The Influence of Ibuprofen on the Healing of Colles' Fracture

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BY
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AALBORG UNIVERSITY
DENMARK

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by

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Dissertation submitted

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CV

Marius Aliuskevicius graduated in 2010 from Aalborg and Aarhus University Hospitals with specialist training in orthopedic surgery. He has been working in the field of hand surgery for the last ten years. He worked as a consultant in hand surgery at BG University Hospital, Hamburg, Germany, from 2018 to 2019 and, since February 2019, is a consultant hand surgeon at Aalborg University Hospital, Denmark.

Since graduating, he has been engaged in teaching hand surgery to medical students at Aalborg University. He has also worked as a sector manager and education coordinator for hand surgery medical trainees at Aalborg University Hospital since October 2014.

ENGLISH SUMMARY

BACKGROUND

Previous studies and experiments on animals have shown that nonsteroidal anti-inflammatory drugs (NSAIDs) could negatively influence bone healing. These results are applicable to humans. Therefore, many patients with fractures are recommended not to use these popular analgesics despite a lack of real evidence from randomized clinical trials indicating that these drugs are harmful to patients with fractures.

This study, therefore, investigates the effect, if any, of ibuprofen on bone consolidation in the distal radius. The hypothesis is that brief treatment with ibuprofen does not hamper bone healing. The aim is also to compare the pain-relieving effect of ibuprofen to a placebo. The expectation is that this study might contribute to better pain management and rehabilitation, thereby making the entire course of treatment of Colles' fractures more comfortable and safer for patients.

METHODS

The study was designed as a non-inferiority trial. A total of 191 patients (age 40 - 85 years) with Colles' fractures were included at Aalborg University Hospital. The patients were divided into two treatment divisions. The conservative division consisted of those patients with stable Colles' fracture (Older classification, type 1 - 2), treated with a plaster cast. The surgical division was scheduled for patients presenting with an unstable fracture (Older classification, type 3 - 4), treated with external fixation.

Three groups of participants were randomly allocated in each division; **the 7-days ibuprofen group** was assigned to 600 mg x 3/day for 7 days, **the 3-days ibuprofen group** was assigned to 600 mg x 3/day for 3 days but then a placebo x 3/day for the 4 days that followed, and **the placebo group** was given a placebo x 3/day for one week. Paracetamol was dosed to all patients, 1g x 4/day for seven days, and tramadol 50 mg on request.

The primary outcome was radiological migration of bone fragments, variation in radius tilt, length, and inclination seen within the first 5 - 6 weeks (depending on conservative or surgical treatment) after injury.

The secondary outcomes were:

The Disabilities of the Arm, Shoulder, and Hand (DASH) score;

Range of motion (ROM) of the injured wrist (range of motion difference in the injured and contra-lateral wrist as a percentage);

The percentage difference of bone mineral density (BMD) for the injured and non-injured forearm;

Changes in biochemical bone biomarkers (Serum CrossLaps and Osteocalcin) during the one-year follow-up;

Histomorphometric estimations (the percentage of the volume and surface fractions in the callus biopsy) at six weeks after surgery;

Patients' pain experience during the first 14 days and the recorded consumption of the rescue medicine.

The intention to treat method was chosen for these analyses.

RESULTS

The observed radiological migration between the groups in the conservative division revealed neither clinically important nor statistically significant differences ($0.09 \leq P \leq 0.5$), and the same in the surgical division ($0.12 \leq P \leq 0.87$).

The DASH score ($0.2 \leq P \leq 0.9$) was not influenced by ibuprofen treatment; neither was the ROM ($0.1 \leq P \leq 0.9$).

During the one-year follow-up, patients regained 87 - 95% of normal wrist movements amplitude.

The injured radius, when compared to the non-injured contra-lateral bone, had a 3 - 7% higher BMD. Findings were not influenced by ibuprofen therapy ($0.69 \leq P \leq 0.72$).

Additionally, this study did not demonstrate any influence of the study drug on the concentration of CrossLaps ($0.06 \leq P \leq 0.95$) and Osteocalcin ($0.15 \leq P \leq 0.99$) during the whole follow-up time.

The differences between study groups in callus' volume and surface estimations were not significant ($0.38 \leq P \leq 0.99$).

Conservatively treated placebo group patients experienced more intense pain by 1.3 VAS-point than the ibuprofen groups ($P = 0.02$) during the first three days. In the surgical division, the tramadol use during the perioperative period was of a lesser extent among the ibuprofen patients than the placebo group ($P = 0.035$), the level of the pain symptoms did not differ significantly ($P = 0.4$).

The most frequent adverse events observed were gastrointestinal disorders along with finger dysesthesia. In the conservative division, we observed the highest adverse event percentage in the 3-days ibuprofen group compared with the placebo (56.6%, $P = 0.03$). In the surgical division, the percentage was highest in the 7-days group versus placebo (55.1%, $P = 0.043$).

CONCLUSIONS

Compared to placebo, the introduction of ibuprofen in the acute phase was not inferior regarding to the radiological, functional, densitometrical, biochemical, and histomorphometric outcomes in both divisions and across all treatment groups. Ibuprofen treatment demonstrated better pain relief for conservatively treated patients and a tramadol-sparing effect for surgically treated patients.

According to our study, ibuprofen may be prescribed as a bone-neutral analgesic in orthopedics; however, potential side effects still need to be considered.

DANSK RESUME

BAGGRUND

Det er en almindelig opfattelse at smertestillende gigtpræparater forsinker knogleheling. Den viden er imidlertid mest baseret på retrospektive studier, ikke kontrollerede studier eller dyreeksperimentelle undersøgelser, hvis resultater er gjort gældende for mennesker. Mange patienter med knoglebrud må derfor undvære den smertestillende effekt af ibuprofen, selv om der mangler randomiserede kontrollerede studier for, at denne behandling er skadelig for patienter.

Formålet med dette studie var at undersøge, om ibuprofen påvirker knogleheling. Hypothesen var at kort behandlingskur med ibuprofen ikke vil have negative indflydelse på knogleheling. Formålet var også at sammenligne den smertestillende effekt af dette præparat med placebo. Forventningen var, at undersøgelsen kunne optimere smertebehandling, gøre genoptræningen samt hele behandlingsforløbet mere komfortabel og sikrere for patienter.

METODER

191 patienter med Colles' fraktur (40 - 85 år) blev inkluderet på Aalborg Universitetshospital. De blev fordelt i to divisioner. Patienter med en stabil Colles' fraktur (Older klassifikation, type 1 - 2) blev tildelt den konservative division og behandlet med en gipsskinne. Patienter med ustabil Colles' fraktur (Older klassifikation type 3 - 4) blev tildelt kirurgisk division og behandlet med ekstern fiksation.

Patienter i hver division blev randomiseret i 3 grupper: **7-dages ibuprofen gruppe** tog ibuprofen 600 mg x 3 i 7 dage, **3-dages ibuprofen gruppe** tog kun ibuprofen i 3 dage og placebo i de resterende 4 dage, **placebogruppe** fik placebo i alle 7 dage. Alle patienter fik desuden paracetamol behandling 1000 mg tablet 4 gange dagligt i 1 uge og tablet tramadol 50 mg efter behov.

Det primære effektmål var radiologisk fragmentmigration - ændringerne i radius hældning, længde og inklination observeret i løbet af 5 - 6 uger (afhængig af behandling – konservativ eller kirurgisk).

De sekundære effektmål var:

Funktionelle resultater - DASH score og de procentvise forskelle i bevægelsesamplituden mellem det skadede og raske håndled;

Den procentvise forskel mellem mineraltætheden i det skadede og uskadte spoleben;

Ændringer i biokemiske knoglemarkører (Serum CrossLaps og Osteocalcin) i løbet af et års opfølgning;

Histomorfometrisk undersøgelse af callus 6 uger efter operation (volumens og overfladens fraktioner);

Patientens smerteoplevelse og forbrug af tramadol inden for 14 dage. Alle analyser blev udført i overensstemmelse med hensigten at behandle.

RESULTATER

Behandling med ibuprofen havde ingen statistisk signifikant indflydelse på knoglefragment-migration hverken i den konservative division ($0.09 \leq P \leq 0.5$), eller den kirurgiske division ($0.12 \leq P \leq 0.87$).

Behandling med ibuprofen havde ingen påvirkning af DASH score ($0.2 \leq P \leq 0.9$) eller den senere håndledsbevægelse, ($0.1 \leq P \leq 0.96$). Alle patienter i alle behandlingsgrupper fulgte det samme forbedringsmønster af håndledsfunktionen og nærmede sig 87 - 95% af den normale håndledsbevægelighed ved 1 års kontrol.

Det brækkede spoleben havde i gennemsnit 3 - 7% større knogle mineral tæthed i den ultra-distale region sammenlignet med det uskadede spoleben hos samme patient. Der var ingen forskel mellem behandlingsgrupperne, $0.69 \leq P \leq 0.72$.

Der var ingen signifikant forskel i målingerne af Serum CrossLaps ($0.06 \leq P \leq 0.95$) og Osteocalcin ($0.15 \leq P \leq 0.99$) mellem behandlingsgrupper i begge divisioner.

Der blev ikke observeret nogle signifikante forskelle af volumens og overfladens fraktioner mellem behandlingsgrupper i den kirurgiske division ($0.38 \leq P \leq 0.99$).

I den konservativt behandlede division havde patienter i ibuprofen-grupperne 1.3 VAS-punkt lavere smertescore i de første 3 dage, sammenlignet med placebogruppe, ($P = 0.02$). I den kirurgisk behandlede division havde ibuprofen ingen indflydelse på

patienternes smertescoring (P = 0.4). Men patienter, som fik ibuprofen, havde signifikant lavere forbrug af tramadol i de første 3 dage (P = 0.035).

Mave-forstyrrelser og fingersnurren var de hyppigste bivirkninger. Der blev registreret flest bivirkninger i konservativt behandlede 3-dages ibuprofen gruppe (56.6%, P = 0.03 sammenlignet med placebo) og kirurgisk behandlede 7-dages ibuprofen gruppe (55.1%, P = 0.043 sammenlignet med placebo).

KONKLUSION

Behandling med ibuprofen i den akutte fase havde ingen indflydelse på de radiologiske, funktionelle, densitometriske, biokemiske og histomorfometriske effektmål, sammenlignet med placebo. Behandling med ibuprofen resulterede i lavere smertescore hos konservativt behandlede patienter og lavere tramadol-forbrug hos opererede patienter.

Resultaterne af dette studie indikerer, at ibuprofen kan ordineres som knogle-neutral smertestillende medicin for Colles' frakturpatienter. Man skal dog tage hensyn til potentielle bivirkninger.

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My gratitude is also extended to all those who worked with me over the years, including Kirsten Lykke Vorbeck at the hospital's pharmacy and GCP monitor Kirsten Østergaard Nielsen, who showed me how funny a great paperwork could be. Thanks to Tenna Severinsen, Cathrine Sørensen, and Lisbeth Fuglsang for always being there when I needed help.

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Per aspera ad astra…

TABLE OF CONTENTS

TABLE OF FIGURES

CHAPTER 1. PREFACE

The current Ph.D. thesis was submitted as part of the requirement for attaining a Ph.D. degree at the Faculty of Medicine and The Doctoral School in Medicine, Biomedical Science, and Technology, University of Aalborg.

The scientific work was conducted between 2010 and 2017 during the appointment as an orthopedic surgeon at Aalborg University Hospital, Department of Orthopedic Surgery.

The following papers, which were based on data from the randomized controlled trial *'The influence of ibuprofen on healing of Colles' fracture'*, formed the basis for this thesis:

I. *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* (1).

II. *Aliuskevicius M, Ostgaard SE, Hauge EM, Vestergaard P, Rasmussen S. Influence of Ibuprofen on Bone Healing After Colles' Fracture: a randomized controlled clinical trial. J Orthop Res. October 2019. doi:10.1002/jor.24498* (2).

III. *Aliuskevicius M, Ostgaard SE, Vestergaard P, Rasmussen S. The influence of Ibuprofen on Healing of Nonsurgically Treated Colles' Fractures. Healio Orthopedics. 2020 Dec 29; 1-6. doi: 10.3928/01477447-20201216-04* (3).

CHAPTER 2. INTRODUCTION

2.1. BACKGROUND

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used in pain, fever, and inflammation treatment since the nineteenth century and are among the most commonly used analgesics (4). NSAIDs, and in particular **ibuprofen**, show treatment potential for acute fracture pain similar to morphine (5), and have an opioid-sparing effect (6–9).

Severe acute pain is an indicator for prescribing opioids, and short-term treatment with opioids may lead to long-term use (8). Opioid consumption has increased by 200% in the United States during the last 14 years and caused more than 33,000 deaths in 2015 (9). NSAIDs can be used as an additive therapy or even an alternative analgesic treatment. Following major surgery, NSAIDs can negate the need for opioids (10) and shorten the required hospital stay (11). Nonetheless, NSAIDs are likely to cause impaired fracture consolidation and are avoided after bone surgery, despite their benefits (12,13).

The main reason for exercising caution in prescribing NSAIDs after bone surgery is their inflammation-inhibiting potential. Inflammation is a crucial process in the initial phase of fracture consolidation, as mechanical destruction of bone cell membranes leads to a release of arachidonic acid, later to be transformed into pain-mediating prostaglandins by cyclooxygenase-2 (COX-2) (Figure 2.1). Broken vessels immediately after injury give rise to fracture hematoma, resulting in hypoxia, low pH, migration of cytokines, and inflammation-mediating cells (Figure 2.2) (14). Cyclooxygenase-2 levels also increase, exhibiting pro-inflammatory activity and leading to angiogenesis and mesenchymal cells differentiating into osteoblasts (15).

Numerous studies on animals have shown NSAIDs to have a potential delaying effect on bone healing (16), although this apparent healing delay requires that NSAIDs are used for more than just a short period (17). Impairing osteogenesis, NSAIDs might be helpful in preventing ectopic ossification after total hip arthroplasty if administered shortly after surgery (18). On the other hand, the loosening of prosthetic components mostly occurs in patients treated with NSAIDs for 7 - 14 days (18). Therefore, the influence of short NSAID therapy (3 - 7 days) on fracture consolidation is not yet sufficiently clarified (19,20).

There is a discrepancy between animal studies, indicating the apparent negative effect of NSAIDs and clinical observations (21). This issue might be explained by different

fracture localization between animal models and clinical studies. Many animal models depict fracture healing in shafts, whereas humans suffer (in most cases) from metaphyseal fractures (21). The nature of the healing in these two localizations is different. Healing in metaphyses is initiated by local marrow cells. It is not as dependent on cell migration from the periosteum and surrounding tissue into the fracture via the bloodstream, as in the case in shaft fractures (22).

From a methodological point of view, trying to understand the influence of NSAIDs on bone healing is challenging because of the numerous confounding factors (e.g., smoking, diabetes, obesity) that might affect bone healing (12). There is a clear need for prospective clinical studies in the future, designed with appropriate care (23,24).

A fracture in the distal radius might be an object of such an investigation. The United States alone reported over 1.46 million new episodes in 1998. It is a common injury, making up for 1.5% of all emergency department admissions (25). There are 15,000 new cases reported in Denmark every year (26). Many older patients experience secondary displacement of a bone fragment and may also suffer from a loss in wrist function after such fracture (27).

Several groups of tools are available to assess the healing process in bone, such as imaging studies, clinical examination, serological markers (28), or histomorphometry (29).

Fragment migration is a sign of higher instability of the Colles' fracture (30,31). Severe comminute Colles' fractures tend to experience secondary displacement during the first few weeks, with a volar tilt moving towards a dorsal tilt and a loss of radial inclination and length (30,31). Lack of radiological healing and secondary dislocation or migration of the fractured bone fragments during the 5/6-week follow-up period are clinically important events (31). This pattern is not only characteristic of displaced Colles' fractures treated with plaster casts (32); it may also appear after surgical fixation (33). The wrist joint may suffer a loss of reduction, negatively influencing its proper function in later life (34).

The non-invasive method of choice used to determine the bone mineral density (BMD) is dual-energy X-ray absorptiometry (DXA scanning), widely used as a diagnostic tool for osteoporosis. Traditional radiographs can result in inter-physician variability of up to 20 - 25% (35) when used for evaluating healing fractures, whereas DXA scanning, focusing on the mineralization process in the maturing callus, allows a more quantified evaluation. Previous studies have reported a strong positive relation between BMD and mechanical rigidity of the new-formed bone (36), and despite not being the tool of choice in orthopedic surgery, DXA scanning is gaining popularity in

experimental studies. This method has been used in evaluating NSAID influence on osteoneogenesis in animals (37) and is a potent tool for better assessment of bone unification in clinical orthopedics (35).

Another tool that can be used to detect physiological hindrance in fracture recovery is osseous biomarkers. The destruction of bony material precedes the creation of a new osteo-matrix (38). Type I collagen is synthesized primarily in bone and makes up over 90% of the organic matrix (39). C-terminal telopeptide (CrossLaps) is released from the collagen (40) and minor peptide particles appear in the blood circulation after the damage and destruction of bony material. Immunoassays can measure the concentration of circulating telopeptide until it is eliminated by renal excretion. Furthermore, the increased activity of osteoblasts during the subsequent fracture healing process can be assessed by evaluating serum osteocalcin concentration, the product of osteoblasts (41), thereby monitoring the bone remodeling process (42). Bone markers are useful as a non-invasive, dynamic method of investigation of healing callus (43). These serum levels present wide-ranging variation in individuals depending on the severity of the injury, the surgery performed (44), and circadian instability (40).

Histomorphometry, or "bone callus counting", is another method with the potential for investigating bone repair (29). Qualitatively assessed bone structures can be counted and quantified in terms of bone (lamellar and woven), fibrous tissue, osteoid volume fractions, and expressed as the percentage of the total tissue volume. The bony healing process and its resorption and regeneration phases can also be evaluated by estimating bone surface fractions (45). Regeneration of bone is represented by a bone surface covered with osteoid and/or osteoblasts, whereas surfaces covered by osteoclasts indicate bone destruction/resorption during fracture healing (46).

Colles' fractures cause pain in the early acute phase and thus raise the indication for the use of analgesics (47,48). Therefore, the research question arises if a brief treatment with ibuprofen is beneficial for patients with Colles' fractures, and whether this can decrease the demand for morphine medications. The question is even more pertinent if the fracture is displaced, as the treatment in these cases relies on surgery, and the patients will likely experience even more pain during the first days after injury (49).

Treatment with NSAIDs may, theoretically, be beneficial for fracture patients. By suppressing inflammation, NSAIDs decrease edema and pain, which are the dominating symptoms in the early phase of fracture healing (47), thereby making rehabilitation more comfortable and efficient. The investigation object might be **ibuprofen**, the most commonly sold NSAID in Nordic countries (50).

The research questions are:

1. Is ibuprofen harmful to patients with Colles' fractures due to delayed osteogenesis in terms of higher fragment migration, impaired wrist function, lower bone mineralization, affected dynamics in bone biomarkers, and delayed histologic callus maturation?

2. Is ibuprofen useful for patients with Colles' fractures due to its pain-calming and opioid-sparing effects?

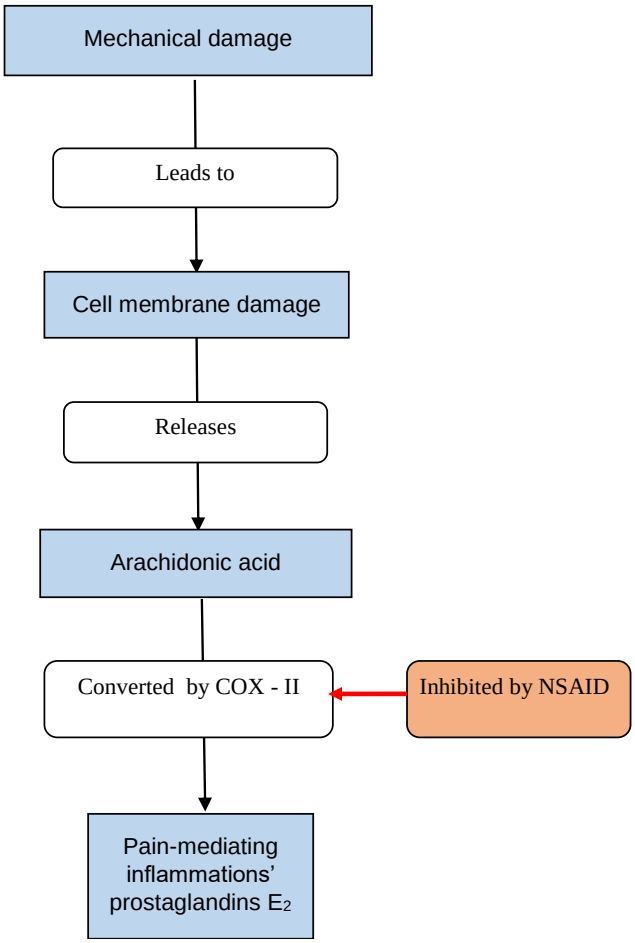


Figure 2.1. Pathophysiological mechanisms of inflammation after bone damage.

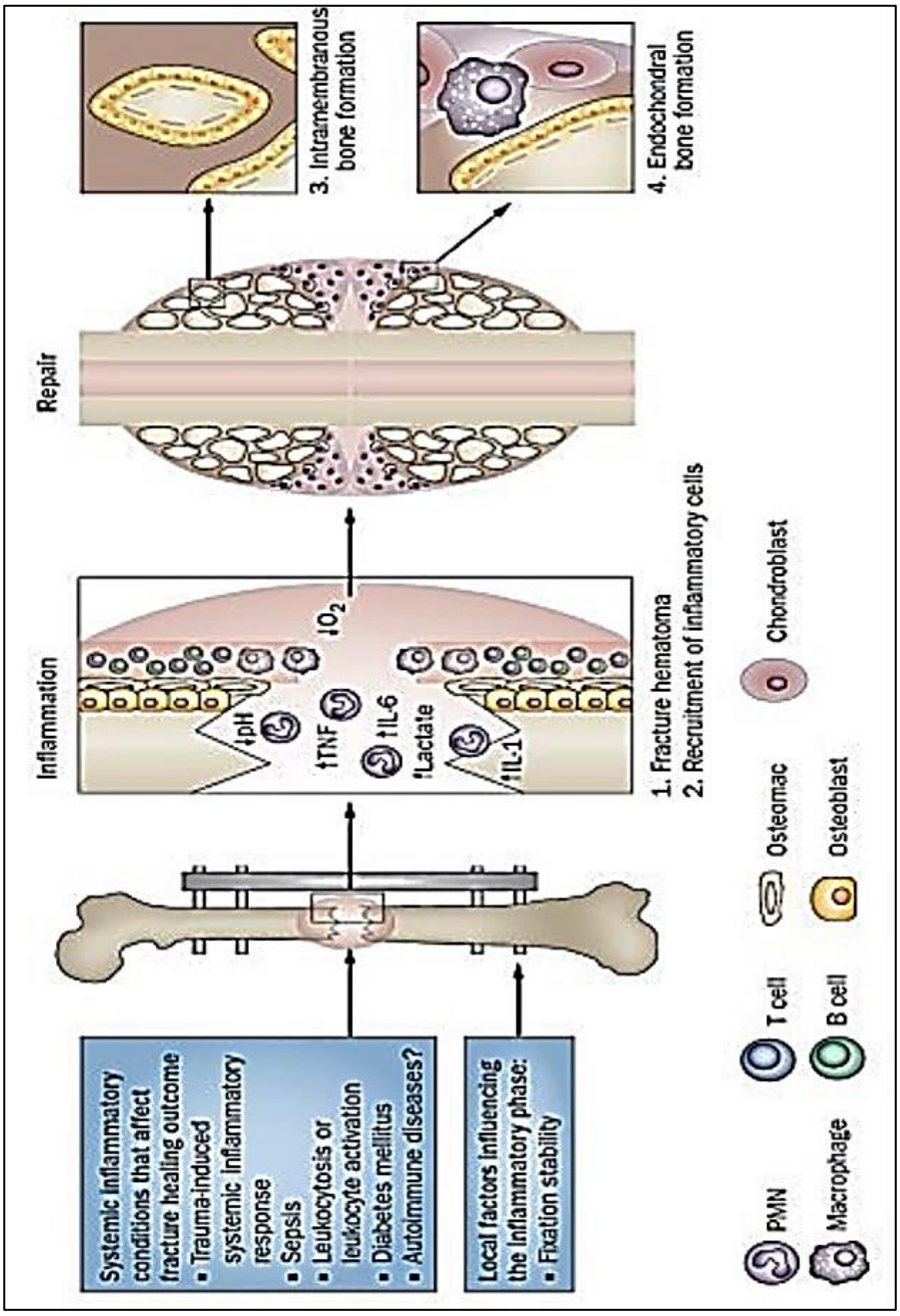


Figure 2.2. Inflammatory mechanisms in the fracture hematoma (reproduced from reference No. 14).

2.2. HYPOTHESES

1. **H_0:** Treatment with ibuprofen causes inferior results in radiological, functional, DXA, biochemical, and histomorphometric outcomes (non-inferiority design).

   H_A: There is no difference in radiological, functional, DXA, biochemical, and histomorphometric outcomes (non-inferiority design).

2. **H_0:** There is no difference in patients' pain experience and tramadol consumption between ibuprofen and placebo treatment groups (superiority design).

   H_A: Treatment with ibuprofen provides different analgesic and tramadol consumption outcomes (superiority design).

2.3. AIM

This work primarily aimed to test the above-mentioned hypotheses by conducting a non-inferiority randomized placebo-controlled triple-blind clinical trial entitled **"Ibuprofen's influence on the healing of Colles' fracture"** and to assess radiological bone fragment migration.

The second aim was to evaluate wrist function, bone mineral density, changes in biochemical bone markers, histological parameters of healing bones, patients' pain experience during the first 14 days, and tramadol consumption as a rescue medicine.

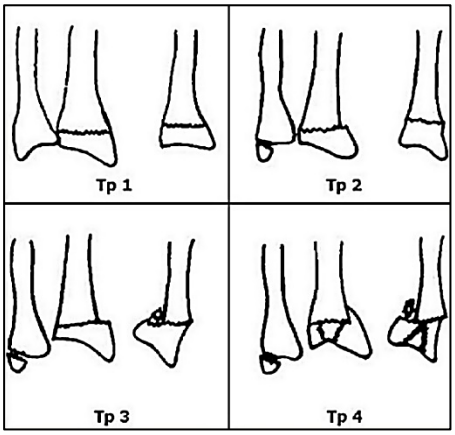
The third aim was also to determine the level of reliability and bias in evaluating of X-ray pictures and bone tissue. To check the intra-observer repeatability, a calculation of the difference between two radiological assessments was performed. For estimation of histomorphometric parameters, a coefficient of variation (CV%) between two assessments was calculated.

CHAPTER 3. METHODOLOGICAL CONSIDERATIONS

3.1. STUDY DESIGN

The study was conducted as a prospective, randomized, triple-blind placebo-controlled non-inferiority trial. Patients were included in the study if they were aged 40 - 85 years old, gave written informed consent, and had a Colles' fracture.

The patients meeting the inclusion criteria were allocated to one of two treatment divisions after written consent. The conservative division consisted of those patients with stable Colles' fracture, Older classification, type 1 - 2 (27), treated conservatively with a plaster cast. The surgical division was scheduled for patients with unstable fracture, Older classification, type 3 - 4 (27), treated surgically with external fixation (Figure 3.1).



Tp 1: dorsal angulation ≤ 5 degrees, length of radial styloid ≥ 7mm;
Tp 2: dorsal angulation > 5 degrees, length of radial styloid < 7 and ≥ 1mm;
Tp 3: dorsal angulation > 5 degrees, length of radial styloid ≤ 4mm slight dorsal comminution;
Tp 4: dorsal angulation > 5 degrees, length of radial styloid usually negative, comminution, often intra-articular involvement.

Figure 3.1. Older classification of Colles' fractures (reproduced from reference No. 27).

Patients were excluded from the study if they were younger than 40 or older than 85 years of age, were systematically treated with NSAIDs, had a previous fracture of the wrist in question, or were unable to follow the relevant instructions due to poor mental and/or physical condition, had medical contraindications to the use of NSAID's, or were pregnant. Patients with secondary fracture-displacement with a need for re-/operation (displacement back to type 2 - 3 despite initial conservative treatment or type 3 - 4 despite initial surgery) were excluded from the study.

Patients in each division were randomly assigned to receive the appropriate intervention analgesic.

All patients were treated at the Department of Emergency Medicine and the Department of Orthopedic Surgery, Aalborg University Hospital. All study participants were included within three days of the injury occurring. Patients began to register their pain in a pain diary from the moment of inclusion in the study and continued for 14 days.

The following evaluations were made during the follow-up period:

- At the Emergency Department: X-ray and pain evaluation before and after fracture reduction or cast immobilization only (if the fracture did not need reduction).

- Preoperatively (surgical division): X-ray evaluation, bone biomarkers.

- 1-week follow-up: X-ray evaluation and measurement of the range of motion in the uninjured wrist, bone biomarkers.

- 2-week follow-up: X-ray evaluation, collection of the pain diary, bone biomarkers.

- 5-week follow-up (conservative division): X-ray evaluation, removal of the plaster cast, bone biomarkers, measurement of the range of motion of the injured wrist, and training instructions.

- 6-week follow-up (surgical division): X-ray evaluation, removal of the external fixator, bone biomarkers, callus biopsy, measurement of the range of motion of the injured wrist, and training instructions.

- 3-months follow-up by the occupational therapist: completing the DASH questionnaire and measurement of the range of motion of the injured wrist, DXA-scanning, bone biomarkers.

- 1-year follow-up by the occupational therapist: completing the DASH questionnaire and measuring the range of motion of the injured wrist, bone biomarkers.

3.2. RANDOMIZATION AND BLINDING

The department allocated pharmacy unit was responsible for dispensing and conducted the block randomization (5×9 + 8×6 + 1×3). The medicine was supplied to the patients in packets according to the randomization process. The patient, surgeon, investigator, and statistician had no information regarding allocated therapy. Only the project-related dispenser knew the medicine bag's exact contents. Unblinding was performed in two steps:

Step 1. Partial unblinding was performed for the data analysis. Patients allocation to one of the three treatment groups (group one, group two, and group three) was disclosed. No information regarding the ibuprofen treatment was revealed at this point.

Step 2. After completing the statistical analysis, total unblinding was performed with detailed information regarding treatment with ibuprofen or placebo.

3.3. INTERVENTION

Ibuprofen (ATC-code: M01AE01) was chosen as the NSAID medication for acute pain treatment. Ibuprofen's absorption from the digestive channel and subsequent analgesic effect is fast; the maximal plasma concentration is achieved within 1 - 2 hours after oral intake; nonetheless, the effect is brief, and the plasma half-life is 1.5 - 2 hours.

The recommended daily dose of ibuprofen is 1.2 - 1.8 g divided over three administrations; therefore, 600 mg tablets of ibuprofen were administered 1x3 daily to ensure sufficient doses for acute pain treatment.

Participants were randomly assigned in a 1:1:1 ratio to receive either 600 mg of ibuprofen 1x3 per day for one week (**7-days group**), or 1 x 3 per day for the first three days, followed by the placebo 1x3 daily for the next four days (**3-days group**), or placebo-only 1x3 per day for the entire 7-days course (**placebo group**) (1–3).

Participants who signed the participation agreement form received a 7-days package of dosed analgesics and a diary to register their pain for 14 days. Each bag was individually numbered and contained paracetamol for 1 g taken 1 x 4/day for seven days, six 50 mg tramadol rescue-tablets, and the predefined amount of either ibuprofen or placebo (or both) for seven days. The study participants received no acid-neutralizing agents in order to avoid unnecessary treatment for placebo groups.

3.4. COLLES' FRACTURE AND TREATMENT

A Colles' fracture is a fracture of the distal radius with both a dorsal and radial displacement of the wrist and hand. The fracture is commonly caused by falling onto a hard surface with outstretched arms. The typical picture of a displaced fracture is the so-called 'bayonet' deformity (Figure 3.41).

Figure 3.41. Displaced Colles' fracture.

In this study, displaced Colles' fractures are characterized by a fracture in the metaphysis of the distal radius, the distal fragment tending to tilt dorsally and radially, and the shortening of the radius compared to the distal ulna (Figure 3.42).

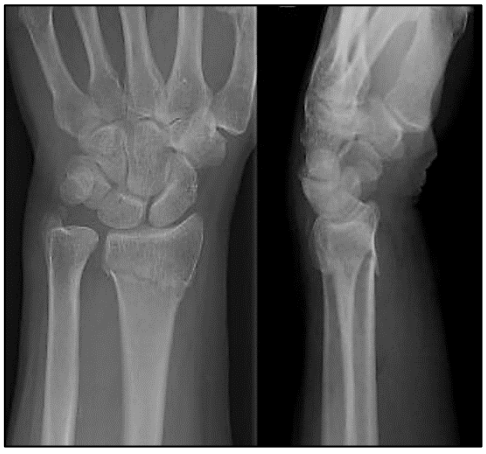


Figure 3.42. X-ray picture of a displaced Colles' fracture.

Older type 1 Colles' fracture was immobilized in the dorsal forearm plaster cast without reposition (Figure 3.43).

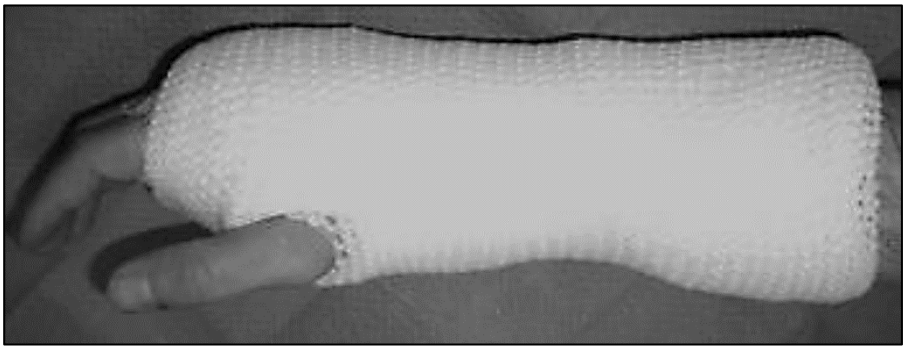


Figure 3.43. Dorsal forearm plaster cast.

Older type 2 - 4 fractures were treated with local hematoma anesthesia injecting 10 milliliters of 0.5 percent of lidocaine. The closed reduction was subsequently performed by traction in the line of the forearm and firm pressure on the distal fragment dorsally, and then by immobilizing within the dorsal forearm plaster cast (Figure 3.44).

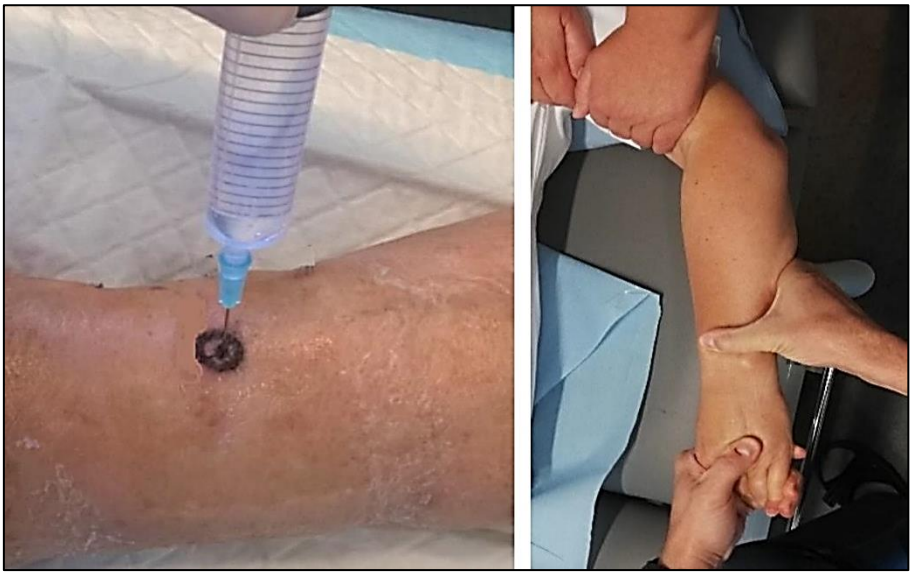


Figure 3.44. Hematoma anesthesia. Technics of closed reduction of Colles' fracture.

The unstable Colles' fractures of Older type 3 - 4 were treated surgically afterwards. We selected an external fixation-type bridging with a Hoffmann II external fixator (Sryker®, MI, USA), and additional 1.4 mm K-wires as the standard surgical method

(1,2). The intervention is recognized both in Denmark (51) and worldwide (52) and is used to treat unstable fractures (33). Furthermore, this technique allows a bone biopsy to be performed six weeks later while removing the external fixator and K-wires and assessing of BMD in recovering distal radius.

The maximum possible standardization of the treatment was obtained by ensuring the same surgeon performed all interventions for the enrolled participants. All operations were performed in the same way, using the following three steps:

1. Closed reduction using finger distraction devices with 2.5 - 3 kg weights.

2. Fixing the fragments in the proper position using 1.4 mm K-wires (Figure 3.45) placed dorsally into the fracture (to ensure the proper tilt of the distal fragment) and radially through both main fragments of the fracture (to ensure the proper length and inclination of the distal radius) using a modified Kapandji technique (53).

3. Locking the wrist joint in a neutral position using Hoffmann II external fixator (Sryker®, MI, USA) type bridging to minimize the risk of secondary dislocation. The proximal fixator pins are placed 7 cm proximally to the fracture; the distal pins are placed in the proximal/middle third of the second metacarpal (Figure 3.46).

An infra-clavicular regional nerve block was applied to all patients, either with or without general anesthesia.

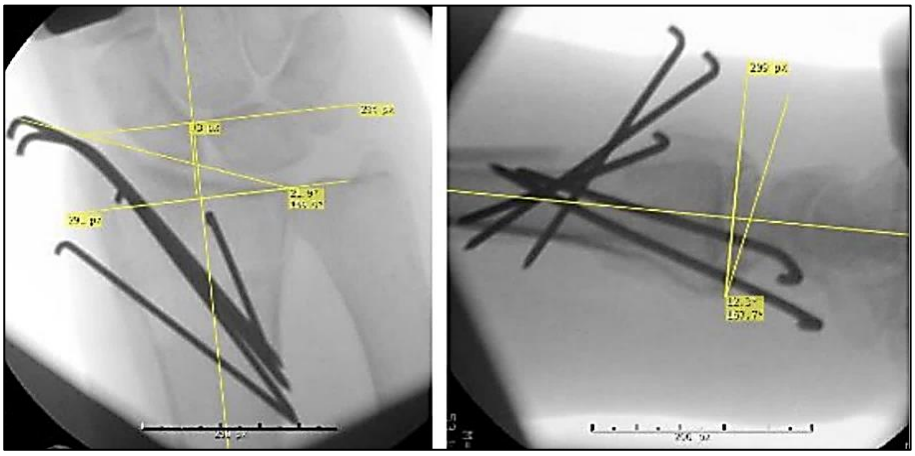


Figure 3.45. Perioperative X-ray pictures.

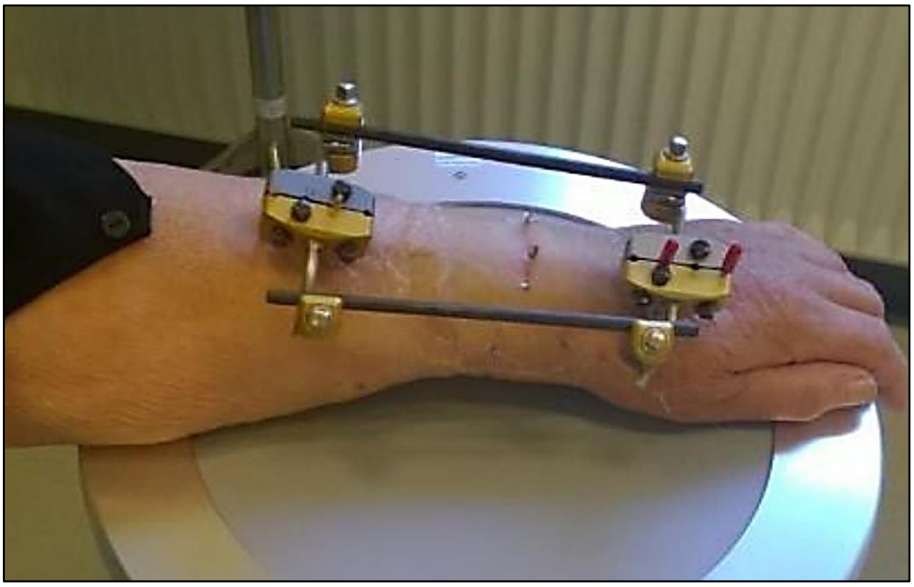


Figure 3.46. Bridging external fixation.

3.5. RADIOLOGICAL EVALUATION

Three radiological outcomes (Figure 3.5) were predefined (1,3):

1. The inclination in the antero-posterior view is defined as the angle between the ulnar corner of the radius in the wrist joint and the radial styloid's tip.

2. The length in the antero-posterior view is defined as the interval from the radial styloid's tip to the horizontal (lowest) joint surface of the distal radius.

3. The tilt in the lateral view is defined as the angle between the distal radius joint surface and the bone shaft.

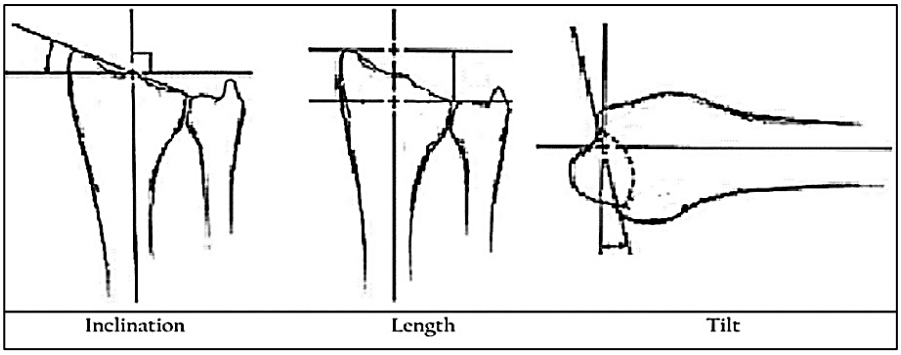


Figure 3.5. Measurement of radiological outcomes.

The same individual performed all the measurements. X-ray pictures were evaluated before the reposition, after the reposition, perioperatively, and at 1, 2, and 6 weeks after the surgery (5 weeks in the case of conservative treatment). All assessments were performed using the EazyViz software package (CE 0413, Karos Health Incorporated, Copenhagen, Denmark), a digital system for primary diagnosis and clinical evaluation of radiographs, which allows determining the angle and distance between points of interest.

The assumption was that fracture fragments would move, thus changing the intra-operative achievements to a less desirable result (32,34,54). The severity of dislocation regarding radius tilt, length, and inclination, was evaluated by calculating the difference between the fragments' position directly after treatment and 5/6-weeks later.

To check the observer's repeatability, the original X-ray pictures were reevaluated after three months by the same observer. The mean difference between the two observations, with a 95% confidence interval, was determined.

3.6. EVALUATION OF THE WRIST JOINT FUNCTION

One of the functional outcomes was the range of motion (ROM) in the injured wrist joint compared to a healthy one. Wrist range of movement was measured in the following directions, resulting in three outcome values: flexion/extension range, pronation/supination range, and radial/ulnar deviation range (1,3). As the physiologic range of movement differs between individuals (55), the healthy wrist movement was assessed as the baseline. The injured wrist's ROM was assessed during five/six weeks, three months, and one-year follow-up sessions. The outcome was calculated as a percentage of the healthy wrist's ROM.

Two occupational therapists performed all the measurements for this part of the study. Wrist joint motion was measured according to the Danish National Standard guidelines (56). Descriptions and pictures are enclosed with the permission of the author, Helle Puggård Hansen (Figures 3.6 - 3.9).

The second functional endpoint was the assessment of the daily Disabilities of the Arm, Shoulder, and Hand (DASH) score. The DASH test is considered a prompt and trustworthy evaluation tool for the patient's everyday function (57,58). Participants filled in the DASH survey form with an occupational therapist's assistance three months after the injury (6 - 7 weeks after the beginning of wrist rehabilitation) and at the final one-year control.

The DASH questionnaire used was a Danish translation of the daily activities module and contained 30 questions regarding everyday situations in daily life. Each question regarding how difficult it was to perform a specified function in daily life was answered using a scale consisting of five points where the answer 'without difficulties' equaled one point, and the answer 'unable' equaled five points. DASH questionnaires containing more than three unanswered questions were removed from the analysis.

The value of the DASH measurement was calculated using the formula: $[((\text{sum of } n \text{ responses})/n) - 1] * 25$, n being the number of answered questions (1).

MEASUREMENT OF THE WRIST MOTION

Measurement of supination (Figure 3.61)
Starting position: elbow held against the body and flexed 90°.
Goniometers focal point: laterally for caput ulnae.
Stable axis: corresponding to the center line of the humerus.
Moving axis: forearms volar side, proximal for the wrist and ulnar styloid.

Figure 3.61. Measurement of supination.

Measurement of pronation (Figure 3.62)
Starting position: elbow held onto the body and flexed 90°.
Goniometers focal point: laterally for caput ulnae.
Stable axis: corresponding to the center line of the humerus.
Moving axis: forearms dorsal side, proximal for the wrist and ulnar styloid.

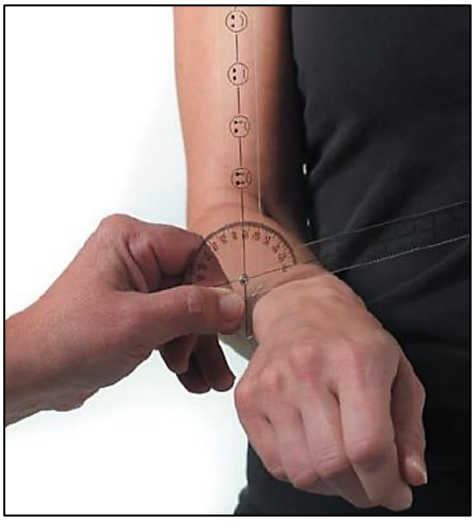


Figure 3.62. Measurement of pronation.

Measurement of the dorsal - volar flexion (Figure 3.63)
Starting position: forearm held in a neutral position.
Goniometers focal point: radially distally to the radial styloid.
Stable axis: along the radius.
Moving axis: radially over the second metacarpal bone.

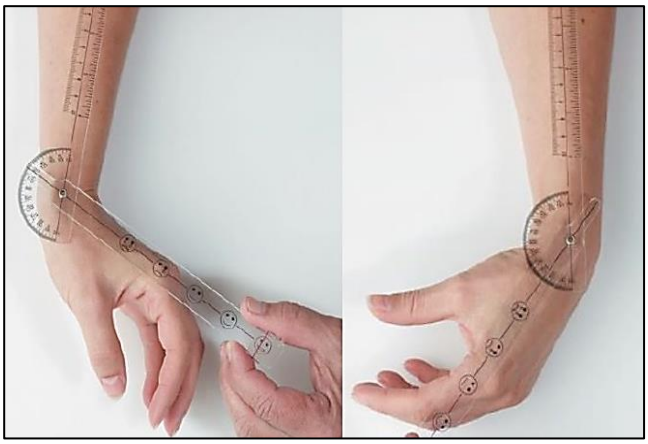


Figure 3.63. Measurement of the dorsal - volar flexion.

Measurement of the radial - ulnar deviation (Figure 3.64)
Starting position: forearm in pronation with the volar side facing down.
Goniometers focal point: dorsally, centrally over the carpus.
Stable axis: dorsally on the forearm in a midline between the radius and the ulna.
Moving axis: dorsally on the third metacarpal bone.

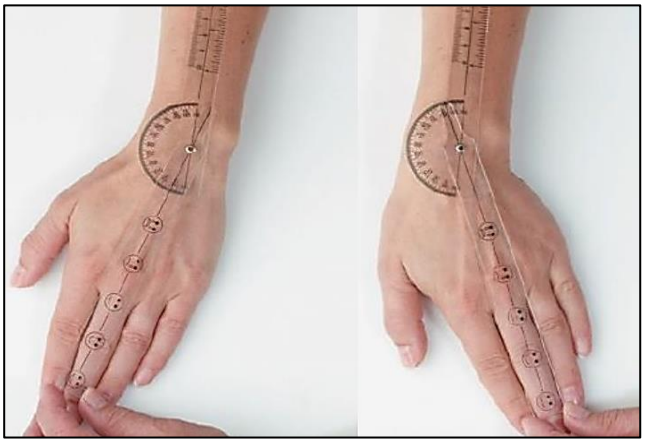


Figure 3.64. Measurement of the radial - ulnar deviation.

3.7. EVALUATION OF DENSITOMETRICAL OUTCOME

A BMD outcome, the difference of mineral density in the fractured distal forearm compared with the contra-lateral healthy area, was measured with a Discovery A DXA-scanner (Hologic Inc., MA, USA). For lumbosacral BMD, the in-vivo accuracy was 0.90%, total hip 1.00%, and the femoral neck, 1.79% (2).

We defined the ultra-distal zone (UD) as the region of interest, the area covering 30 mm proximally from the distal radio-ulnar joint (Figure 3.7). According to the reference UD-BMD of the contra-lateral forearm, we registered the percentage of the affected forearm's UD-BMD.

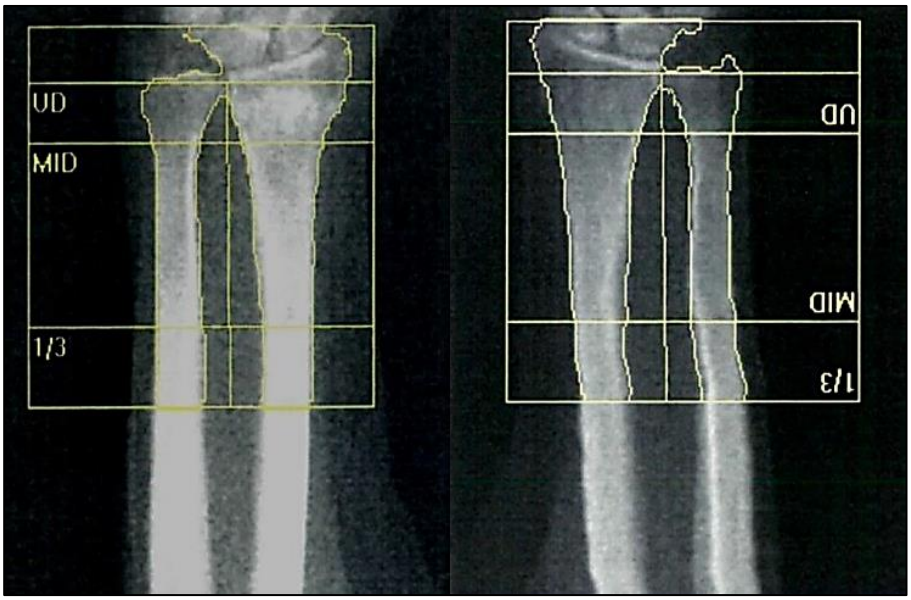


Figure 3.7. DXA scanning, regions of interest of distal forearm.

3.8. EVALUATION OF BIOCHEMICAL OUTCOMES

A biochemical outcome - serum CrossLaps and Osteocalcin levels were determined by the Cobas e 411 ECLIA immunoassay analyzer (Roche Diagnostics®, Basel, Switzerland) (2,3). A medical laboratory technician collected the blood at 9.00 a.m. from fasting patients to prevent the varying circadian concentrations of biomarkers. The samples were taken for each patient before surgery and at one-week, two-weeks, three-months, and one-year controls. K3-EDTA, along with Li-heparin plasma, was

supplied in the tubes, which, after taking the sample, were stored at a temperature of 5ºC. Bone biomarkers were then analyzed at the end of follow-up. The immunoassay was conducted after two-point calibration and creation of the master-curve of monoclonal anti-ß-CrossLaps and anti-N-MID Osteocalcin antibodies (mouse-derived) (2,3).

3.9. EVALUATION OF HISTOMORPHOMETRIC OUTCOMES

A biopsy was taken from the callus at 6-weeks post-surgery, at the point when the Hoffmann II fixator and K-wires were removed. The spot of incision, mid-dorsal over the distal radius, was marked on the skin after being determined using an image intensifier. 5 ml of 0.55 Lidocaine was injected for local anesthesia, and a T-Lok™ Bone Marrow Biopsy Needle of 13 G (Product No. DBMNJ1304, ARGON® Medical devices, TX, USA) was used to retract a 5 - 7 mm extended callus tissue biopsy (2) (Picture 3.91).

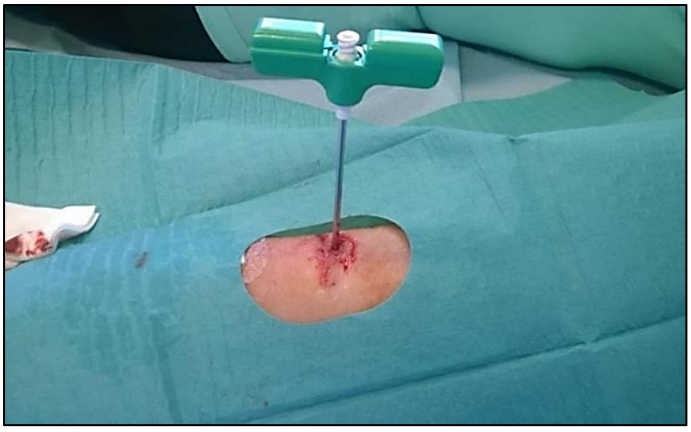


Figure 3.91. Bone biopsy procedure.

After placing in a plastic tube-container with 70% ethanol solution, the biopsy material was stored at 8ºC. Methylmethacrylate was used for embedding the biopsies after decalcifying. Sections of seven-micrometer thickness were performed using a Jung microtome K (R. Jung GmbH, Heidelberg, Germany) with a tungsten knife provided (2). To cover the largest possible area, a middle cut in the biopsies was performed in four levels with three sections per level with a distance of 175 μm between them. The staining was made with Goldner Trichrome (Figure 3.92).

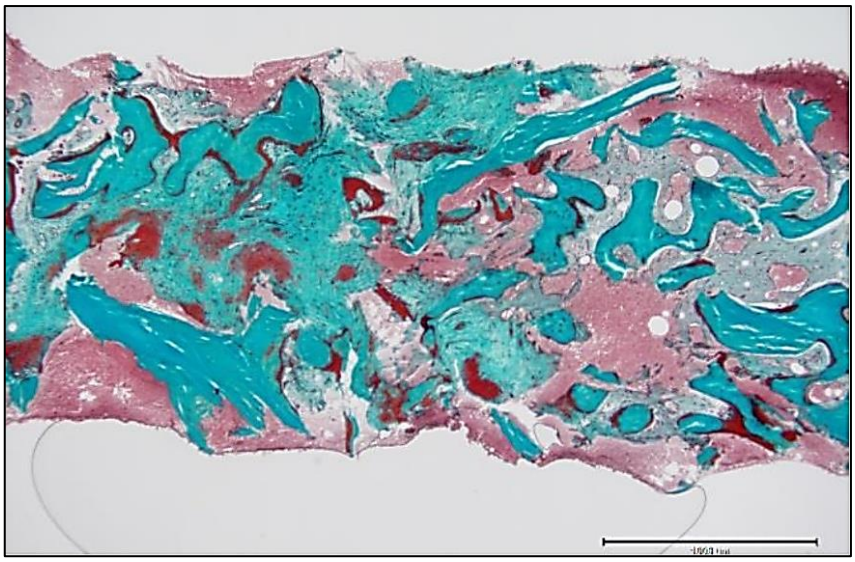


Figure 3.92. Stained section of biopsy material.

In study groups, the following callus histomorphometric volume and surface estimates were compared: bone volume/tissue volume (BV/TV%), lamellar bone volume/tissue volume (LBW/TV%), woven bone volume/tissue volume (WBV/TV%), osteoid volume/tissue volume (OV/TV%), fibrous tissue volume/tissue volume (FV/TV%), and osteoid surface/bone surface (OS/BS%), osteoblast surface/bone surface (ObS/BS %), osteoclast surface/bone surface (OcS/BS%) (2,45).

All analyses were performed by the same individual using an Olympus BH microscope with 200-times magnification and polarized lights facility (used to distinguish lamellar from woven bone) (2). All biopsies sections were assessed in five sight-fields per section using a 10×10 point ocular-grid for volume estimations (counting the number of times the point hit the tissue fraction of interest and dividing the number by the number of reference points hitting all the tissue in the sight field) (2). For surface estimations, ten-line-grids were used (counting how many times the lines intersect the bone surface fraction of interest and then dividing by the total number of bone surface intersections in the sight field). Random rotation of the line-grid was performed before analyzing every new sight-field. Biopsies were randomly selected (10% of all samples) for evaluation three months later to depict the variation coefficient (CV) as an estimate of observer repeatability in this part of the study. The formula: $CV = 100 * \sqrt{\frac{\sum(d/m)^2}{2n}}$, where d - the difference between two observations, m - the mean of two observations, and n - the number of observations (2).

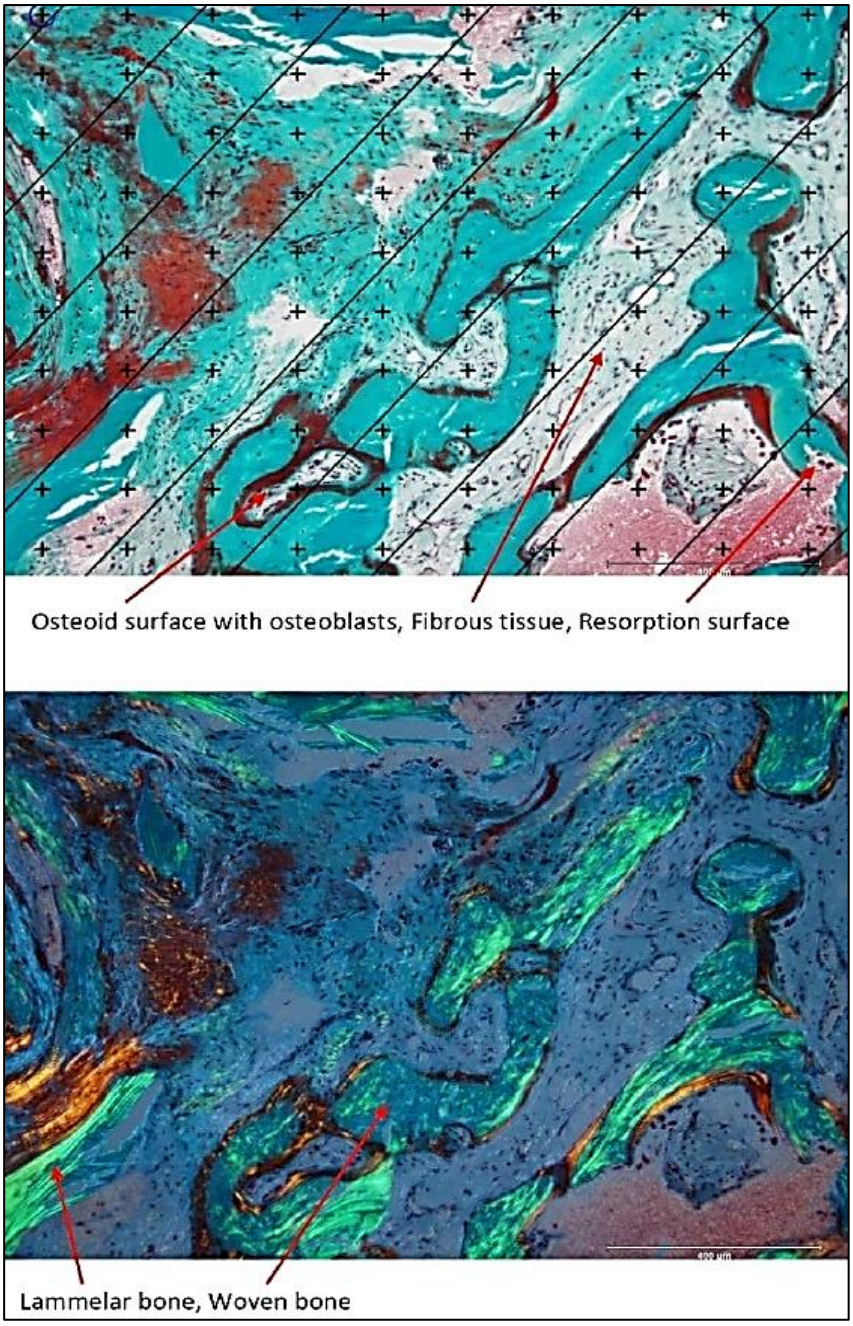


Figure 3.93. Histomorphometric assessment of bone tissue in normal and polarized light (reproduced from reference No. 2).

3.10. EVALUATION OF PAIN

Patients registered their pain using a Likert 10-point assessment scale (59,60). Pain experience was recorded for 14 days from enrollment, three times daily in the morning, midday, and evening when the subject took the study medication. One point indicated 'no pain,' and 'unbearable pain' scored 10 points. Participants were also obliged to record their consumption of tramadol as a rescue-analgesic.

The average daily pain was calculated for each patient in each treatment group. Three periods, at days 1 - 3, 4 - 7, and 8 - 14, were selected as pain outcomes. These periods corresponded to the treatment duration with ibuprofen 600 mg; two groups (the 3-days and 7-days groups) received ibuprofen during the first period. Only one group (7-days group) received ibuprofen during the second period; no group was treated with ibuprofen during the third period. The escape medicine tramadol taken during these periods was also recorded for each day of analgesic follow-up.

3.11. CONSENT

We followed The CONSORT 2010 guidelines in this study (61). Written and signed informed consent was collected from all participants before they were included in the study.

The project was conducted following the Good Clinical Practice guidelines (62) and following the conditions and allowance of the Danish Data Protection Agency, the Danish Regional Ethics Committee (registration number N-20100015), and the Danish National Medicine Agency (registration number 1253599). The study was also registered in the clinicaltrials.gov database (registration number NCT01567072) and the European Medicines Agency (EudraCT number 2010-018543-34).

No financial sponsors of this randomized controlled trial contributed to designing or conducting the study, analyzing the data, or preparing the manuscripts. The primary author is responsible for the correctness of both the data and the results reported.

CHAPTER 4. STATISTICAL METHODS

4.1. SAMPLE SIZE

Before completing the follow-up or performing any analyses, a detailed statistical analysis was published on the Aalborg University's web page (63). We determined the sample size with reference to this study's primary outcome; dorsal angulation of the distal radius fragment.

Sample size estimation was performed to ensure the proper power for testing the null-hypothesis of ibuprofen treatment being inferior to paracetamol-only therapy, resulting in more remarkable radiological fragment migration. Non-inferiority design and radiological fragment migration were chosen for the power and sample size calculation.

A literature-based non-inferiority margin of one SD (64), equal to 9.4 (65), and an 8º reliable measurement limit (66) was set for this study, with the power defined at 90%. Thus to reject H_0 when H_A is true at a 0.05 level of significance, 132 respondents were required (i.e., 22 patients in every treatment group in both divisions). On the other hand, a total of 192 respondents (i.e., 32 patients in every treatment group in both divisions) were needed to estimate the normal distribution and allow a dropout rate of at least 20% (1,3).

A posthoc sample size and power calculation for other outcomes were made, according to the standard deviation as a non-inferiority margin (64) in our study population and an overview of the literature.
A one SD = 14.5% non-inferiority margin for the difference in the range of wrist extension/flexion, as the main important movement component (67), was used for the sample size calculation. It was estimated that 22 patients in each treatment group would yield a power of 0.90 with a significance level of 0.05, commonly used in non-inferiority trials (68).

According to the BMD difference between the injured and healthy UD zone of the distal forearm, posthoc sample size and power calculation were taken for densitometrical outcomes. We used a value of the standard deviation of the difference between the healthy-side BMD and post-fracture BMD for the calculation. In the literature, the standard deviation was reported to be 4.35% (69). Then, we subtracted 1% error of precision (70) and determined a value of 3.35% as the non-inferiority margin in the sample size calculation. Therefore, to attain a power of 90% with a one-

sided 0.05 level test, it was necessary to recruit 186 participants (three 31-patient groups in each of two divisions) (2).

For the pain score, the sample size was calculated to test the null hypothesis (according to the superiority design) that there is no difference in patients' pain experience between ibuprofen and placebo treatment groups. A minimal clinical pain score difference of 1.5 VAS-points was chosen (71). With a significance level of 0.05, a power of 90%, and an SD of 1.41 (71), a total of 23 patients were needed in each group.

4.2. STATISTICAL METHODS OF THE OUTCOME ANALYZES

Frequency histograms, boxplots, and Q - Q plots were employed to check each sample's distribution pattern (1,2). If there were homoscedasticity and normal distribution of the sample data, the ANOVA test was applied with a posthoc Tukey test if necessary.

According to the initial statistical analysis plan (63), Student's t-tests with a Dunn - Šidák correction were foreseen. In cases where a comparison had to be made between three groups, the α significance level with a Dunn - Šidák correction was $\alpha = 1 - (1 - 0.05)^{1/3} = 0.017$.

Subsequently, the experience was that the ANOVA test was more applicable as it handles more than two samples and compares the variation within treatment groups to variation between treatment groups. Therefore, this test was applied in two of our publications; *"Influence of ibuprofen on bone healing after Colles' fracture - a randomized controlled clinical trial"* (2) and *"The Influence of Ibuprofen on the Healing of Nonsurgically treated Colles' Fractures"* (3).

In this thesis, the ANOVA test is used to compare the outcomes between three treatment groups across the entire study. The change from t-test with Dunn - Šidák correction to ANOVA test did not influence the significance of our study results and conclusions.

In case of a not normal distribution, we applied a Kruskal - Wallis nonparametric significance test.

Additionally, to compare the severity of complications and adverse events between treatment groups, a Z-test was chosen.

The power was set to 90% for all tests.

4.3. MANAGEMENT OF MISSING DATA

The endpoint assessment suffered from some missing data due to improper quality of radiographs or biopsy, DXA scanning, blood analyses not being performed, or forgotten records in the patient's pain diary, not answered questions of DASH survey. The missing values were multiply imputed in the database to avoid potential bias and increase the outcome's reliability. All imputations were reviewed to warrant the sane values being developed, and multiple imputations were applied on both baseline and outcome variables (63).

4.4. STATISTICAL ANALYSIS PROCEDURE

The statistical analysis plan published on the Aalborg University website was used to instruct the statistician performing the analyses. The same statistician performed all analyses using the statistical program package R.

The statistical analysis procedure consisted of the following five steps:

1. A "data collection form" was drafted as a teamwork platform between the study's data manager (sponsor/investigator) and the statistician.

2. The study pharmacist coded each therapy arm in both divisions as "group one," "group two," and "group three," hence, blinded analysis of the data was ensured.

3. The collection form containing blinded, raw data was transferred to the statistician.

4. Primary and secondary outcome analyses were blinded regarding the therapy.

5. Results were submitted to the trial investigator, after which any uncertainties were resolved, and blinded outcome results were interpreted before the data then being unblinded.

CHAPTER 5. SUMMARY OF RESULTS

5.1. SCREENING, INCLUSION, AND FOLLOW-UP

Between 1. June 2012 and 20. June 2015, a total of 564 patients were screened. 284 of these patients had the Older type 1 - 2 Colles' fracture, and 280 suffered from the Older type 3 - 4 fracture. 191 patients were enrolled in the study, an enrollment percentage of 33.8. There was a significant 2.5 ± 0.99 years difference between enrolled (mean age 63.7 years) and non-enrolled (mean age 66.2 years) patients, P = 0.01. The proportion of males was 22% among enrolled individuals and 15% among non-enrolled individuals, P = 0.03.

96 of the total of 284 patients with Colles' fractures considered stable were recruited to **the conservative division**, an enrollment percentage of 33.8 (Table 5.11). 122 patients were not informed about the study. 47 patients were not interested, and 19 patients fulfilled the criteria for exclusion. 69 patients were women, the mean age being 62.1 ± 9.8 years. 91 of the enrolled participants received the study pharmaceuticals, five patients did not (met exclusion criteria, non-compliance). 19 patients withdrew from participating while one patient lost his pain records. Three patients experienced nausea after treatment and quit the study. Seven patients were excluded because of secondary dislocations. Two patients did not undergo DXA scanning because of logistical reasons. The conservative division analysis was conducted on 80 patients, divided into three groups based on the intention to treat (Figure 5.12).

	placebo group	3-days ibuprofen group	7-days ibuprofen group
Female\Male	**22\8**	**17\7**	**17\9**
Mean age (years ± 1SD)	**61.3 ± 8.3**	**63 ± 11.2**	**62 ± 9.9**
Smokers\Non-smokers	**6\24**	**4\20**	**4\22**
Osteoporosis treatment +\-	**1\29**	**0\24**	**0\26**
Dominating\Not	**13\17**	**10\14**	**16\10**
Displaced/non-displaced	**14/16**	**12/12**	**19/7**
Pre-treatment pain score	**6.4 ± 2.6**	**6.2 ± 2.6**	**6.9 ± 2.5**
BMI	**26.6 ± 3.2**	**26.5 ± 4.7**	**26.4 ± 4.3**
Total analyzed	**30**	**24**	**26**

Table 5.11. Baseline characteristics of the patients in the conservative division.

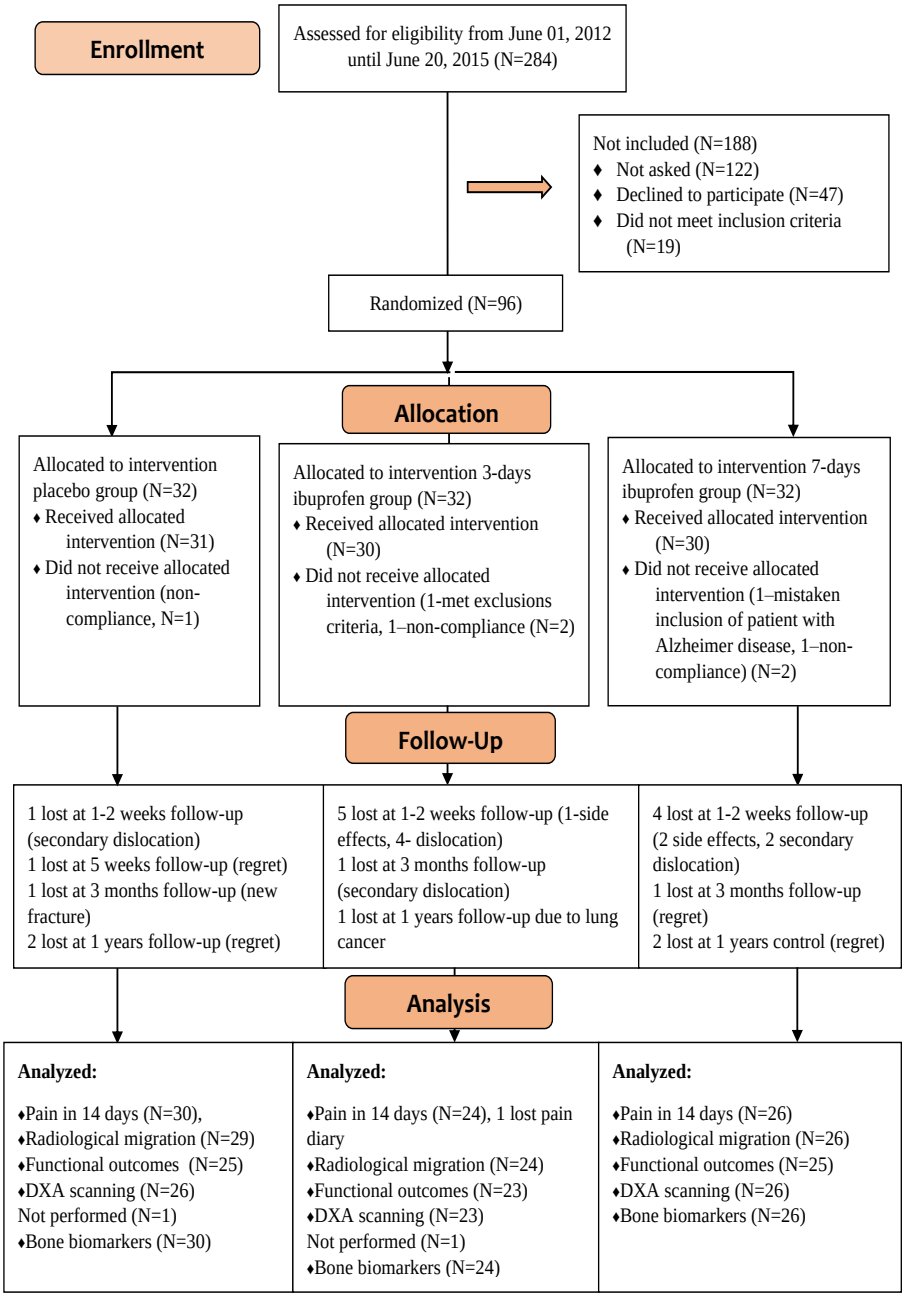


Figure 5.12. Conservative division - consort flow diagram (reproduced from reference No. 3).

In the surgical division, 95 participants out of 280 screened with Older type 3 - 4 Colles' fracture were recruited, an enrolment percentage of 33.9%. Of the initial 280, 121 patients were not included due to time limitations at the hospital, 45 declared no interest in taking part, and 19 exhibited the exclusion criteria. One patient with a different fracture type than described in the protocol received a pack containing study medication.

95 patients were included (Table 5.13). The largest proportion (N = 80) of participants were female, with a mean age of 64.7 ± 9.2 years. 89 out of the 95 recruited participants received the study medicine. The other six participants did not, either due to changing their mind or their noncompliance. Four patients subsequently withdrew their willingness to be a part of the study; three patients mislaid their pain-experience recordings; one participant experienced therapy-related side-effect (nausea) and cancelled further study treatment. One participant suffered unexpected death (by drowning accident) before the last follow-up visit. One participant, who received a different operation than described in the protocol, was excluded due to secondary displacement. As a result of poor-quality, one participant's X-ray pictures were also excluded from the evaluation. For logistical reasons, it was not possible to perform DXA scanning on one patient. Finally, due to tissue material being of improper quality, four further patients were excluded from the histomorphometric evaluation. An intention to treat analysis was applied for 89 participants, allocated to three different treatment groups. (Figure 5.14).

	placebo group	**3-days ibuprofen group**	**7-days ibuprofen group**
Female\Male	**25\5**	**25\5**	**24\5**
Mean 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**
Pre-treatment pain score	**6.5 ± 2.7**	**6.8 ± 2.5**	**6.7 ± 2.3**
BMI	**26.7 ± 4.6**	**24.9 ± 3.9**	**23.7 ± 3.5**
Total analyzed	**30**	**30**	**29**

Table 5.13. Baseline characteristics of the study patients in the surgical division.

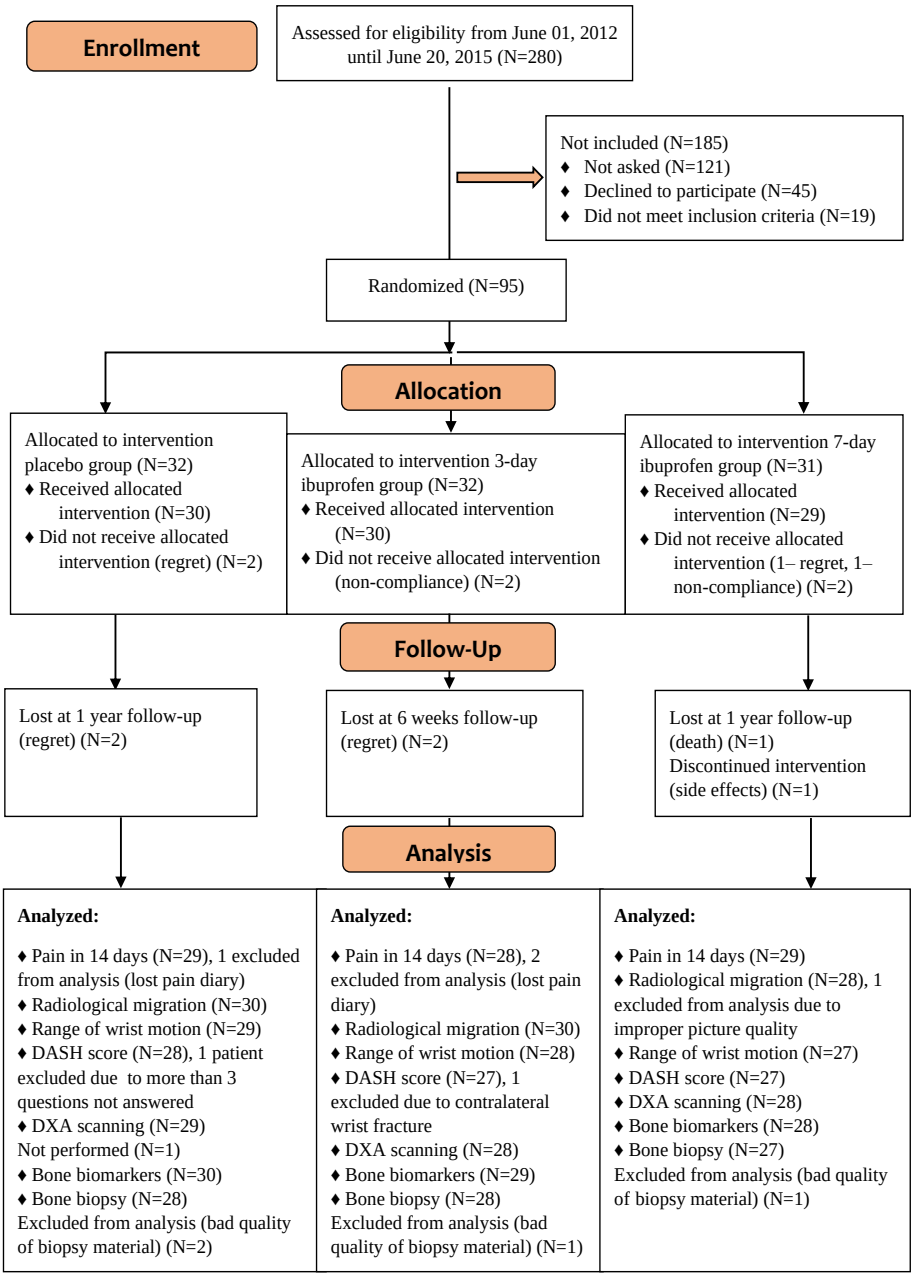


Figure 5.14. Surgical division - consort flow diagram (reproduced from references No. 1 and No. 2).

5.2. RADIOLOGICAL OUTCOMES

The primary outcome was to assess the mean difference in radius tilt between the first measurement and the 5/6-week follow-up. The results showed that this difference followed the same trend in all groups, moving from a volar tilt towards a dorsal tilt. The secondary outcome in this part of the study was to assess the mean difference in radius length between the first measurement and the 5/6-week follow-up. The results showed that this difference followed the same trend in all groups; the radius was shortened after 5 - 6 weeks. Another secondary outcome was to assess the mean difference in radius inclination between the post-treatment measurement and the 5/6-week follow-up assessment, wherein a decreased radius inclination was found in all groups.

There were no clinically important or significant changes in radial tilt, length, or inclination **in the conservative division**, $0.09 \leq P \leq 0.5$ (Figure 5.21). Severe secondary dislocations were reported in one participant in the placebo group, two participants in the 3-days ibuprofen group, and four participants in the 7-days ibuprofen group at the first one-week follow-up. Three patients were enrolled with an unstable Colles' fracture (one in each treatment group) despite not meeting the inclusion criteria. All these patients were subsequently excluded and treated surgically.

There were neither clinically nor statistically significant differences **in the surgical division** ($0.12 \leq P \leq 0.87$) in the movement of radiological fragments (Figure 5.22).

Length, tilt, and inclination were measured twice in each X-ray picture by the same evaluator. The mean difference in length was −0.184 mm (95% CI: −0.29 to −0.79 mm), indicating a trend for the radius to be longer at evaluation two. The mean difference in tilt was 0.21° (95% CI: −0.011° to 0.43°). The mean difference in inclination was 0.037° (95% CI: −0.16° to 0.23°).

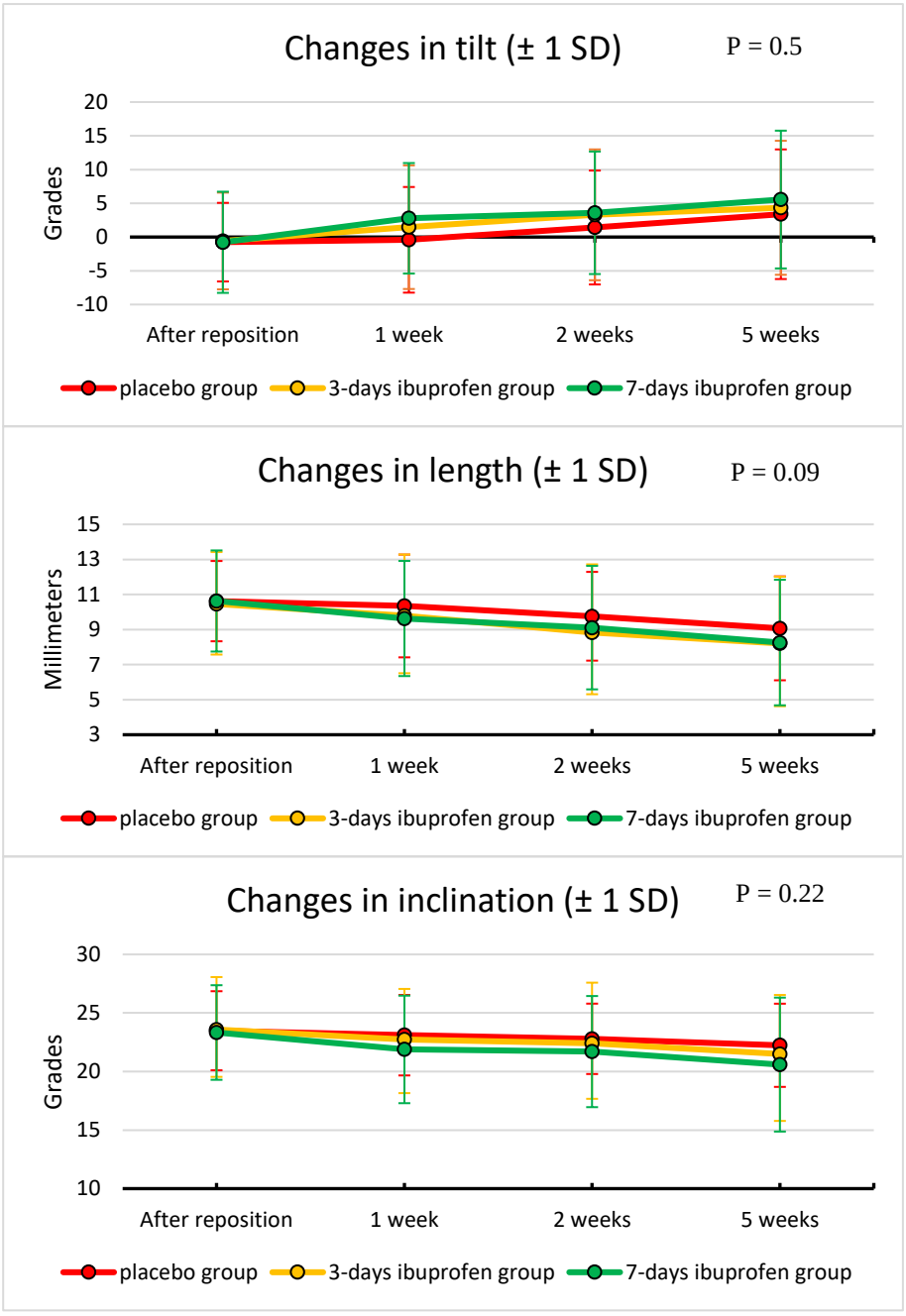


Figure 5.21. Radiological fragment migration of the radius in the conservative division.

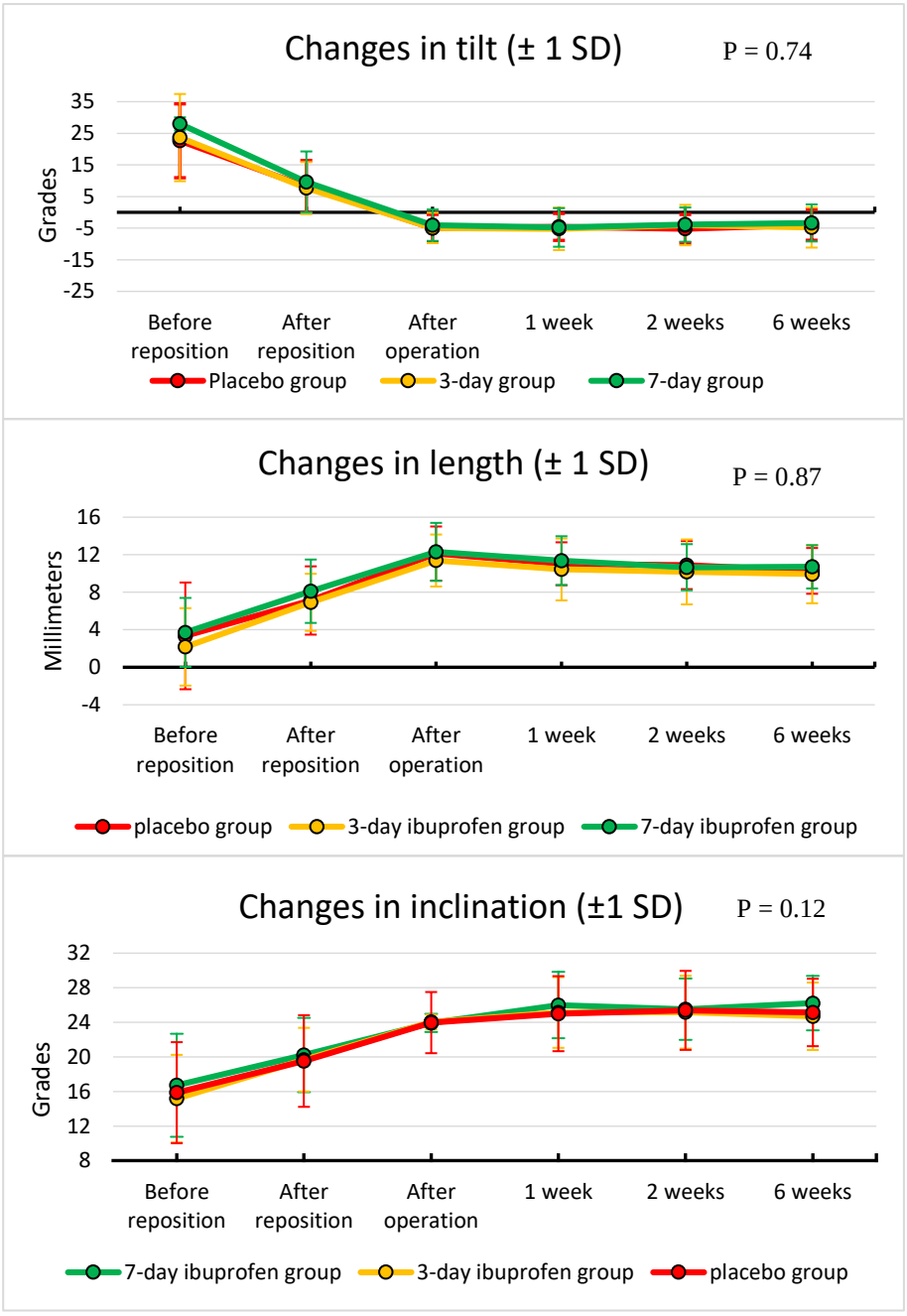


Figure 5.22. Radiological fragment migration of the radius in the surgical division.

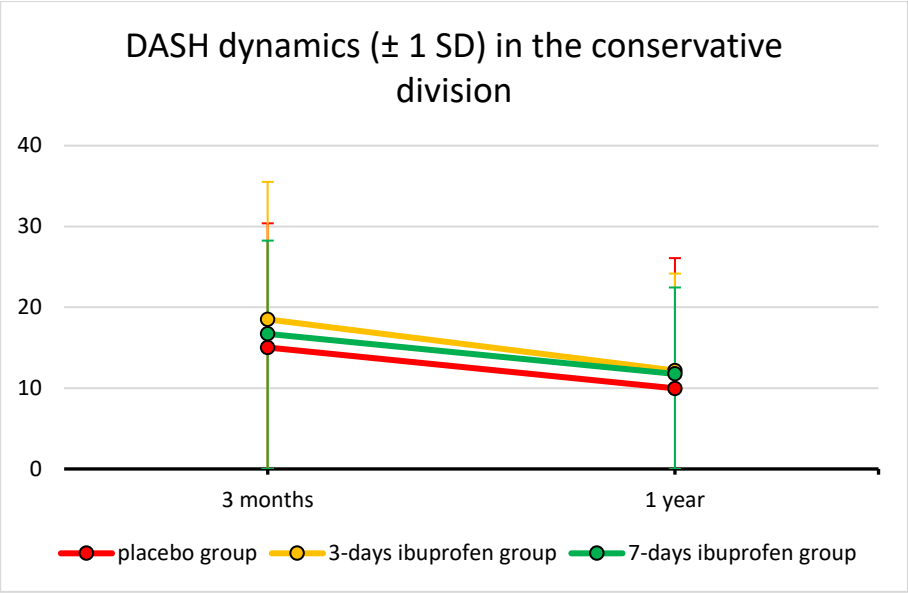
5.3. FUNCTIONAL OUTCOMES

The mean DASH score measurement followed the same trend in all groups in both divisions, with a high score at three months (**conservative division** 16.7 ± 14.5, **surgical division** 21.7 ± 14.7) and a lower score at one year (**conservative division** 11.3 ± 13, **surgical division** 13.5 ± 12.8). We did not detect any significant differences in ibuprofen and placebo groups at any of the follow-up moments. In the **conservative division**, $0.7 \leq P \leq 0.9$, in the **surgical division**, $0.2 \leq P \leq 0.7$ (Figure 5.31).

Participants in all three intervention groups of **the conservative division** recorded a similar improvement in wrist joint motion during subsequent control sessions. This improvement was as great as 88 - 95% of the physiologic ROM at the end of follow-up (Figure 5.32). No significant differences between the study groups were observed during all follow-up time $0.1 \leq P \leq 0.9$.

In the surgical division, patients in all groups showed improved wrist joint motion corresponding to 87% - 95% of the normal contra-lateral wrist movement at the final visit (Figure 5.33). The differences between the therapy groups were not significant during the entire follow-up process, $0.1 \leq P \leq 0.6$.

There was no difference in the distribution of injured hand domination between the groups (Tables 5.11 and 5.13).



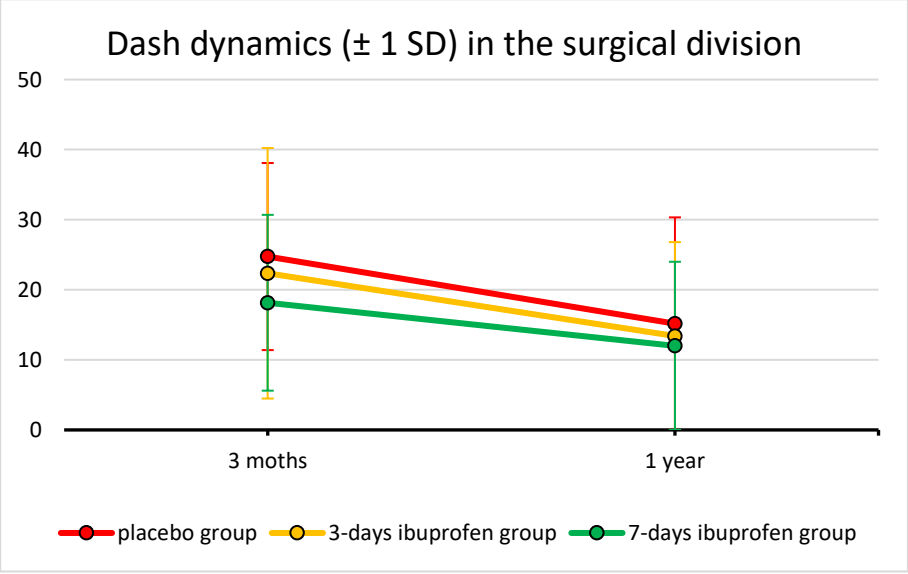


Figure 5.31. Changes in DASH score.

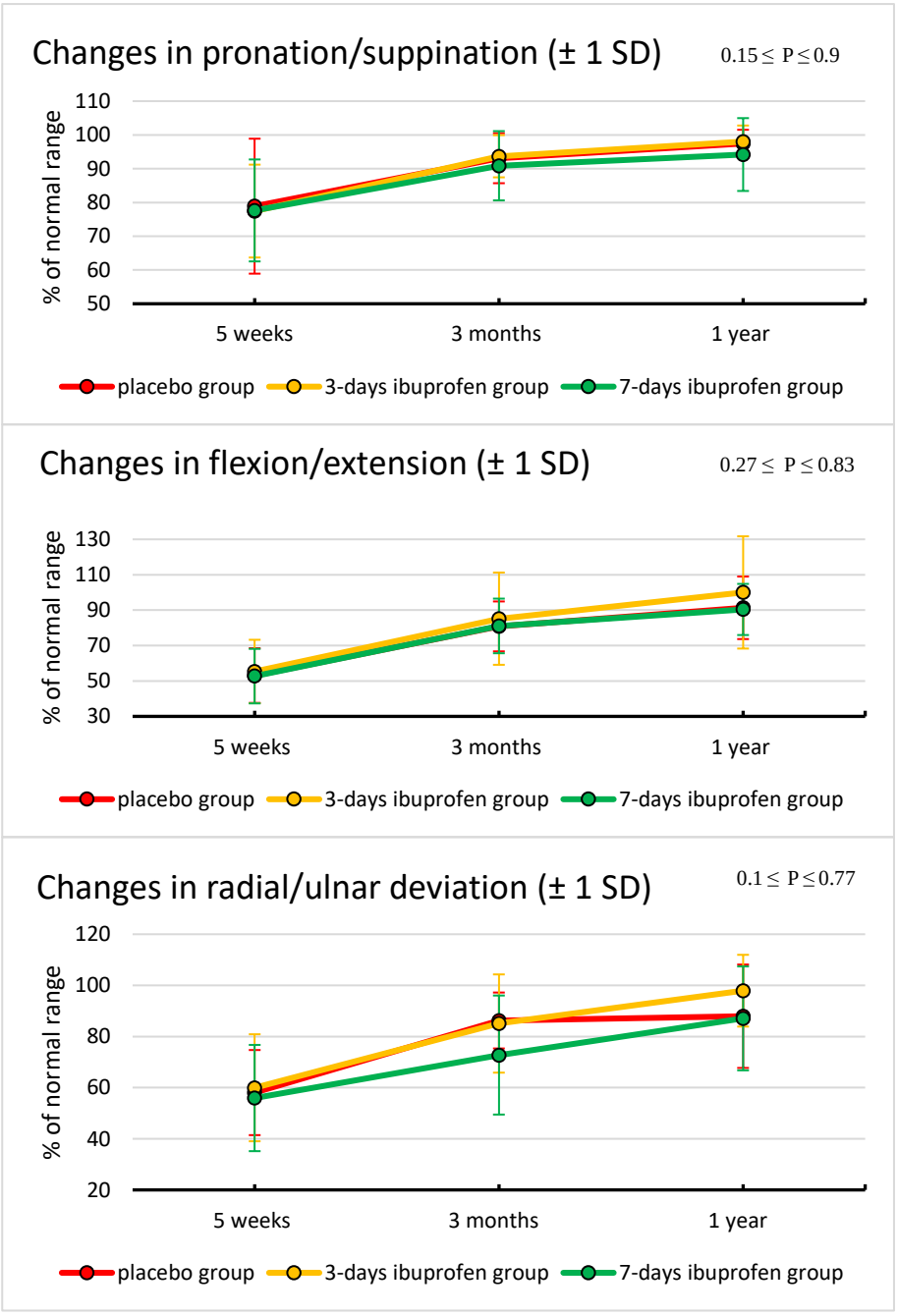


Figure 5.32. ROM changes in the injured wrist, conservative division.

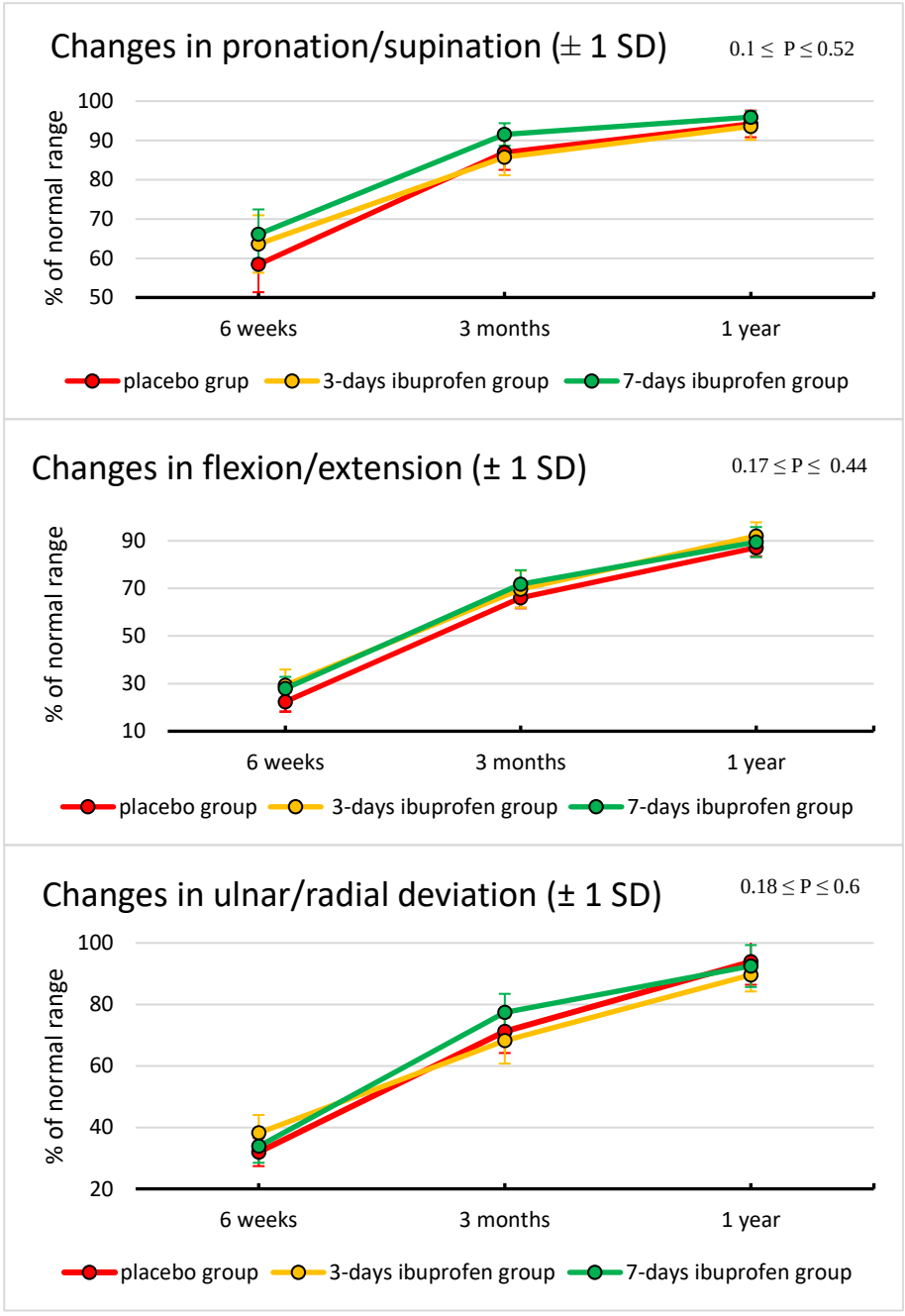


Figure 5.33. ROM changes in the injured wrist, surgical division.

5.4. DENSITOMETRICAL OUTCOMES

In both divisions, the injured bone showed a mean BMD that was 3 - 7 % higher in the ultra-distal region of interest than in the healthy contra-lateral radius. This trend was observed in all treatment groups, with no significant difference between them. (Figure 5.4).

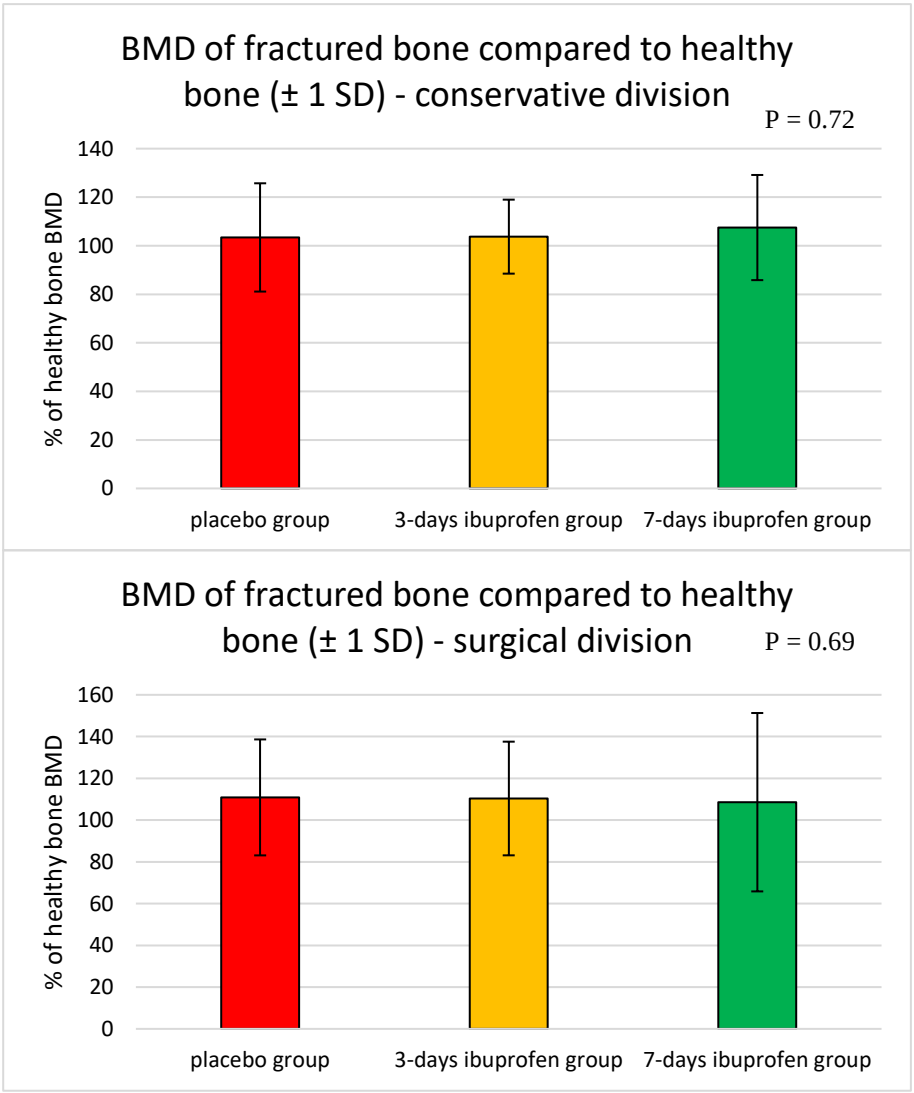


Figure 5.4. Densitometrical outcomes in treatment groups.

5.5. BIOCHEMICAL OUTCOMES

This study did not demonstrate any difference in CrossLaps and Osteocalcin levels at any moment of the follow-up time. **In the conservative division**, the significance was $0.06 \leq P \leq 0.7$ for CrossLaps, and $0.15 \leq P \leq 0.84$ for Osteocalcin (Figure 5.51). **In the surgical division**, it was $0.37 \leq P \leq 0.95$ for CrossLaps, and $0.43 \leq P \leq 0.99$ for Osteocalcin (Figure 5.52).

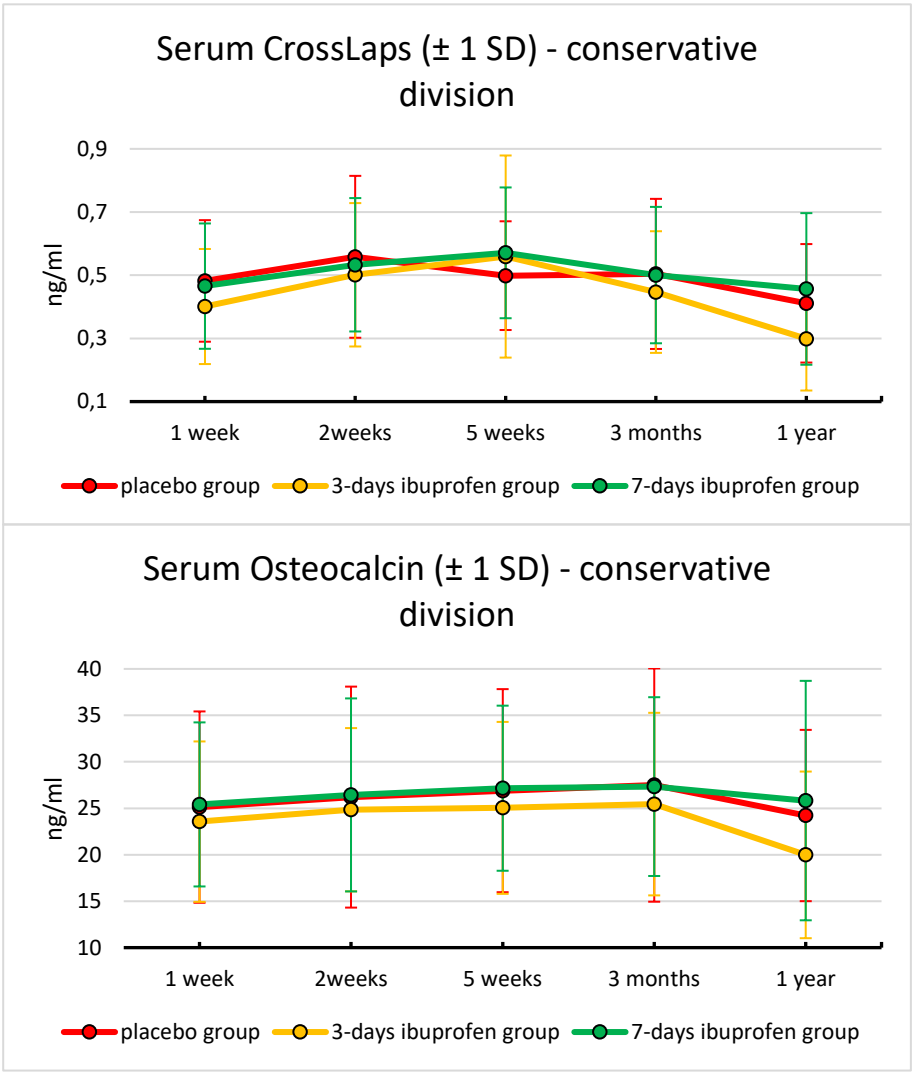
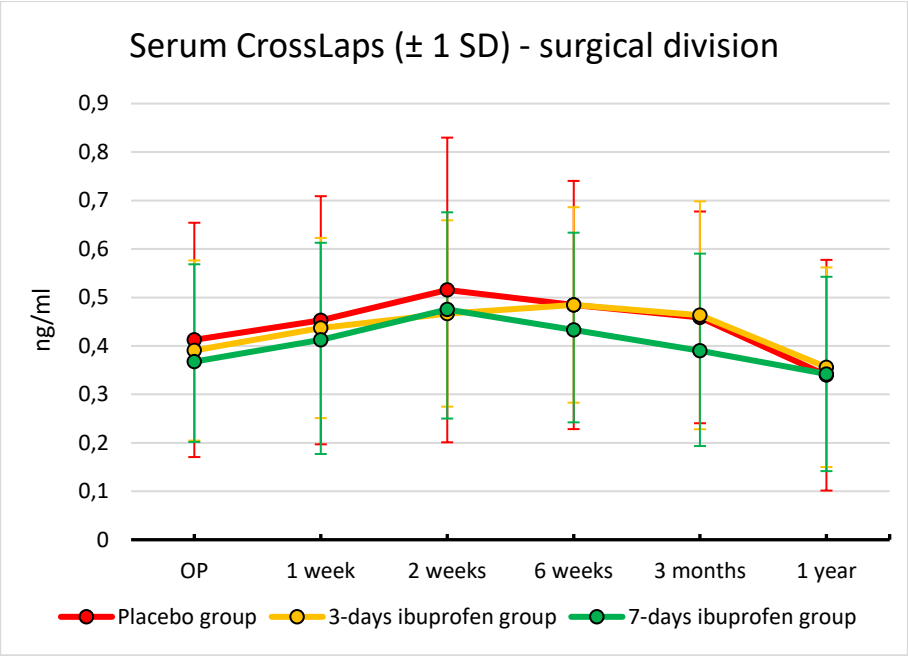


Figure 5.51. Biochemical outcomes in the conservative division.



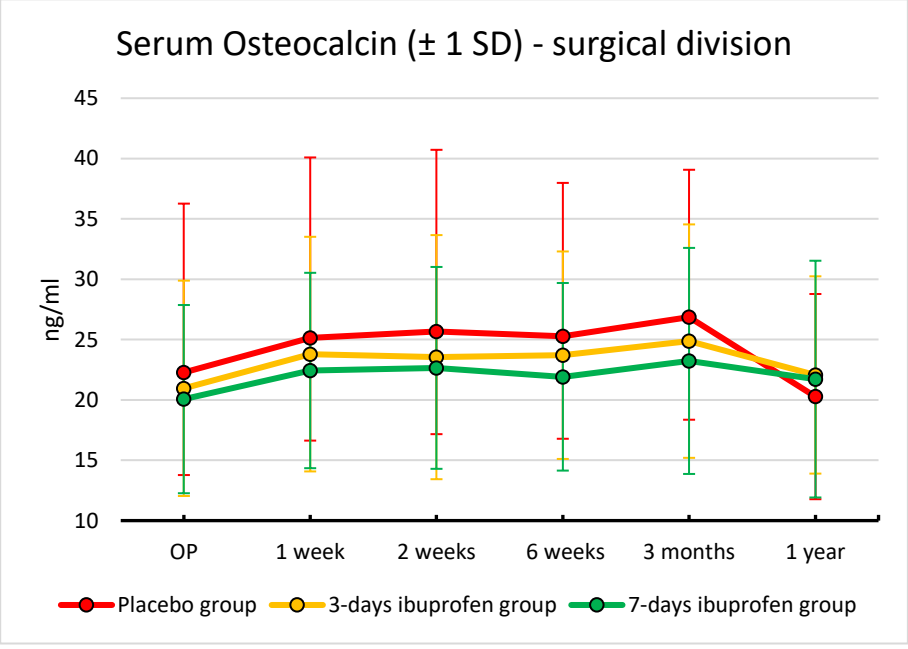


Figure 5.52. Biochemical outcomes in the surgical division.

5.6. HISTOMORPHOMETRIC OUTCOMES

Neither volume nor surface estimations were significantly different in intervention groups, $0.38 \leq P \leq 0.99$ (Table 5.6). The median intra-observer CV was equal to 4.7%, ranging from 0 - 36.9%. The evaluator tended to identify less tissue as a woven bone and less bone surface as a "quiet" type (without signs of bone resorption or formation/remodeling) (2).

	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 5.6. Histomorphometric estimations (mean ± 1 SD) in treatment groups of the surgical division.

5.7. ANALGESIC OUTCOMES

The mean daily pain score evaluation showed a constant decrease in pain in all treatment groups across all 14 days **in the conservative division**. Pain in the first three days was 1.3 VAS points (on average) less intense among the ibuprofen patients (P = 0.02) in comparison to the placebo therapy, where the peak difference of 1.75 VAS points was noticed during the second day (Figure 5.71).

The placebo group demonstrated a slighter decrease in pain until day 8. Pain experienced in this group was 0.8 VAS points higher during the 4 - 7 days follow-up (compared to the ibuprofen groups). During the third period of 8 - 14 days, all the groups scored equally between 2 and 3 VAS points. No significant differences were observed during these follow-up periods. (Table 5.72).

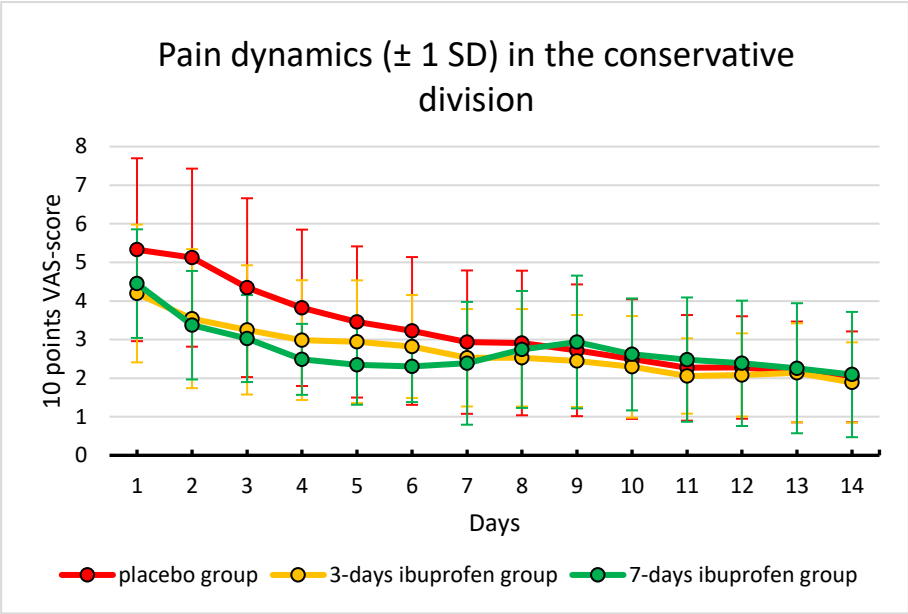


Figure 5.71. Pain dynamics in the conservative division.

Day	placebo group	3-days ibuprofen group	7-days ibuprofen group	P
1-3	**4.93 (SD 2.25)**	**3.66 (SD 1.63)**	**3.61 (SD 1.15)**	**0.02**
4-7	**3.35 (SD 1.86)**	**2.8 (SD 1.33)**	**2.38 (SD 0.89)**	**0.23**
8-14	**2.38 (SD 1.37)**	**2.2 (SD 1.07)**	**2.5 (SD 1.49)**	**0.58**

Table 5.72. Mean pain score in treatment groups of the conservative division.

Tramadol consumption was seen in 12.5% of the population in the 3-days ibuprofen group, 26% of the population in the 7-days ibuprofen group, and 33.3% of the group population in the placebo group **of the conservative division** (Figure 5.73). The treatment groups showed no significant difference in tramadol consumption (P = 0.12).

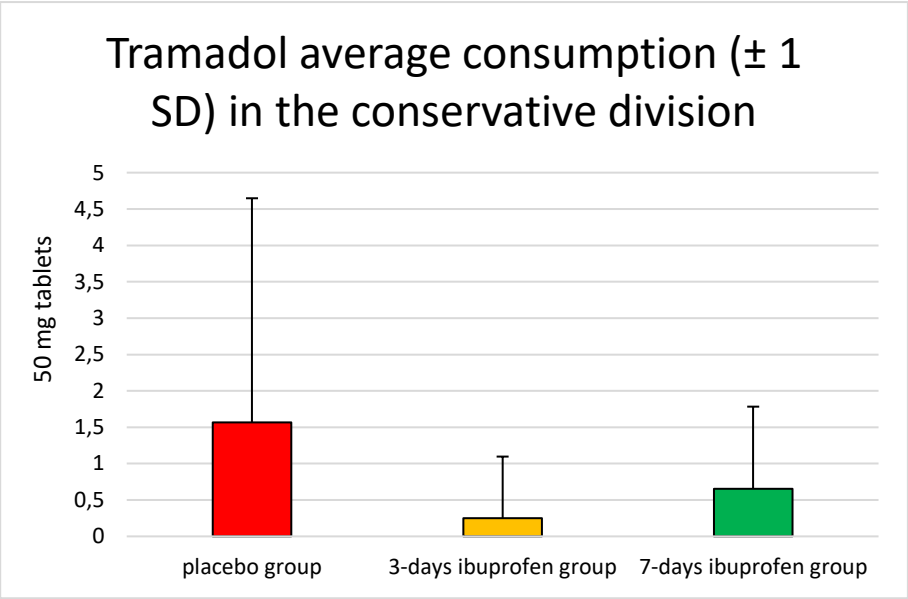


Figure 5.73. Tramadol use on request in the conservative division.

Measurement of the mean daily pain score **in the surgical division** showed a constant decrease in pain in the 7-days ibuprofen group across all 14 days. The mean pain score was not significantly different between the treatment groups in the predefined follow-up intervals mentioned above (Table 5.74).

The placebo group demonstrated increasing pain between day one and day two (3.9 to 4.4 points), after which the pain score decreased continually. The 3-days ibuprofen group experienced increasing pain from the third to fourth day. The peak pain score was 4.4 and decreased from day 4 to day 14. This decrease was seen to a lesser extent than in the other treatment groups (Figure 5.75).

Day	placebo group	3-days ibuprofen group	7-days ibuprofen group	P
1-3	**4.18 (SD 1.9)**	**4.25 (SD 1.71)**	**4.3 (SD 1.92)**	**0.4**
4-7	**2.98 (SD 1.88)**	**3.88 (SD 2.04)**	**2.98 (SD 1.47)**	**0.13**
8-14	**2.18 (SD 1.35)**	**2.54 (SD 1.75)**	**2.17 (SD 1.0)**	**0.98**

Table 5.74. Mean pain score in the different treatment groups of the surgical division.

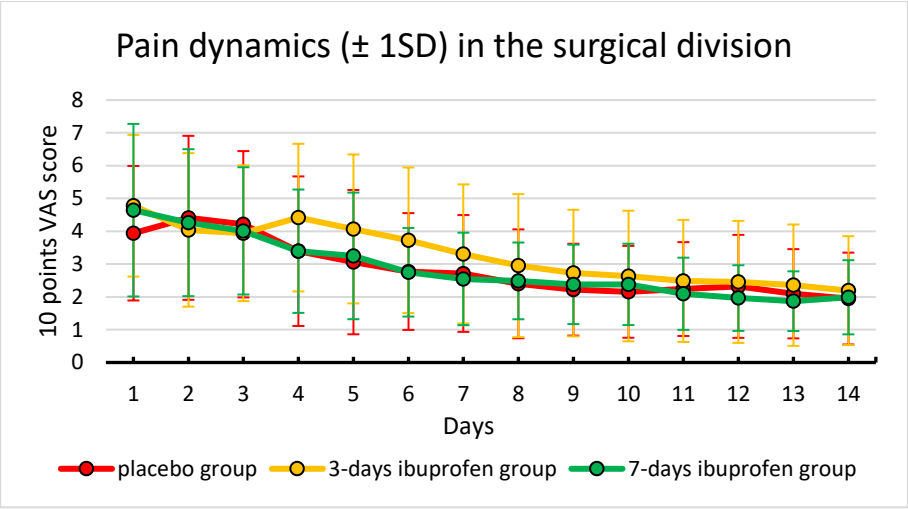


Figure 5.75. Pain dynamics in the surgical division.

In surgical division, tramadol consumption was seen in 79% of the population in the placebo group, 71% of the population in the 3-days ibuprofen group, and 57% of the population in the 7-days ibuprofen group. The peak difference was seen on the second day (Figure 5.75). The median of tramadol consumption during the first three days was 2 (range 0 - 7) pills in the placebo group and 1 (range 0 - 9) pill in the NSAID population (P = 0.035) (1).

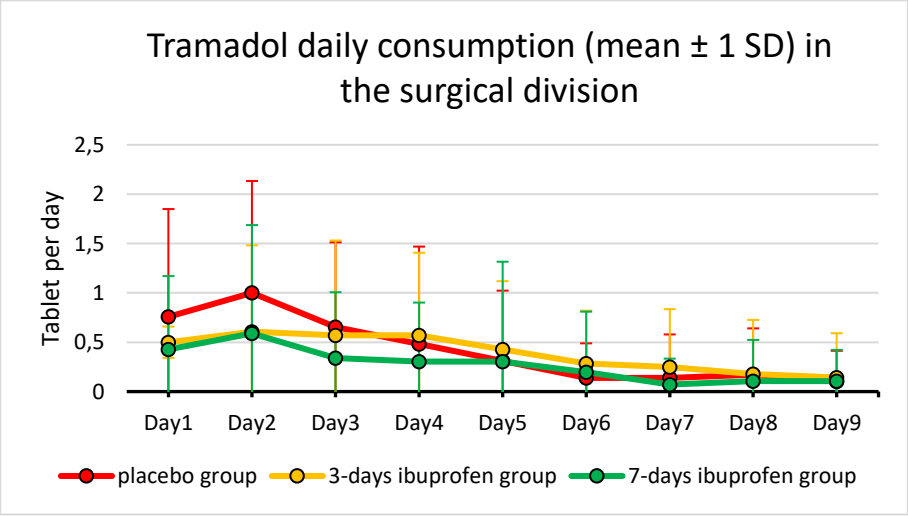


Figure 5.76. Tramadol use (50 mg) on request in the surgical division.

5.8. COMPLICATIONS AND ADVERSE EVENTS

Conservatively treated patients complained mostly of gastrointestinal disturbances and finger dysesthesia (Table 5.81). For this part of the study, the total percentage of adverse events counted was 46.1%, with significant differences between 3-days ibuprofen and placebo groups, Z = 1.91, P = 0.03 (Figure 5.82).

Adverse events	placebo group	3-days group	7-days group
Overall	11 of 31 (35.5%)	17 of 30 (56.6%)	13 of 30 (43.3%)
Gastrointestinal disorders	3	3	7
Numbness	4	6	3
Swelling	3	4	1
Serious secondary displacement	1	4	2

Table 5.81. Adverse events in treatment groups of the conservative division.

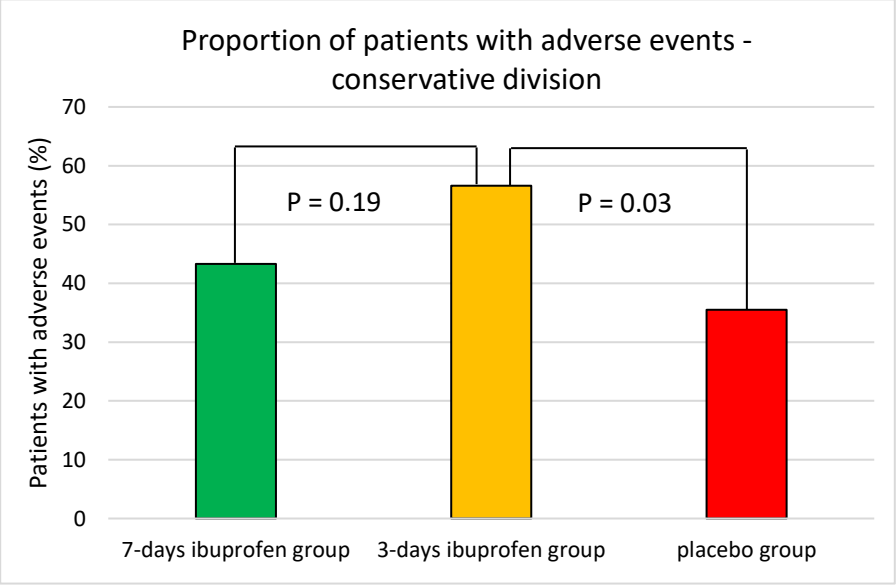


Figure 5.82. Proportion of patients with adverse events – conservative division.

The surgical division's overall adverse events rate was 43.9%. The gastrointestinal disorder was the most common complication; however, no therapy-related severe complications were observed in any treatment group. Other complications relating to fracture or surgery, nerve numbness, pinhole infections, loosening of osteosynthesis material, and secondary fracture-dislocation, were observed in 19 patients, 21.3% of the division population (Table 5.83).

There were significant differences in the number of adverse events between ibuprofen and placebo-treated patients (Z = 1.709, P = 0.043, Figure 5.84).

Adverse events	placebo group	3-days group	7-days group
Overall	**10 of 30 (33.3%)**	**12 of 30 (40%)**	**16 of 29 (55.1%)**
Gastrointestinal disorders	**4**	**7**	**8**
Numbness	**6**	**2**	**5**
Pinholes Infection	**0**	**1**	**2**
Loosening of osteosynthesis material	**0**	**2**	**0**
Serious secondary displacement	**0**	**0**	**1**

Table 5.83. Adverse events in treatment groups of the surgical division.

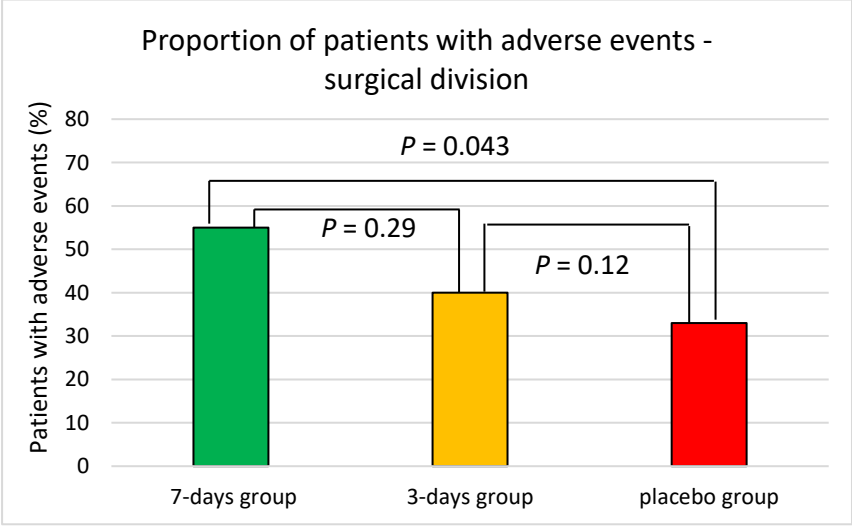


Figure 5.84. Proportion of patients with adverse events - surgical division.

CHAPTER 6. DISCUSSION

6.1. MAIN FINDINGS

- All treatment groups with a Colles' fracture demonstrated the same bone fragment migration pattern regardless of the ibuprofen therapy for conservatively and surgically treated patients.

- All treatment groups in both divisions demonstrated the same improvement in DASH score and wrist joint motion amplitude, regardless of whether they were treated with ibuprofen (and for how long) or not.

- All treatment groups in both divisions presented the same results expressed in bone mineral density in the fracture zone three months after injury.

- The same trend of serum CrossLaps and Osteocalcin concentration changes were demonstrated in all treatment groups, regardless of the ibuprofen treatment.

- There were no differences in histomorphometric volume and surface estimations in callus biopsies in all surgical division groups, regardless of the ibuprofen treatment.

- This study demonstrated statistically significant pain relief in the ibuprofen groups of the conservative division and a tramadol-sparing effect in the ibuprofen groups of the surgical division.

- The overall adverse effects (predominately gastrointestinal disturbances) were more frequent among ibuprofen than placebo-treated individuals in both divisions. In the conservative division, most secondary displacements occurred in the 3-days ibuprofen group.

6.2. INTERPRETATION OF THE RADIOLOGICAL OUTCOMES AND COMPARISON WITH THE LITERATURE

This study has shown that short-term ibuprofen therapy did not affect the consolidation of distal radius fracture in terms of radiological outcomes. Embase and PubMed's search engines helped us identify two studies describing analgesic, functional, and radiological outcomes after Colles' fracture related to NSAID therapy (49,72).

Davis and Ackroyd (49) treated Colles' fracture patients conservatively for two weeks in a double-blind, prospective randomized study using flurbiprofen. The authors examined the anatomy of the post-traumatic radius in one year's radiographs. They reported 64% of injuries uniting in an excellent position according to Lidström classification, matching the excellent anatomy near in 61% of our study population. Additionally, Davis and Ackroyd reported a paracetamol-sparing and noticeable analgesic effect of flurbiprofen during the first three days. However, the different flurbiprofen dosing in the treatment group and the differing ages of 8.4 years on average between the individuals in study groups make the direct analogy with our results somewhat challenging. Furthermore, the authors reported the analgetic results in categorical units.

Adoplphson et al. carried out an RCT consisting of two groups with 21 women after menopause suffering from Colles' fracture and treated conservatively (72). The intervention group was assigned to piroxicam for eight weeks, while the other group was given a placebo and paracetamol as an escape medication. Shortening of the radius by 2 - 3 mm and progressing dorsal tilt by 12 - 14° in both study groups was not significantly different. This study also contained a minor sample of severe, multi-fragmented fractures allocated to conservative treatment, and 14% of the participants were later treated surgically, applying an external fixation. These may be seen as confounding factors in this study's results.

A bridging external fixation with supplemental K-wires for fixation of Colles' fracture being described as a valid tool in fracture stabilization (73), osteosynthesis's rigidity remains not entirely static, and bone fragments may migrate as much as six weeks after the operation (74). Using the keywords "Colles' fracture" and "NSAIDs" in the PubMed and Embase search systems produced only two studies (49,72) with the radiological migration of Colles' fractures following NSAID treatment as the main topic. However, both these studies involved conservative treatment, and their outcomes are, therefore, not closely comparable with the fragment migration in our surgical division.

Other studies reporting radiological outcomes of bridging external fixation of Colles' fracture were compared with this study, although none used NSAIDs for pain treatment.

Wei et al. compared different osteosynthesis types six weeks after surgery in their randomized prospective study (65). They observed inclination, tilt, and length in the individuals treated with external fixation, similar to the results observed in our trial.

Wright et al., in the prospective/retrospective cohort study on external fixation and palmar plate osteosynthesis, compared radiological outcomes at the 47-month follow-up and observed volar tilt and radial inclination outcomes comparable to our results (75).

Howard et al. used external fixator-type bridging (without additional K-wires) and found an approximate 1 mm radial shortening and a 1° volar tilt reduction on average in a population of 50 patients at three months (76). Jenkins and Jones used external fixator-type non-bridging for 58 patients and found the loss of volar tilt to be 0.1°, the inclination to be 0.7°, and the length to be 0.3 mm. The authors noted that this was below the measurement accuracy level (77).

Intra-observer variation in this study was expressed as the mean difference between the two measurements. The difference was smaller than 1° or 1 mm, which Watson et al. (66) considered as the limits of reliable measurements and was below the clinically-relevant margin described by Gartland et al. (54). The minor difference between the repeated measurements may be explained by having both positive and negative differences, which can neutralize each other. The intra-observer coefficient of variation may be used as an alternative estimate (78); however, such an assessment cannot demonstrate the systematic measurer’s error.

Our work demonstrated an identic trend of radiological migration in all intervention groups, and the grade of secondary dislocation was not significantly different. The differences in the groups' primary and secondary outcomes were smaller than the standard deviation inside the groups; therefore, the radiological outcomes are entirely comparable. Patients in the surgical division achieved sufficient distal radius inclination, tilt, and length, which, compared to the bone's normal anatomy, crucial for later wrist movement as depicted by Dario et al. (34). The intra-observer agreement needs to be considered when more significant differences between treatment groups are shown.

6.3. INTERPRETATION OF THE FUNCTIONAL OUTCOMES AND COMPARISON WITH THE LITERATURE

This study did not identify a significant effect of a brief ibuprofen therapy wrist movement after Colles' fracture. No differences within the DASH score between the intervention groups were revealed during the follow-up period in either the conservative or surgical divisions.

The search engines Embase and PubMed helped us identify two studies describing functional outcomes after Colles' fracture related to NSAID therapy (49,72).

Davis and Ackroyd (49) treated Colles' fracture patients conservatively using flurbiprofen for two weeks in a double-blind, prospective randomized research. According to the researchers, both intervention groups' participants regained 95 - 99% of normal wrist flexion after one year, which matched our study results. Different flurbiprofen dosing along the differing ages of 8.4 years on average in the treatment groups make direct comparability rather tricky.

An RCT conducted by Adolphson et al. (72) investigated two groups of 21 postmenopausal females, each with conservatively treated Colles' fractures. The researchers prescribed piroxicam to one group for eight weeks, while the other group received a placebo, and paracetamol was used as a rescue drug. They observed similar functional outcomes after three months of follow-up. Patients achieved 70% of normal wrist deviation, 76% of normal wrist flexion, and 95% of regular forearm rotation. A minor number of displaced multi-fragmented fractures were allocated to cast treatment, and 14% of the participants were later treated surgically, applying an external fixation. These factors may also be confounding this study's results.

In this study, ibuprofen was prescribed in the acute phase of pain after surgical treatment. Therefore, a further study with a prolonged NSAID treatment of several weeks to months might provide more persuasive arguments in revealing the actual influence on clinical outcomes and adverse events. Such prolonged therapy tends to increase the risk of renal, gastrointestinal, and cardiovascular disorders (79); in our opinion, the postoperative pain after osteosynthesis of Colles' fractures does not require extended treatment.

A search using Medline and Embase, performed with the keywords Colles' fracture AND ibuprofen AND DASH score, did not identify any studies that described ibuprofen's influence on the DASH score after Colles' fracture. A retrospective study (80), which investigated predicting factors to DASH score after Colles' fracture, reported a median DASH of 6 at six months for conservatively treated patients, a result

similar to our one-year outcome of 6.3. Grafstein et al., in their prospective study of conservatively treated Colles' fractures, reported a mean eight-week DASH equal to 34.6, and a six-month DASH equal to 20.3 (81). The two-year follow-up control of displaced Colles' fractures by Aktekin (82) found the same result. Enrolment of participants with unstable fractures can explain the higher score.

Wright et al. (75) performed a retrospective study to compare the functional outcomes following palmar plate osteosynthesis and external fixation of Colles' fractures, reporting a comparable DASH outcome in the external fixation group at the 47-month follow-up. In their cohort study of volar plated fractures, Kamath et al. (83) found mean DASH values and wrist motion results at the 18-month follow-up similar to the outcomes presented here. The patients in this study's surgical division also presented DASH scores similar to participants in the palmar plating group in a survey by Richard et al. (84).

Werber and al. (73) performed a five-pin external fixation, comparable to the osteosynthesis method in this study. They also compared the range of motion with the contralateral wrist and found that, at the six-month control, pronation/supination was 85% ± 12, flexion/extension was 78% ± 23, and radial/ulnar deviation was 62% ± 20. These results fill the gap between our three-month and one-year observations.

External fixation-type bridging with additional K-wires is an efficient operation (51), and our study supports this conclusion. Wrist mobility and function improved in all surgically treated patients during the first year after injury; they achieved 87% - 95% of normal wrist range of motion on average. All treatment groups demonstrated similar improving patterns without any statistically significant differences.

6.4. INTERPRETATION OF THE DENSITOMETRICAL OUTCOMES AND COMPARISON WITH THE LITERATURE

We did not observe any differences in BMD values in the distal radius between both divisions' treatment groups. The average BMD was 3 - 7 % higher in the ultra-distal region of the affected radius than in the healthy contra-lateral bone.

As far as we are aware, there is only one previous study investigating NSAID's influence on the mineral density of an injured and non-injured distal radius. The double-blinded RCT conducted by Adolphson et al. (72) revealed no difference in bone mineral content changes between groups on piroxicam and placebo treatments at the eight-week control. However, because the researchers examined the radius

proximal from the fracture, it is not easy to directly compare their outcomes with our results. This study's validity might also be affected by the minor sample size, enrollment of displaced, multi-fragmented distal radius fractures allocated to conservative therapy (which were then treated surgically and excluded from BMD evaluation).

An investigation of alendronate's influences on BMD in the distal radius was conducted by Van der Poest et al. (69). In the present study, baseline DXA scanning carried out three months after the injury found the total BMD of the distal radius equal to 0.40 g/cm^2 ± 0.05. As a majority of Colles' fractures appear at distal 38 mm of the radius (85), we believe assessing the ultra-distal region of interest to evaluate bone consolidation is more reasonable.

Eastell (86) measured the UD distal radius region in 40 females following Colles' fracture and reported a BMD similar to our findings. Moreover, researchers state that fracture risk increases significantly with a BMD below 0.4 cm^2 in the distal radius. Our densitometry demonstrated a total BMD in the healthy contra-lateral bone of 0.33 ± 0.06 g/cm^2, which confirms the authors' observation.

6.5. INTERPRETATION OF THE BIOCHEMICAL OUTCOMES AND COMPARISON WITH THE LITERATURE

All the treatment groups in our study demonstrated similar patterns of changes in serum CrossLaps and Osteocalcin concentration, irrespective of ibuprofen treatment.

Bone biomarkers are often used as an evaluation tool for the investigation of the treatment of osteoporosis. Nevertheless, because fracture recovery is related to increased bone turnover, some attempts have been made to observe fracture recovery using biochemical assays. Three studies describing changes of Osteocalcin and CrossLaps following Colles' fracture were identified in our review of the literature.

Ingle et al. recorded changes in bone resorption and remodeling markers (87); they observed a 15% increase of Osteocalcin. We observed an increase of 7% in the conservative division until the third month of control, and CrossLaps also increased during the first two weeks of follow-up, returning to original levels at one years' control in both divisions.

Mallmin et al. (88), in their study, recruited 16 participants suffering from a Colles' fracture and observed a small but continual Osteocalcin's rise of 1 ng/ml during their 16 weeks follow-up, similar to our 3-months findings in both divisions.

Wolfl et al. looked at 30 patients suffering from fractures in metaphyses, 14 of whom sustained a Colles' fracture (89), and found that CrossLaps continuously increased in the regular BMD-bone group, whereas, from the first week, these levels dropped significantly in the low BMD-bone group. Because enrolled patients received both surgery and conservative treatment, and the follow-up was brief, the results cannot match our outcomes closely.

The findings allow us to conclude that the explicit agreement regarding bone biomarkers' role in monitoring fracture recovery is still not validated (90,91). The notably variating biomarkers' concentrations between individuals imply the presence of numerous confounders such as sex (92), age (93), osteoporosis, and metabolic diseases (94). Therefore, further investigation is necessary to adequately describe the value of resorption and remodeling biomarkers in monitoring bone consolidation.

6.6. INTERPRETATION OF THE HISTOMORPHOMETRIC OUTCOMES AND COMPARISON WITH THE LITERATURE

The research of metabolic diseases and fracture healing makes wide use of animal models for histomorphometric bone analysis (29). However, there is little data that describes the human cancellous bones' fracture recovery in terms of histomorphometric estimations (46). Our study assumed that the fracture undergoes the process of endochondral ossification and the building of a new woven bone. We presumed that, by impaired fracture, fewer bone fractions and more fibrous tissue would be presented, and we hypothesized less bone formation and more resorption surfaces to be found. The importance of the histologic part of the study was amplified as no difference in volume and surface estimations was depicted despite carrying out eight statistical analyses between three intervention groups.

6.7. INTERPRETATION OF THE ANALGESIC OUTCOMES AND COMPARISON WITH THE LITERATURE

This study reveals significantly different analgesic symptoms in the conservatively treated ibuprofen and placebo groups. Patients treated with ibuprofen reported the first days' pain experience, which was lower by 1.3 VAS points on average, than in the placebo group. Ibuprofen groups also demonstrated a trend for better pain relief as long as they were treated with NSAID. This analgesic effect and pain reduction were delayed from day 4 in the 3-days ibuprofen group, related to ibuprofen-placebo

turnover. There was a tendency for higher tramadol consumption in the placebo group, but the difference was not significant in the conservative division.

In the surgical division, all patients using paracetamol as the primary medication and tramadol as a rescue pharmaceutical received sufficient analgesic treatment, regardless of ibuprofen therapy. The participants in the 3-days ibuprofen group also experienced more intense pain during the third and fourth day, which corresponds with the replacement of ibuprofen with the placebo. Furthermore, the pain continued to be more intense during the whole 14-day follow-up time in the 3-days ibuprofen group.

The placebo group showed significantly higher tramadol use over the first three days than the ibuprofen-treatment groups in the surgical division. This study also demonstrated a clinically relevant tramadol-sparing effect. Individuals allocated to three days' ibuprofen or placebo therapy experienced a higher demand for tramadol than participants allocated to the 7-days group. The explanation might be that they tended to use escape medication to suppress their pain to the level they were likely to accept.

Davis et al. (49) studied flurbiprofen's use for treating Colles' fracture in a 14-day long prospective study. The researchers observed a significant reduction in pain and paracetamol use during the first three days in the intervention group. The outcome was reported, however, in categorical units. The interpretation of these results is also difficult due to the significantly differing age (8.4 years on average) and different study medication doses.

Adolphson et al. (72) conducted a double-blind RCT allocating postmenopausal women suffering from Colles' fractures to two intervention groups, each with 21 participants. One group was prescribed piroxicam for eight weeks, with the other group receiving a placebo, and paracetamol was provided as an escape analgesic. Using a VAS scale, the pain was assessed as 3.1 in the placebo group and 2.1 in the piroxicam group on day ten. The demand for escape analgesics was significantly higher among placebo patients. The research was conducted with a small number of participants suffering from severe multi-fragmented fractures, allocated for plaster cast therapy, and subsequent operation with an external fixation on 14% of them. The pain experience and functional outcomes in this study may have been somewhat distorted by the severity of the injury and treatment method.

The influence of transcutaneous electric nerve stimulation (TENS) on analgesic symptoms after a Colles' fracture was assessed by Lee et al. (95). They reported that the TENS therapy diminished the mean pain score symptoms from the average of 5.5 VAS points on the first day to 3.5 VAS points on the fourth day. All patients were

treated surgically by using a palmar plate and received NSAIDs. The outcome is comparable with the results of our study. Participants in the surgical division reported minor pain experiences over the first few days, probably due to the minimally invasive surgery in our study.

The data presented in this work shows reduced tramadol consumption during and after short-term ibuprofen treatment (compared to placebo) in treating unstable Colles' fractures. The pain level was not significantly different between these groups in the surgical division.

These results suggest that ibuprofen treatment in the acute phase may be favorable as an analgesic, as Kyriacou reported (6). Furthermore, ibuprofen may have an opioid-sparing effect, as our study also indicates. The mean age of participants in this study was 62 - 65 years, and up to 18% of all fractures in the > 65s are distal radius fractures (85). Opioid-induced side effects and complications in the acute phase (i.e., urinary retention, constipation, delirium, and respiratory depression) increase with age (96); therefore, the opioid-sparing treatment with ibuprofen may be beneficial for older patients in orthopedics.

6.8. INTERPRETATION OF COMPLICATIONS AND ADVERSE EVENTS AND COMPARISON WITH THE LITERATURE

All treatment groups presented some degree of gastrointestinal disorders in both divisions, including those patients treated with a placebo only (13.3% incidence rate in the conservative division, 14.2% in the surgical division). It indicates that some patients may have experienced gastrointestinal disorders due to reasons other than ibuprofen during the first days after trauma and operation. This fact is worth considering when making decisions about the side-effects of ibuprofen.

The adverse event rate in the conservative division was 10% in the 3-days and 23.3% in the 7-days group. For surgically treated patients, the number was 23.3% and 27.6% in respective groups.

Our study's adverse event rates were more numerous than the 15% revealed in published works reporting oral NSAIDs therapy (97). The results become comparable if gastrointestinal disorders in the placebo group are considered. No prophylactic proton pump inhibitors were used (unnecessary for patients receiving placebo). On the other hand, acid-neutralizing medicine might have reduced the number of gastrointestinal symptoms in the study population.

The secondary fracture displacements in the conservative division we observed might advocate the dose-independent ibuprofen's affection of radiological migration, but we did not observe the pattern in surgically treated patients. The explanation might be that due to ibuprofen's oedema-reducing effect, the injured wrist regains the normal scope earlier, and thus the immobilizing cast becomes relatively too loose.

6.9. METHODOLOGICAL CONSIDERATIONS AND STUDY LIMITATIONS

The first limitation of this trial is the shortage of a pilot study. Such a pilot project would allow the precise and proper power calculation in all outcomes and define the subsequent study as definitive. Due to the shortage of time, specific local regulations, and pilot studies requirements, a literature-based power calculation was made. Therefore, it is reasonable to define this study as exploratory one.

A selection bias might also be considered as the enrolment rate was limited to 33.8%. This rate can likely be explained by the fact that thorough participants' information, signing the consent, assessing and recording the baseline values resulted in a significant logistical challenge. The personnel involved had insufficient time for the process. Furthermore, there were differences in age (non-included patients were 2,5 ± 0.99 years older) and sex (7% more males among included patients). These significant differences might be explained by the large sample sizes of 191 enrolled and 373 non-enrolled patients.

The difficulty of treatment standardization was a third potential limitation of this study; as patients did not sustain their fractures simultaneously, some received medication at the beginning of the first day while the remaining patients were injured (and suffered from pain) in the afternoon of day one. This injury-time variation may cause some inconsistency in the timing of their first and last medication intake after the injury. In turn, uncertainty about the first day's pain symptoms and diary records might appear. While efforts were made to enroll all participants during the first hospital visit, it was impossible to guarantee that all participants were taking analgesics simultaneously after the accident. Furthermore, some persons, believing that they only suffered from a sprain or contusion, waited one or more days, thus only presenting at the hospital after several days. Others were not invited to be part of the study because the personnel had no time to inform patients, and so the investigator was left to inform the patients 1 - 2 days later. As a result of these logistical difficulties, ensuring that ibuprofen was simultaneously administered during the inflammation phase of the fracture was unachievable.

To some extent, this variability is atoned by the randomization and sufficient size of the treatment groups.

Despite our instructions to the contrary, three participants suffering from Older type 3 - 4 fractures were admitted to the conservative division due to unexpected successful anatomic reduction. These patients were excluded from the study at the one-week control when secondary dislocation was detected (due to the high instability of the fracture).

The surgical treatment chosen in this study was external fixation. In the middle of our study's enrollment phase, a volar plating became the osteosynthesis method of choice, as depicted in the new Danish National Guidelines for treatment of distal radius fracture 2014 (98). Volar plating allows early mobilization (which could be better suited for early evaluation of ibuprofens' influence on functional outcomes) and minimizes the risk of secondary fragment dislocation (99). Nonetheless, this trend of using volar plating for unstable Colles' fracture is not always supported by evidence-based superiority (100) and still remains one among several methods of choice (52). External fixation offers bone healing research opportunities such as callus biopsy and DXA-scanning of both wrists, free from metal artifacts. For those reasons, we did not change the study protocol.

It was also not realistic to perform the surgery simultaneously after trauma due to a busy acute operations schedule and a lack of hospital capacity. This irregularity resulted in varying moments when the pain was reduced by peripheral nerve block over the first three days. It might also explain some inconsistencies in patients' pain-diary records.

The use of escape medication was self-reported in the patients' pain diary. To compensate for this limitation, occupational therapists assigned to this study counted pills at one-week and two-week controls. As most of the analgesic treatment took place in participants' homes, we had no opportunity to use automated dispensation recorders.

A lack of exact standardization in placing the injured arm in the X-ray beam at lateral projections provided another potential limitation. It is not unlikely that the arm's position may differ by a few grades of rotation, affecting the following tilt evaluation. The measuring of the radius length also provided some uncertainty. The operations were performed with an image intensifier as a quality control implement, and the radiographs were stored for documentation and assessment. The length was reported by the EazyViz software in pixels in those radiographs, while standard X-ray EazyViz software from the outpatient clinic reported in millimeters in its length evaluation. For

this reason, a 1.4 mm osteosynthesis K-wire was chosen as the calibration tool to assess the thickness of the wire in pixels and establish an individual pixel value. Thus, the perioperative length of the radius was determined. Despite this, the blurring of the lines of the K-wire on the digitally zoomed radiograph caused some uncertainty. These limitations and the intra-observer agreement need to be considered, mostly if any statistically significant differences are observed.

A current local standard regime for follow-up after Colles' fracture allowed radiological controls after one, two, and five/six weeks. The possibility of a late collapse of the fracture after removal of K-wires and external fixation persists, although this complication is unlikely (101). A further radiological evaluation would also mean higher patients' exposure to X-ray radiation. We decided, therefore, not to perform further radiological investigations.

We did not include finger movement and grip strength in the functional outcomes for specific reasons. Grip strength varies between individuals and, even in the same individual, may be influenced by the patient's handedness (102,103). Finger movement may be influenced by the positioning of fixator pins in the second metacarpal bone and was not selected as an outcome in this study's planning.

A small number of patients did not attend their final follow-up sessions to evaluate the wrist range of motion and DASH-score. Another limitation was the measurement of range of motion, which may be subject to inter and intra-observer variation. The DASH-score is a composite self-reported outcome with some information lost by calculating the score's final value (104). For these reasons, functional outcomes are classified only as exploratory in this study.

As the current state of the art does not recommend treatment with NSAIDs for fracture patients (12,13), a non-inferiority design for the majority of the outcomes was chosen. The main research question was whether ibuprofen is harmful to patients with Colles' fractures. Therefore, the study was designed as a non-inferiority trial with an appropriate one-sided significance test (68) of radiological, functional, biochemical, and histomorphometric outcomes. A superiority test can be added without losing the power and adjusting p-value for multiple comparison tests (68) if the results demonstrate a trend towards the unexpected (being better) effect. We did not observe such a trend.
A notable restriction of the non-inferiority trial is whether the sample size used included a sufficient number of participants. Nonetheless, in this study, the between-group differences were minor, less than 10% - 30% of the within-group standard deviations. Therefore, this study's sample size can be considered sufficient to ensure

sufficient power with a 0.05 level of significance as favored in non-inferiority studies (68).

There are further influencing factors such as sex, age, suffering from osteoporosis, alendronate therapy, body mass index (105), smoking, endocrine diseases, and even ethnicity (106,107) that may affect bone metabolism, response mechanisms to the injury, and recovery. Hence, ibuprofen can, in theory, affect bone consolidation to a different extent. However, the purpose of this study was not to stratify according to cofounders such as BMI, ethnicity, or sex. Colles' fracture incidence is highest in women aged over 50 and suffering from osteoporosis (108), and control of these cofounders is rather challenging.

The central limit theorem was a crucial issue we relied on while designing our research. Following the theorem, the body mass index along with other cofounders would be similarly distributed in study groups consisting of 30 or more participants (91,109). Participants in our study were all Caucasian individuals from the local Danish population. None of the patients enrolled suffered from severe obesity. Further attempts were made to enhance internal validity. The study was triple- blinded with a "blind" surgeon responsible for all interventions and assessing the outcomes. Only two occupational therapists measured the range of motion, and a blinded statistician worked with the data analysis (1,2,91).

In our research, we worked under the usual conditions, experienced everyday clinical situations (91), targeted at the wide population of Colles' fracture patients. The external validity is hereby ensured (110), making us, to some degree, confident in generalizing (111). It allows us to declare that ibuprofen therapy of one week's duration is unlikely to hamper the fracture consolidation in the distal radius. Still, there are some reservations, and this generalization cannot be automatically adapted in other orthopedic issues as treatment of shaft fractures or non-unions.

CHAPTER 7. CONCLUSIONS

This study demonstrated that ibuprofen does not hamper fracture healing in the distal radius.

Participants in all study groups presented the same trend of fragment migration during the first 5 - 6 weeks as well as bone biomarkers change during one year.

All patients, regardless of the ibuprofen treatment strategy, regained a similar wrist function level by their 1-year follow-up, which was close to 87 - 95% of the uninjured contralateral wrist's range of motion.

All patients experienced the same pattern of reduction in DASH score points.

Regardless of ibuprofen treatment and dose, bone mineral density was, on average, 7% higher in the injured distal radius three months after injury.

There were no differences between study groups in histomorphometric volume and surface outcomes of the newly formed bone.

Between-groups variation of all these outcomes, as mentioned above, was as high as 10-30% of the variation within groups.

This study showed the significant analgesic effect of ibuprofen during the fracture's acute phase for patients treated conservatively. Ibuprofen influenced a reduced tramadol consumption during the perioperative period of the Colles' fracture.

The complication rate in the intervention groups was above the rate observed in the placebo groups.

In conclusion, ibuprofen therapy in the acute phase, compared to placebo, was not inferior regarding the radiological, functional, densitometrical, biochemical, and histomorphometric outcomes in both divisions and all treatment groups. Ibuprofen treatment demonstrated better pain relief for conservatively treated patients and a tramadol-sparing effect for surgically treated patients.

Our study's findings support the use of ibuprofen as a bone-neutral analgesic. These results may have relevance for other fields of orthopedics and traumatology treating primary cancellous bone fractures. The risks of side-effects from ibuprofen do, however, need to be considered.

CHAPTER 8. FUTURE RESEARCH

This study's primary purpose, which aimed to investigate whether ibuprofen slows healing of Colles' fracture, is hereby achieved. The results advocate the prescription of NSAID as a potentially harmless pharmaceutical in the acute bone healing phase.

The outcomes variation between individuals is high, with some participants presenting perfect results and some poor.

There are other data recorded in our study database: smoking habits, alcohol consumption, handedness, osteoporosis treatment, occupation, and pain threshold, which might be considered confounding factors, and the database, therefore, offers the opportunity to perform a multiple regression analysis.

The expectation is that this analysis will contribute to increased knowledge of the effects of ibuprofen, making pain management, rehabilitation, and the entire course of treatment more comfortable and safer. Hence, patients recover faster and can return to their usual activities more quickly. The multiple regression model has the potential to predict poorer outcomes allowing patients to receive the optimal treatment and plan a follow-up regime to avoid the risk of further wrist malfunction.

This analysis is expected to be performed within the next two years.

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