comparison to our study is difficult as the authors looked at the radius just proximal of the fracture. A small sample size, and inclusion of severe comminuted Colles' fractures scheduled for conservative treatment and subsequently operated, and excluded from BMD measurement, may influence the validity of this trial.

Van der Poest et al. [31] looked at effect of alendronate on bone mineralisation in the distal radius. The baseline DXA scanning in this study was performed approximately three months after injury and was 0.40 g/cm^2 ± 0.05 in total distal radius at the fracture site. In our opinion, it is more reasonable to evaluate only the ultra-distal region of interest to assess the quality of fracture healing, as the majority of notable callus fractures occur at the distal 38 mm.[33] Eastell at al. measured the UD region of the distal radius for 40 women after Colles' fracture and found a BMD comparable with our results.[34] Furthermore, this work concluded that with a BMD below 0.4 cm^2, the risk of the fracture in the distal radius increases significantly. Our study, with the overall BMD in the non-injured distal radius of 0.34 ± 0.26 g/cm^2 supports this conclusion.

Bone biomarkers are often used for investigation purposes of osteoporosis and its' treatment. Despite this, some attempts were made to monitor fracture healing by using biochemical assays, as fracture healing is associated with increased bone turnover. We identified three studies that described changes of Osteocalcin and CrossLaps after the

Colles' fracture. Ingle et al. looked at changes of bone remodeling and resorption markers [35] and found a 15% increase of Osteocalcin, consistent with our results. CrossLaps increased during the first two weeks also in our study, returning to baseline at one years' follow-up visit. Mallmin et al. enrolled 16 patients with Colles' fracture and found a minor constant increase of osteocalcin of 1 ng/ml during the 16 weeks follow-up [36], comparable to our results during 3-months follow-up. Wolfl et al. included 30 patients with metaphyseal fracture, 14 of them with Colles' fracture.[37] They found CrossLaps increased in the bone of the normal BMD group constantly, whereas these levels decreased significantly in the bone of the group with low BMD from the first week. Direct comparison to our results is difficult because of the short follow-up, and patients enrolled received both surgical and conservative treatment.

This indicates there is still no consensus regarding the use of bone biomarkers for fracture healing control. The high variability of plasma levels may suggest plenty of confounding factors such as age, the presence of osteoporosis, and metabolic diseases. A further investigation is needed to determine the role of remodeling and resorption biomarkers in the monitoring of fracture healing.

Histomorphometric bone analysis is widely used in research of metabolic diseases and fracture healing in animal models. [16] There is scant data describing histomorphometric characteristics of fracture healing in cancellous bones.[18] We presumed that the fracture was in the stage of endochondral ossification and formation of new woven bone. By affecting bone healing, we expected to detect more fibrous tissue and fewer bone fractions, respectively. We presumed to find more resorption and fewer bone formation surfaces. No difference in volume and surface fractions was detected after performing

eight statistical analysis methods between three treatment groups, thus increasing the importance of the histomorphometric part of the study.

Prolonged treatment with NSAIDs is related to an increased risk of cardiovascular, gastrointestinal, and nephrological disorders.[38] From a clinical perspective, a lengthy treatment is not necessary to relieve pain in the acute period and the following osteosynthesis of Colles' fracture. In our study, no differences in pain experience between treatment groups were observed. Treatment with ibuprofen demonstrated a sparring effect of escape-tramadol already during the first three days after enrolment, P=0.035. [12]

The rate of complications and side effects was significantly higher in the 7-days ibuprofen group compared to the placebo group, and gastrointestinal disorders were observed in all three treatment groups. A few patients in Placebo group 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 the ibuprofen-related adverse effects. The incidence rates for gastrointestinal disorders in the 3- and 7-days groups were 23.3% and 27.6%, respectively. These rates were higher than in other studies reporting oral treatment with NSAIDs.[39] We did not use prophylactic medication with proton pump inhibitors or other acid neutralising agents. Given this, the number of side effects attributable to the NSAID use may probably be less.

Our study has several limitations. Patients sustained the fracture at different times of the day; some received analgesics on the morning, others on the evening of day one. This may lead to some variability when the patient received ibuprofen or placebo treatment after the injury. Attempts were made to include all patients during their first visit to the

emergency department. It was not possible to assure that all patients received the medication at the same time after the injury.

A few 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 the 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. The randomization procedure to some extent do compensate for these weaknesses.

The outcomes in our study may be further influenced by many factors such as smoking, alcohol consumption, age, and the presence of osteoporosis and its' treatment. All confounding factors, however, were equal distributed among treatment groups.

The part of the study describing the 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 BMD that was less than 25% of the SD within groups and differences in bone biomarkers that were less than 10% of the SD within groups. With the significance level of 0.05 (according to recommendations for non-inferiority trials [40]), the sample size in this study was considered to have proper strength.

CONCLUSION

The treatment with ibuprofen did not affect densitometric, histological, and biochemical outcomes for Colles' fracture patients. These findings may offer an indication for ibuprofen as a bone-safe analgesic treatment in the acute fracture phase.

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REFERENCES

1. Williams A. Should non-steroidal anti-inflammatory drugs be given to orthopaedic patients with fractures? *Br J Hosp Med (Lond)*. 2007;68(8):452. doi:10.12968/hmed.2007.68.8.24506

2. Vuolteenaho K, Moilanen T, Moilanen E. Non-steroidal anti-inflammatory drugs, cyclooxygenase-2 and the bone healing process. *Basic Clin Pharmacol Toxicol*.

2008;102(1):10-14. doi:10.1111/j.1742-7843.2007.00149.x

3. Pountos I, Georgouli T, Calori GM, Giannoudis P V. Do Nonsteroidal Anti-Inflammatory Drugs Affect Bone Healing? A Critical Analysis. *Sci World J*. 2012;2012. doi:10.1100/2012/606404

4. Chung KC, Spilson S V. The frequency and epidemiology of hand and forearm fractures in the United States. *J Hand Surg Am*. 2001;26(5):908-915. doi:10.1053/jhsu.2001.26322

5. Solgaard S. Distal radius fractures. Classification, function and recommendations to treatment. *Dan Med Bull*. 1993;40(3):351-364.

6. Claes L, Recknagel S, Ignatius A. Fracture healing under healthy and inflammatory conditions. *Nat Rev Rheumatol*. 2012;8(3):133-143. doi:10.1038/nrrheum.2012.1

7. Cottrell J, O'Connor JP. Effect of Non-Steroidal Anti-Inflammatory Drugs on Bone Healing. *Pharmaceuticals (Basel)*. 2010;3(5):1668-1693. doi:10.3390/ph3051668

8. Endo K, Sairyo K, Komatsubara S, et al. Cyclooxygenase-2 inhibitor delays fracture healing in rats. *Acta Orthop*. 2005;76(4):470-474. doi:10.1080/17453670510041439

9. Krischak GD, Augat P, Sorg T, et al. Effects of diclofenac on periosteal callus maturation in osteotomy healing in an animal model. *Arch Orthop Trauma Surg*. 2007;127(1):3-9. doi:10.1007/s00402-006-0202-x

10. Sculean A, Berakdar M, Donos N, Auschill TM, Arweiler NB. The effect of postsurgical administration of a selective cyclo-oxygenase-2 inhibitor on the healing of intrabony defects following treatment with enamel matrix proteins. *Clin Oral Investig*. 2003;7(2):108-112. doi:10.1007/s00784-003-0200-0

11. Meunier A, Aspenberg P, Good L. Celecoxib does not appear to affect prosthesis fixation in total knee replacement: A randomized study using radiostereometry in 50 patients. *Acta Orthop*. 2009;80(1):46-50. doi:10.1080/17453670902804976

12. Aliuskevicius M, Østgaard SE, Rasmussen S. No influence of ibuprofen on bone healing after Colles' fracture – A randomized controlled clinical trial. *Injury*. 2019:1-9. doi:10.1016/j.injury.2019.06.011

13. Augat P, Morgan EF, Lujan TJ, MacGillivray TJ, Cheung WH. Imaging techniques for the assessment of fracture repair. *Injury*. 2014;45 Suppl 2:S16-22. doi:10.1016/j.injury.2014.04.004

14. Tiedeman JJ, Lippiello L, Connolly JF, Strates BS. Quantitative roentgenographic densitometry for assessing fracture healing. *Clin Orthop Relat Res*. 1990;(253):279-286.

15. Dimmen S, Nordsletten L, Engebretsen L, Steen H, Madsen JE. Negative effect of parecoxib on bone mineral during fracture healing in rats. *Acta Orthop*. 2008;79(3):438-444. doi:10.1080/17453670710015373

16. Gerstenfeld LC, Wronski TJ, Hollinger JO, Einhorn TA. Application of histomorphometric methods to the study of bone repair. *J Bone Miner Res*. 2005;20(10):1715-1722. doi:10.1359/JBMR.050702

17. Dempster DW, Compston JE, Drezner MK, et al. Standardized nomenclature, symbols, and units for bone histomorphometry: a 2012 update of the report of the ASBMR Histomorphometry Nomenclature Committee. *J Bone Miner Res*. 2013;28(1):2-17. doi:10.1002/jbmr.1805

18. Diamond TH, Clark WA, Kumar S V. Histomorphometric analysis of fracture healing cascade in acute osteoporotic vertebral body fractures. *Bone*. 2007;40(3):775-780. doi:10.1016/j.bone.2006.10.009

19. Kostenuik P, Mirza FM. Fracture healing physiology and the quest for therapies for delayed healing and nonunion. *J Orthop Res*. 2017;35(2):213-223. doi:10.1002/jor.23460

20. Bjarnason NH, Christiansen C. Early response in biochemical markers predicts long-term response in bone mass during hormone replacement therapy in early postmenopausal women. *Bone*. 2000;26(6):561-569.

21. Lotz J, Gaertner T, Hahn M, Prellwitz W. Collagen type I metabolism after bone surgery. *Arch Orthop Trauma Surg*. 1999;119(3-4):212-216.

22. Stoffel K, Engler H, Kuster M, Riesen W. Changes in biochemical markers after lower limb fractures. *Clin Chem*. 2007;53(1):131-134. doi:10.1373/clinchem.2006.076976

23. Akesson K, Vergnaud P, Delmas PD, Obrant KJ. Serum osteocalcin increases during fracture healing in elderly women with hip fracture. *Bone*. 1995;16(4):427-430.

24. Kurdy NM, Bowles S, Marsh DR, Davies A, France M. Serology of collagen types I and III in normal healing of tibial shaft fractures. *J Orthop Trauma*. 1998;12(2):122-126.

25. Taniguchi T, Matsumoto T, Shindo H. Changes of serum levels of osteocalcin, alkaline phosphatase, IGF-I and IGF-binding protein-3 during fracture healing. *Injury*. 2003;34(7):477-479.

26. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053

27. CHMP. GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2) by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *Eur Med Agency*. 2016;6(December 01):1-70.

28. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *Int J Surg*. 2012;10(1):28-55. doi:10.1016/j.ijsu.2011.10.001

29. McQueen MM, Simpson D, Court-Brown CM. Use of the Hoffman 2 compact external fixator in the treatment of redisplaced unstable distal radial fractures. *J Orthop Trauma*. 1999;13(7):501-505.

30. Wei DH, Poolman RW, Bhandari M, Wolfe VM, Rosenwasser MP. External fixation versus internal fixation for unstable distal radius fractures: a systematic review and meta-analysis of comparative clinical trials. *J Orthop Trauma*.

2012;26(7):386-394. doi:10.1097/BOT.0b013e318225f63c

31. van der Poest Clement E, Patka P, Vandormael K, Haarman H, Lips P. The effect of alendronate on bone mass after distal forearm fracture. *J Bone Miner Res*. 2000;15(3):586-593. doi:10.1359/jbmr.2000.15.3.586

32. Kim H-S, Yang S-O. Quality Control of DXA System and Precision Test of Radio-technologists. *J bone Metab*. 2014;21(1):2-7. doi:10.11005/jbm.2014.21.1.2

33. Adolphson P, Abbaszadegan H, Jonsson U, Dalen N, Sjoberg HE, Kalen S. No effects of piroxicam on osteopenia and recovery after Colles' fracture. A randomized, double-blind, placebo-controlled, prospective trial. *Arch Orthop Trauma Surg*. 1993;112(3):127-130.

34. Eastell R, Riggs BL, Wahner HW, O'Fallon WM, Amadio PC, Melton LJ 3rd. Colles' fracture and bone density of the ultradistal radius. *J Bone Miner Res*. 1989;4(4):607-613. doi:10.1002/jbmr.5650040419

35. Ingle BM, Hay SM, Bottjer HM, Eastell R. Changes in bone mass and bone turnover following distal forearm fracture. *Osteoporos Int*. 1999;10(5):399-407. doi:10.1007/s001980050246

36. Mallmin H, Ljunghall S, Larsson K. Biochemical markers of bone metabolism in patients with fracture of the distal forearm. *Clin Orthop Relat Res*. 1993;(295):259-263.

37. Wolfl C, Schweppenhauser D, Guhring T, et al. Characteristics of bone turnover in the long bone metaphysis fractured patients with normal or low Bone Mineral

Density (BMD). *PLoS One*. 2014;9(5):e96058. doi:10.1371/journal.pone.0096058

38. Dahl JB, Nielsen R V, Wetterslev J, et al. Post-operative analgesic effects of paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: a topical review. *Acta Anaesthesiol Scand*. 2014;58(10):1165-1181. doi:10.1111/aas.12382

39. Heyneman CA, Lawless-Liday C, Wall GC. Oral versus topical NSAIDs in rheumatic diseases: a comparison. *Drugs*. 2000;60(3):555-574.

40. Vavken P. Rationale for and methods of superiority, noninferiority, or equivalence designs in orthopaedic, controlled trials. *Clin Orthop Relat Res*. 2011;469(9):2645-2653. doi:10.1007/s11999-011-1773-6

LIST OF FIGURES AND TABLES

Figure 1. Consort flow diagram

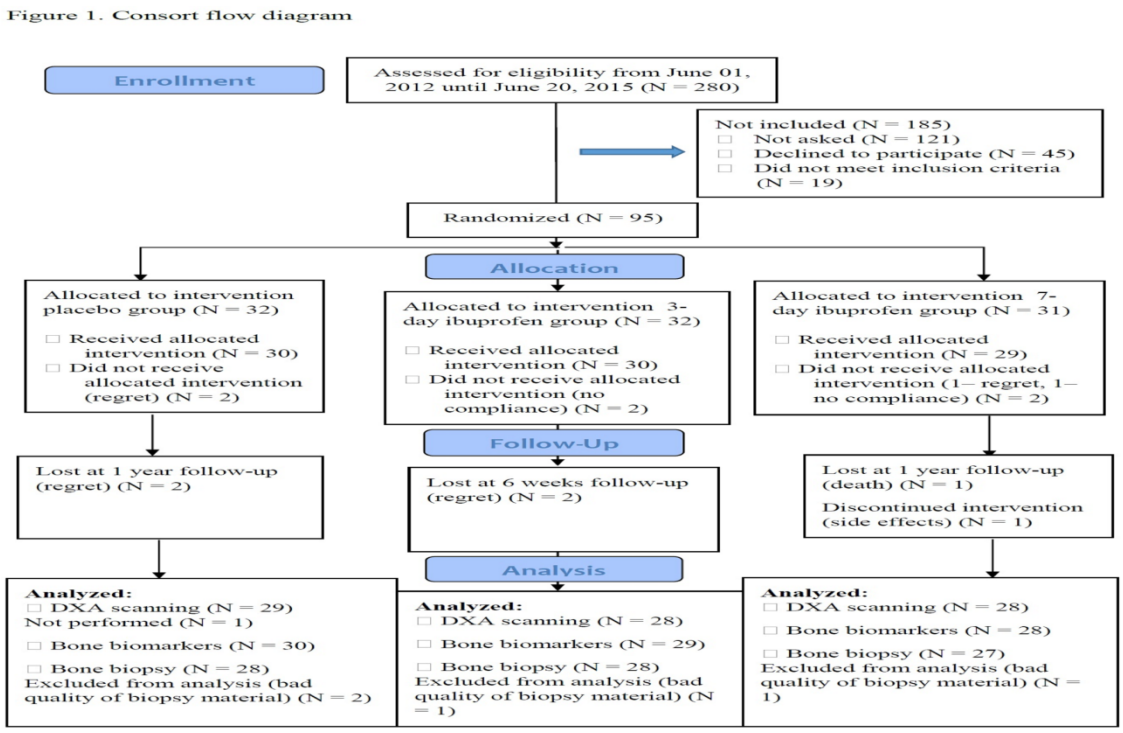

Figure 2. DXA scanning, regions of interest of distal forearm

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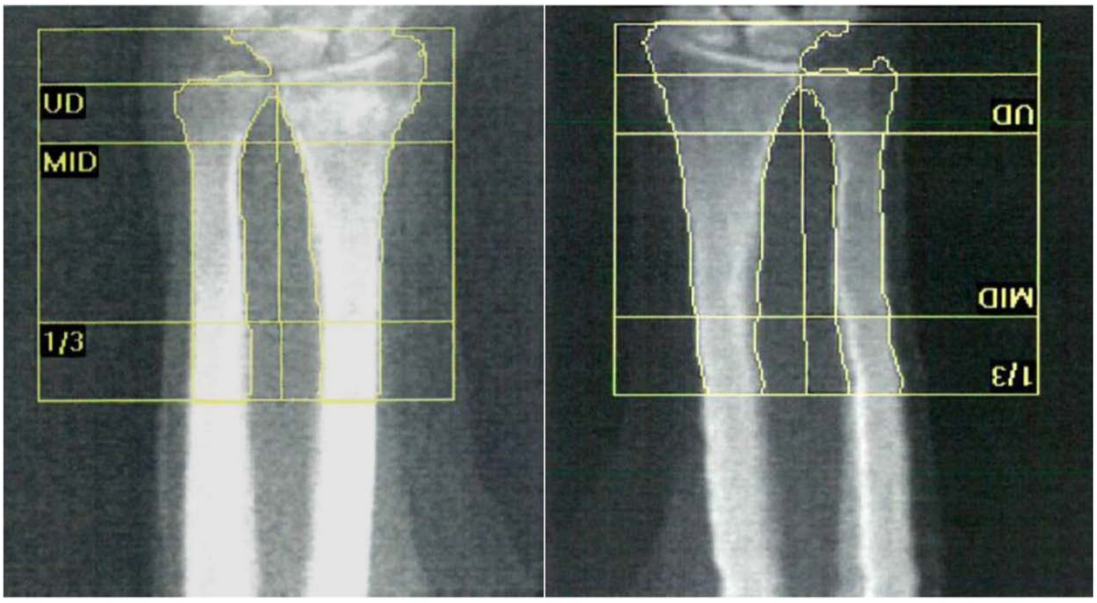

Figure 3. BMD outcomes

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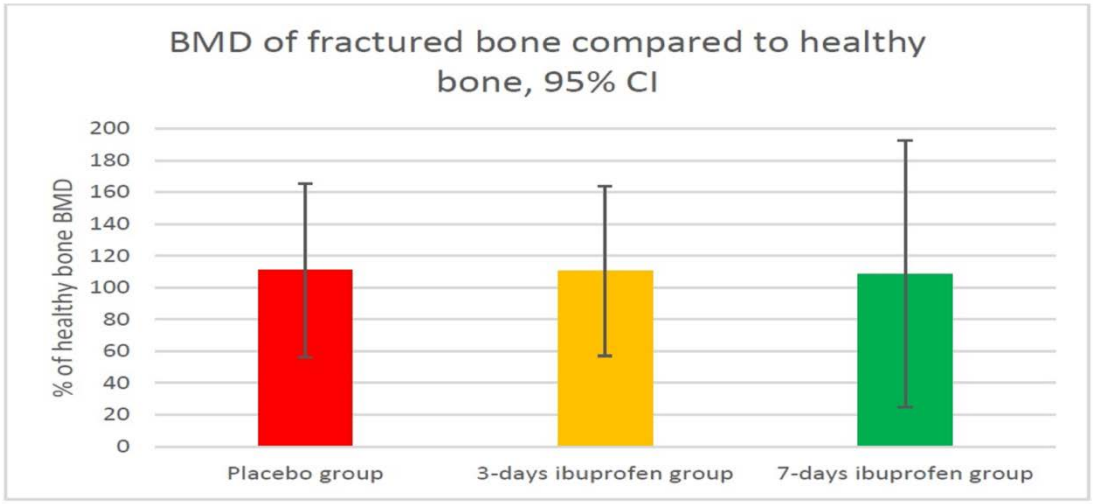

Figure 4. Histologic evaluation of biopsy material in normal and polarized light

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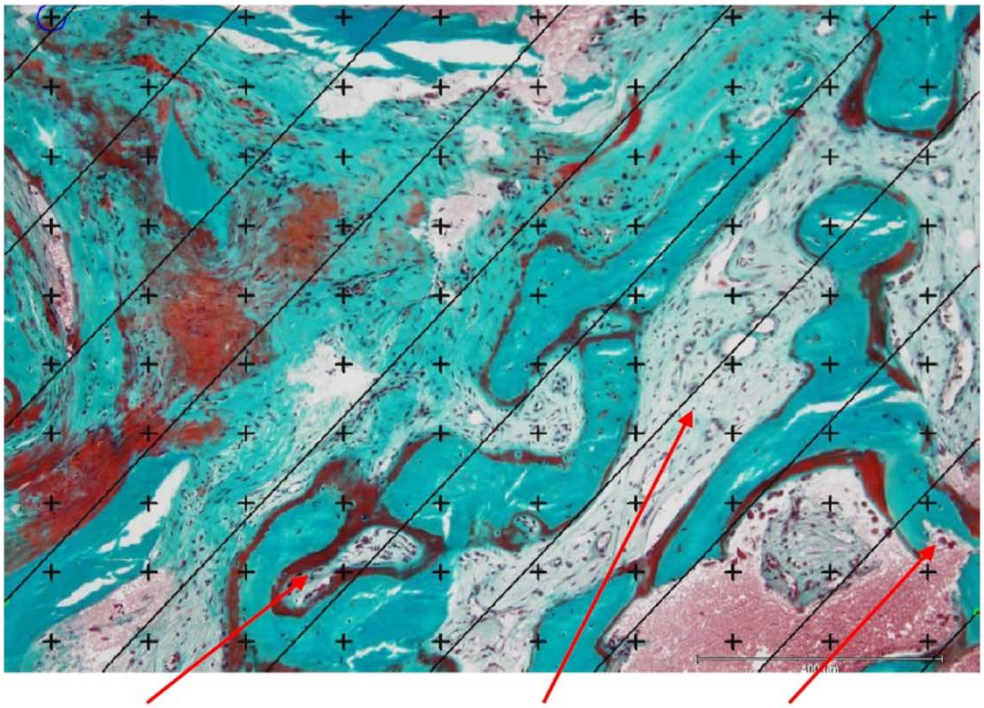

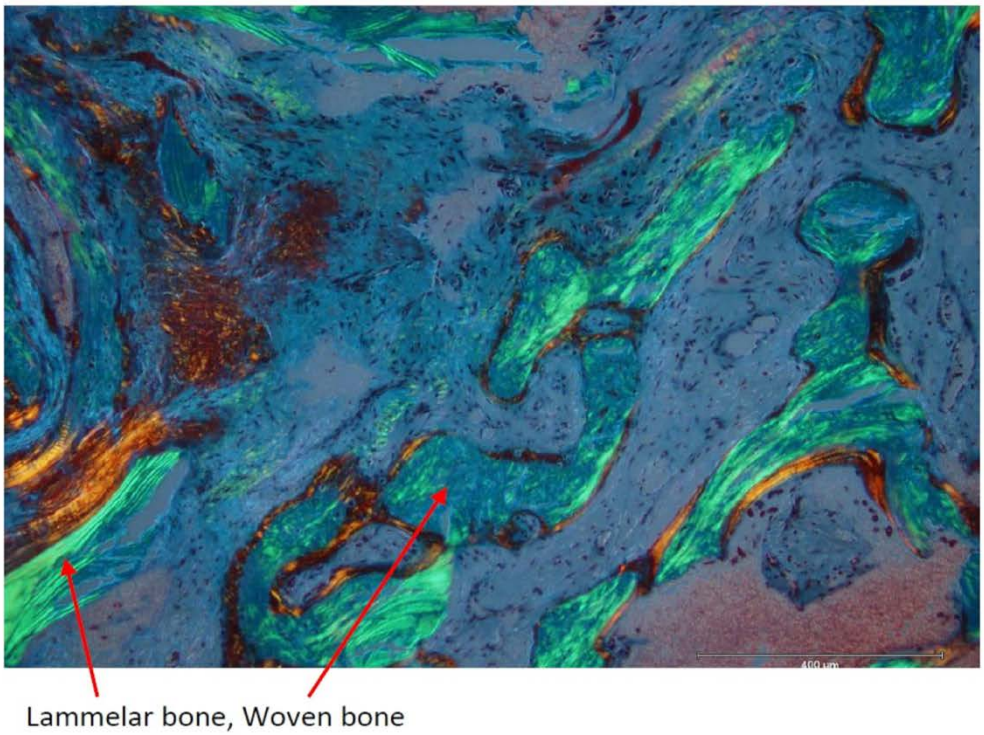

Figure 5. Dynamics of bone biomarkers in treatment groups

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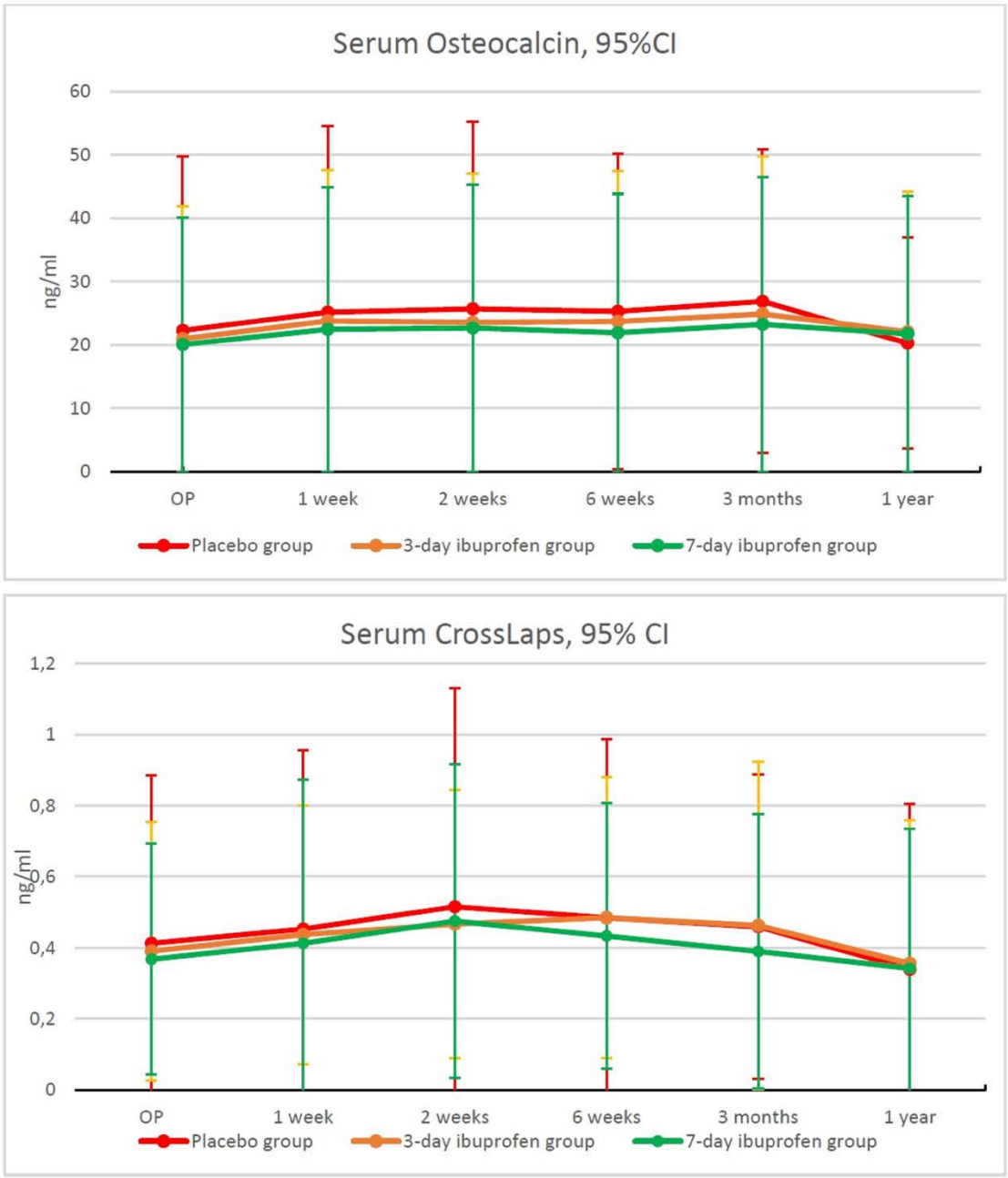

Table 1. Baseline characteristics of the study patients

	Placebo group	3-days ibuprofen group	7-days ibuprofen group
Female\Male	**25\5**	**25\5**	**24\5**
Average age (years ± 1SD)	**64.3 ± 4.4**	**67,8 ± 10**	**65,4 ± 7.9**
Smokers\Non-smokers	**3\27**	**1\29**	**3\26**
Osteoporosis treatment +\-	**6\24**	**5\25**	**7\22**
Dominating\Not	**15\15**	**13\17**	**14\15**
Total analyzed	**30**	**30**	**29**

Table 2. Histomorphometric outcomes

	Placebo group	3-days ibuprofen group	7-days ibuprofen group	P
BV/TV %	**26.6±8**	**28±8.5**	**26.3±5.7**	**0.68**
WBV/TV %	**4.4±2.5**	**6±5.3**	**4.2±2.3**	**0.77**
LBW/TV %	**18.5±8.5**	**18.5±7.7**	**18.5±7.5**	**0.99**
FV/TV %	**50±17.1**	**46.4±12.2**	**49±12.3**	**0.61**
OV/TV %	**3.6±1.5**	**3.4±1.8**	**3.6±1.6**	**0.84**
OS/BS %	**47.3±14**	**41.4±16.5**	**43.7±17.3**	**0.38**
ObS/BS %	**14.8±8.7**	**11.7±9.9**	**14.6±11**	**0.43**
OcS/BS %	**9.8±5.6**	**10.3±5.6**	**10.4±5.8**	**0.91**

Table 3. Adverse events **comparison of the placebo group and the 7-days group*

	Placebo group	**3-days ibuprofen group**	**7-days ibuprofen 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**	