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Maastricht University

Faculty of Medicine and Life Sciences
School for Life Sciences
Master of Biomedical Sciences

Masterthesis

Metamizole versus ibuprofen to treat postoperative pain at home after ambulatory surgery: a randomised controlled non-inferiority trial

Caroline Pelckmans

Thesis presented in fulfillment of the requirements for the degree of Master of Biomedical Sciences, specialization Clinical Molecular Sciences

SUPERVISOR :
dr. Ingrid ARIJS

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2016
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Hasselt University and the Jessa hospital made it possible to perform my senior practical internship at the department of anaesthesiology and are gratefully acknowledged. This internship gave me the opportunity to work with several interesting people that supported and guided me throughout this project.

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List of abbreviations

ASA	American Society of Anaesthesiologists
BMI	Body mass index
CI	Confidence interval
COX	Cyclooxygenase
GI	Gastrointestinal
GSR	Global Surgical Recovery
ITT	Intention-To-Treat
IV	Intravenous
IQR	Interquartile Range
MIA	Metamizole-Induced Agranulocytosis
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
PACU	Post-Anaesthesia Care Unit
POD	Postoperative Day
PP	Per Protocol
QOR	Quality Of Recovery
SD	Standard Deviation
SFQ	Surgical Fear Questionnaire
SPSS	Statistical Package for Social Sciences
VAS	Visual Analogue Scale
VRS	Verbal categorical Rating Scale

Samenvatting

Inleiding: De gouden standaard voor de behandeling van postoperatieve pijn na dagchirurgie bestaat uit een combinatie van paracetamol en niet-steroïde ontstekingsremmers (NSAIDs), zoals ibuprofen. Desondanks, kunnen NSAIDs door de aanwezigheid van contra-indicaties niet worden voorgeschreven bij 25% van de patiënten. Het analgeticum metamizol heeft minder contra-indicaties en een gunstig gastro-intestinaal en cardiovasculair profiel in vergelijking met NSAIDs. Daarom was het hoofddoel van deze studie om te onderzoeken of een combinatie van metamizol en paracetamol niet-inferieur is ten opzichte van de gouden standaard bij de behandeling van postoperatieve pijn thuis na pijnlijke dagchirurgie.

Methoden: Volwassenen (18-70 jaar) die pijnlijke dagchirurgie ondergingen, werden geïncludeerd in een gerandomiseerde, dubbelblinde, non-inferioriteit trial met als doel een 4-daagse postoperatieve pijnbehandeling bestaande uit een combinatie van metamizol (4 g/dag) en paracetamol (4 g/dag) (n= 98) te vergelijken met de gouden standaard [ibuprofen (2.4 g/dag) en paracetamol (4 g/dag)] (n= 98). Data werd verzameld bij baseline en op postoperatieve dagen (POD) 1 tot 4, 7, 14 en 28. Om non-inferioriteit na te gaan, werden 95% betrouwbaarheidsintervallen (BI) berekend voor het verschil van de primaire uitkomstmaat (gemiddelde pijn gemeten door een numerieke pijnschaal van 0 tot 10) voor POD 1. Bijkomend werd er ook getest voor verschillen tussen de behandelingsgroepen op valk van kwaliteit van herstel (QOR) en secundaire uitkomstmaten (gebruik van rescue medicatie, compliantie, patiënt-gerapporteerde neveneffecten en patiënten tevredenheid). Een P-waarde ≤ 0.05 werd beschouwd als een statistisch significant verschil.

Resultaten: Het 95% BI van de per protocol [-0.913; 0.596] en intention-to-treat [-0.647; 0.710] populatie van het verschil in de primaire uitkomstmaat van de gemiddelde pijn scores (respectievelijk -0.158 en 0.032) lagen volledig onder de non-inferioriteitsmarge 1 en bevestigde een niet-inferieur resultaat. Resultaten van de follow-up vertoonde geen significante verschillen tussen de behandelingsgroepen op vlak van QOR, compliantie en patiënten tevredenheid en het gebruik van rescue medicatie was enkel significant hoger in de controlegroep op POD 2 ($p = 0.024$).

Conclusie: Op basis van deze resultaten kan er worden geconcludeerd dat de postoperatieve pijnbehandeling van paracetamol en metamizol niet-inferieur is ten opzichte van de gouden standaard en als mogelijk alternatief kan gebruikt worden voor de postoperatieve pijnbehandeling na dagchirurgie.

Abstract

Background: The gold standard to treat postoperative pain after day surgery is a combination of paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen. Nevertheless, NSAIDs are not suitable in up to 25% of patients due to contraindications. The analgesic metamizole has fewer contraindications and a favourable gastrointestinal and cardiovascular profile in comparison to NSAIDs. Therefore, the primary objective of this study was to investigate whether a combination of metamizole and paracetamol is non-inferior to the gold standard in the treatment of postoperative pain at home after painful day surgery.

Methods: Adults (18-70 years) undergoing painful day surgery were included in a randomised, double blind, non-inferiority trial to compare a 4-day postoperative pain treatment of the combination of metamizole (4 g/day) and paracetamol (4 g/day) (n= 98) to the gold standard [ibuprofen (2.4 g/day) and paracetamol (4 g/day)] (n= 98). Data was collected at baseline and on postoperative days (POD) 1 to 4, 7, 14 and 28. To test for non-inferiority, the primary outcome measure mean average pain measured by an 11-point numerical rating scale (NRS) on POD 1 was analysed by computing 95% confidence intervals (CI) of the difference of the mean NRS scores. In addition, between-treatment differences for quality of recovery (QOR) and secondary outcome measures (compliance, side effects, use of rescue medication and patient satisfaction) were analysed. A P-value ≤ 0.05 was considered a statistically significant difference.

Results: Both 95% CI of the per protocol [-0.913; 0.596] and intention-to-treat [-0.647; 0.710] population of the primary outcome measure of the difference in mean NRS scores (respectively -0.158 and 0.032) were lower than the predefined non-inferiority margin 1, confirming a non-inferior result. Results of the follow-up showed no significant between-treatment differences for QOR, compliance and patient satisfaction and use of rescue medication was only significantly higher in the control group on POD 2 ($p = 0.024$).

Conclusion: Based on these findings, there can be concluded that the postoperative pain treatment of metamizole and paracetamol is non-inferior to the gold standard, suggesting the combination of metamizole and paracetamol is a potential alternative to treat postoperative pain after ambulatory surgery.

1 Introduction

Over the last decade day surgery, also known as ambulatory surgery, has expanded rapidly and has become a common place for almost all elective surgical procedures. This increasing trend of day surgery can be attributed to the improvements in anaesthetic and minimally invasive surgical techniques, as it allowed to perform more complex and painful surgical procedures in an ambulatory setting. Moreover, this cost-effective approach contributes to a more effective use of hospital beds and a decreased incidence of hospital associated complications (1). Despite the increased awareness of postsurgical pain management, 9 to 40% of all patients still experience moderate to severe postoperative pain at home after ambulatory surgery (2, 3). This can prolong recovery and reduce patient satisfaction. Given this, it is important to further improve the postoperative pain protocol to enhance postoperative pain relief and quality of recovery (QOR).

1.1 Postoperative pain management after day surgery

Acute postsurgical pain is a known risk factor for the development of chronic pain and can cause several psychological and pathophysiological changes (e.g. immobility, deep vein thrombosis, ischemic cardiac events, depression and insomnia), which can lead to unanticipated hospital admissions and increased medical costs (3, 4). Consequently, adequate postoperative pain management is found essential and has been recognized to be one of the primary endpoints after ambulatory surgery. However, postoperative pain management after day surgery remains very challenging in contrast to the inpatient setting, since patients are already discharged a few hours after surgery. This gives patients the responsibility to control their postoperative pain at home by themselves and limits the type of analgesics (i.e. no use of strong opioids) as well as the route of analgesic administration (i.e. no epidural, intravenous (IV), subcutaneous or intramuscular route) (5). Therefore, pain therapy after ambulatory surgery requires effective oral analgesics with minimal side effects that can be easily administered at home.

Nowadays, the method of choice to treat postoperative pain after ambulatory surgery is a multimodal analgesic approach combining paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and weak opioids. Furthermore, the surgeon is advised to infiltrate the wound with local anaesthesia or to use peripheral nerve blocks to prevent as much pain as possible during the first 8 to 24 hours after surgery (3).

Published studies state that a combination of paracetamol and an NSAID, such as ibuprofen, can provide better analgesic efficacy in comparison with either drug alone (6). This is the reason why patients are specifically recommended to use this combination as a gold standard to treat postoperative pain at home after ambulatory surgery. Nevertheless, it is important to point out that NSAIDs have numerous contraindications and therefore cannot be prescribed in up to 25% of all patients (7). Because of this, the following important question immediately arises: 'Is there a potential substitute for NSAIDs to treat postoperative pain at home after ambulatory surgery?'. To answer this question, it is important to understand the limitations of the current gold standard.

1.2 The gold standard: paracetamol and NSAIDs

Paracetamol is one of the most commonly used drugs around the world with an analgesic and antipyretic action (8). It is cheap, well tolerated and has nearly no contraindications (9). Besides possible allergic skin reactions, no serious side effects have been observed when the drug is administered in therapeutic doses (<4 g/day) (8). Therefore, it is the most frequently used background analgesic in multimodal approaches.

NSAIDs are more effective than paracetamol and have analgesic, antipyretic and anti-inflammatory properties. This type of analgesic reduces prostaglandin synthesis by inhibiting COX-1 and COX-2 cyclooxygenase (COX) isoenzymes (8). COX-2 plays an important role in the formation of the prostaglandins involved in the promotion of pain, fever and inflammation, while COX-1 is primarily involved in the synthesis of prostaglandins that play a role in platelet aggregation, maintaining the renal blood flow and the protection of the stomach lining (figure 1). Thus, besides the favourable (analgesic, antipyretic and anti-inflammatory) effects, several adverse events can occur by blocking these COX enzymes (8, 10). For example, blockage of the gastro-protective prostaglandin synthesis can lead to the development of ulcers or haemorrhage in the gastrointestinal tract. Therefore, patients with current symptoms or a history of gastrointestinal bleeding or ulcers are contraindicated for NSAIDs. Furthermore, NSAIDs can lead to hypertension, oedema and adverse cardiovascular events and should be avoided in patients with pre-existing renal disease, congestive heart failure or cirrhosis to prevent acute renal failure. Moreover, patients with asthma, nasal polyposis or recurrent sinusitis are at higher risk to develop bronchoconstriction and rhinitis symptoms in presence of an NSAID (10). Taken all this into account, NSAIDs cannot be

prescribed in all patients, limiting the overall use of the gold standard to treat postoperative pain at home after ambulatory surgery.

In case pain relief is not sufficient after the administration of a combination of paracetamol and an NSAID, the use of a rescue medication is recommended. Codeine and tramadol are weak opioids and well-known examples of rescue medication that can provide additional pain relief. Nevertheless, opioids are associated with a high incidence of several side effects (e.g. dizziness, nausea and constipation) (11). Therefore, the use of opioids is not recommended as a substitute for NSAIDs. Moreover, the multimodal approach is an opioid sparing method to minimise adverse effects and the occurrence of opioid addiction (12).

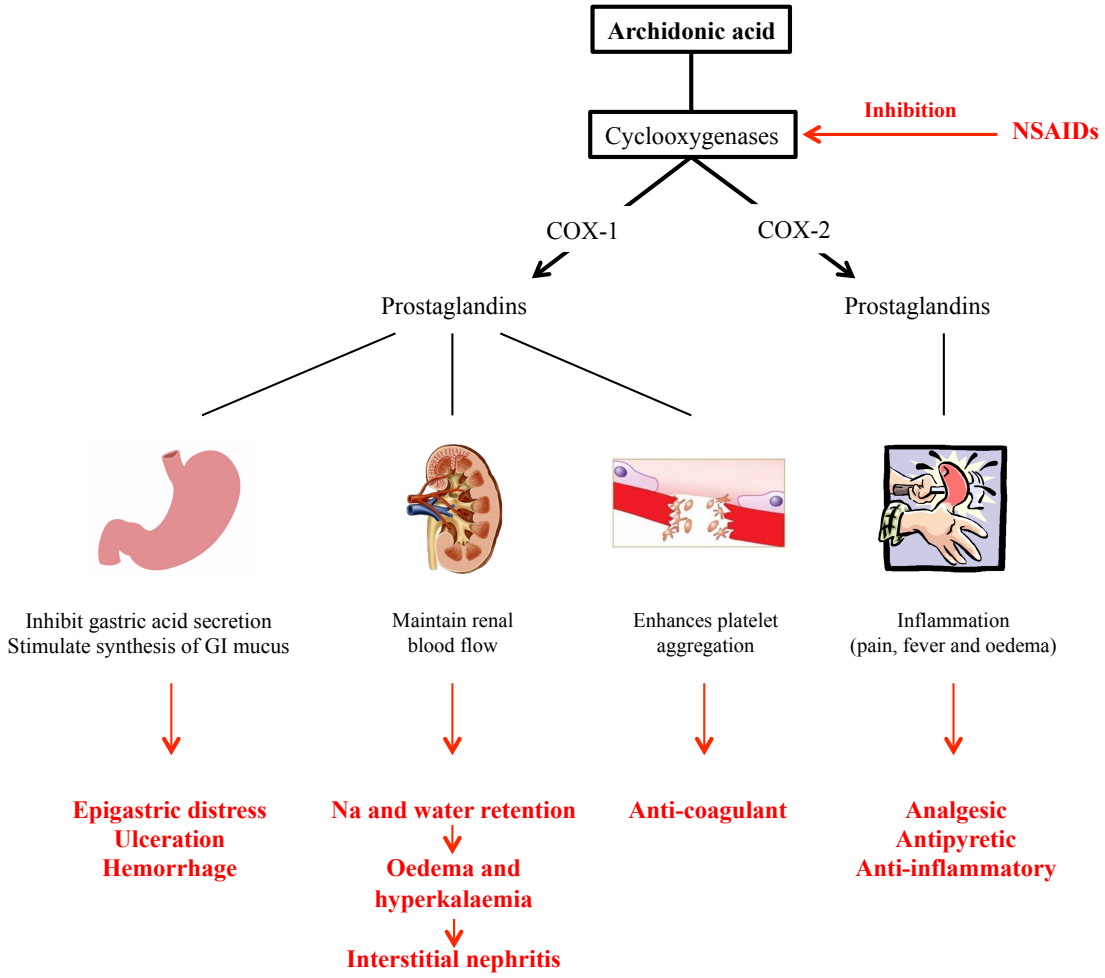


Figure 1: The mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs). *NSAIDs inhibit cyclooxygenases leading to several actions that are presented in red. GI: gastrointestinal, COX: cyclooxygenase.*

1.3 Metamizole: a potential substitute for NSAIDs

Since opioids are not recommended due to the association with several side effects, the analgesic options to treat postoperative pain at home for patients with contraindications for NSAIDs are rather limited. This leads to the challenge of finding an alternative non-opioid analgesic to add to the gold standard.

In the continuous search for an alternative to treat postoperative pain at home after ambulatory surgery, the forgotten drug metamizole has regained interest. Metamizole, also known as dipyrone, is a non-opioid drug with analgesic, antipyretic and spasmolytic actions (13, 14). It was first marketed in Germany in 1922 and became a popular analgesic that was commonly used in human and veterinary medicine (13). In the seventies, metamizole was prohibited from several countries based on two studies that indicated a high incidence of metamizole-induced agranulocytosis (MIA: a neutrophil count $< 0.5 \times 10^9$ cells/l that can be accompanied by severe infections (15)) in the range of 0.79-0.86% (16, 17). However, more recent studies reported very low incidences of agranulocytosis of approximately 0.5 to 1 MIA case per million per year (13, 18, 19). Due to the favourable gastrointestinal and cardiovascular profile compared to NSAIDs, the excess risk of MIA is also negligible compared to the risk of cardiovascular and gastrointestinal events induced by NSAIDs (12-14). Moreover, according to Andrade et al. the absolute risk of mortality associated with metamizole is comparable to paracetamol (acetaminophen) and substantially lower than the absolute risk of mortality for the NSAID diclophenac (figure 2) (20).

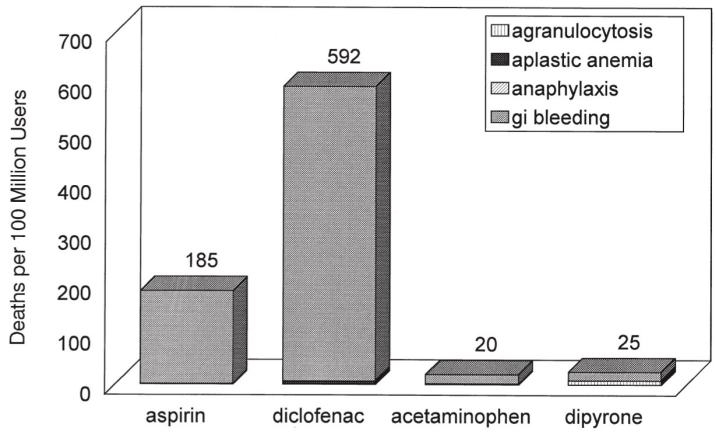


Figure 2: Excess mortality associated with short-term use of non-opioid analgesics.

GI: gastrointestinal (20).

Metamizole is administered as a prodrug that is immediately hydrolysed to its active metabolites in the body (13). The exact molecular mechanism of metamizole's analgesic action is still not fully understood. However, several mechanisms are proposed, including COX-3 (splice variant of COX-1) inhibition (21), activation of the endocannabinoid/ endovanilloid system (22, 23) and activation of the opioidergic system (13, 24). Despite the lack of knowledge about the working mechanism, the analgesic efficacy of metamizole has been reported in several human studies (14). For example, Rawal et al. investigated the analgesic efficacy of individual tramadol, metamizole and paracetamol in patients undergoing ambulatory hand surgery. The results showed that metamizole gave effective analgesia in 69% of patients on day 1 and in 85% of patients on day 2. The group of patients that administered metamizole had a significantly lower incidence of nausea in comparison with the group that administered tramadol and had the highest scores on satisfaction with study medication and postoperative pain management (25). Furthermore, literature indicates that metamizole 1 g is as effective as ibuprofen 600 mg in treating pain after lower third molar surgery (figure 3) (26).

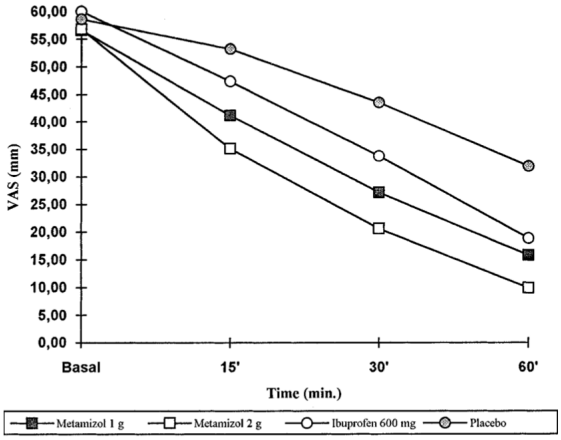


Figure 3: The analgesic efficacy of four types of treatment after lower third molar surgery.

Pain scores were measured with the visual analogue scale (VAS): 0 means no pain, 100 means worst imaginable pain (26).

Thus, metamizole is an effective and relatively safe drug with few contraindications in comparison to NSAIDs. In contrast to tramadol, it has also fewer side effects. Therefore, it is a potential substitute for NSAIDs to treat postoperative pain at home after ambulatory surgery. However, further research is needed because to our knowledge, the combination of metamizole and paracetamol has never been compared to the gold standard.

1.4 Measuring postoperative pain

Nowadays, the visual analogue scale (VAS) and the 11-point numerical rating scale (NRS) are often used to measure acute postoperative pain in adults and are more powerful to detect differences in pain intensity than the four-point verbal categorical rating scale (VRS) (figure 4) (27). Pain intensity scores can be measured in millimetres by a VAS after the patient placed a mark on a 10-cm line or can be verbally assessed by an NRS (28). The latter option is more practical because this allows us to measure the intensity of pain during telephone follow-up, making it possible to also reliably assess pain after day surgery over the last 24 hours, at rest (important for comfort) and at movement (important for function and risk of postoperative complications) (27). Postoperative pain scores lower or equal to three on an NRS are generally defined as mild pain (29).

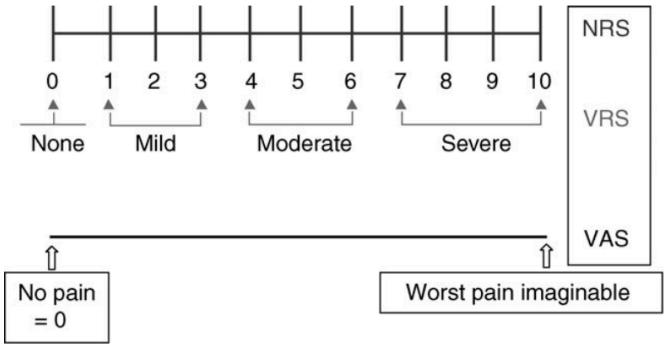


Figure 4: Pain intensity scales that can be used to measure postoperative pain in adults.

NRS: Numerical rating scale, VRS: verbal rating scale, VAS: visual analogue scale (27).

1.5 Quality of recovery

Besides postoperative pain management, QOR is also defined as a primary endpoint of ambulatory surgery. Since mortality and major morbidity are rare events and unanticipated admission/readmission rates are rather low in an ambulatory setting, QOR became more important to evaluate recovery and patient satisfaction (30-32). QOR is related to the patient's ability to resume normal activities and therefore encompasses several dimensions (32, 33). More specific, psychological, functional, socio-cultural, cognitive and physical dimensions are part of QOR. Moreover, postoperative pain plays an important role, because it can influence all these dimensions, for example it may lead to anxiety, interference of mobility and a decrease in socio-cultural activities (34, 35). Therefore, the optimisation of the pain

protocol is also an asset for a good QOR and essential to meet the expectations of the patients (rapid improvement, fast recovery and low or moderate pain).

1.6 Aims of the study

Thus, postoperative pain management and QOR are two primary endpoints after ambulatory surgery. As postoperative pain influences QOR, it is important to provide all patients with an adequate postoperative pain treatment. However, due to contraindications for NSAIDs, the current gold standard is not applicable in all patients. Therefore, we would like to answer the previous stated question: 'Is there a potential substitute for NSAIDs to treat postoperative pain at home after ambulatory surgery?'.

Metamizole could be this potential substitute. Nevertheless, to our knowledge no information is available about the use of a combination of metamizole and paracetamol. Therefore, the general aim of this study is to investigate whether a combination of metamizole and paracetamol is non-inferior to a combination of an NSAID (ibuprofen) and paracetamol to treat postoperative pain at home after painful ambulatory surgery. The primary endpoints average postoperative pain intensity and QOR and the secondary endpoints compliance, use of rescue medication, side effects and patient satisfaction will be assessed to determine whether the combination of metamizole and paracetamol is a good alternative for the gold standard in patients with contraindications for NSAIDs.

2 Material and methods

The trial was conducted at the JESSA hospital (Hasselt, Belgium) between February 2016 and June 2017 in accordance with the declaration of Helsinki. Approval was granted by the medical ethical committee of the JESSA Hospital (Hasselt, Belgium, registration number: 15.105/pijn15.02) and the trial was registered with the European Union Drug Regulating Authorities Clinical Trials (EudraCT registration number: 2015-003987-35) before start.

2.1 Study design

The study was designed as a double blind, randomised controlled, non-inferiority trial to compare the analgesic efficacy and QOR between two treatment groups. The experimental group received paracetamol 1000 mg and metamizole 1000 mg, while the control group received paracetamol 1000 mg and ibuprofen 600 mg. Both groups were instructed to orally administer the medication for four days according to a fixed dose schedule, in which paracetamol was taken four times a day and metamizole or ibuprofen three times a day. Additionally, all patients received tramadol 50 mg, a rescue medication that could be used if there was no satisfactory pain relief after the administration of the study medication. Patient allocation to the treatment groups was based on a computer-generated randomisation list, created by the study statistician.

2.2 Participants

American Society of Anaesthesiologists (ASA) physical status I to III patients, aged 18 to 70, scheduled for elective unilateral hernia repair, arthroscopic shoulder or knee surgery or haemorrhoid surgery in an ambulatory setting were eligible to participate. Exclusion criteria included a weight of less than 50 kilograms, cognitive impairment, insufficient understanding of the Dutch language, preoperative pharmacologic pain treatment, a history of chronic pain, allergy to or a contraindication for taking the study medication (paracetamol, metamizole, ibuprofen, tramadol or another NSAID), porphyria, a history of severe renal, hepatic, pulmonary or cardiac failure, current symptoms or a history of gastrointestinal bleeding, ileus or chronic obstipation, a history of substance abuse or use of medication with a suppressive effect on the central nervous system, hypotension, haematological disease, use of antirheumatic drugs, rhinosinusitis or nasal polyposis, glucose-6-phosphate dehydrogenase deficiency, fever or other signs of infection, pregnancy or lactation and patients undergoing arthroscopy shoulder who refused an interscalene block.

2.3 Procedure

Eligible patients were asked to participate in the study when they arrived at the outpatient clinic. After obtaining written informed consent, participants were randomised to one of the treatment groups based on a 1:1 ratio stratified for type of surgery and were given written and verbal instructions about the medication schedule. Afterwards, the participants were instructed to fill in a baseline questionnaire and to administer the first dose of study medication 30 minutes before the surgery. Furthermore, the attending surgeon and anaesthesiologist were informed and instructed to follow a similar perioperative analgesic procedure for any included patient. After discharge, patients were followed-up by telephone on postoperative days (POD) 1 to 4, 7, 14 and 28 to evaluate the outcome measures (figure 5).

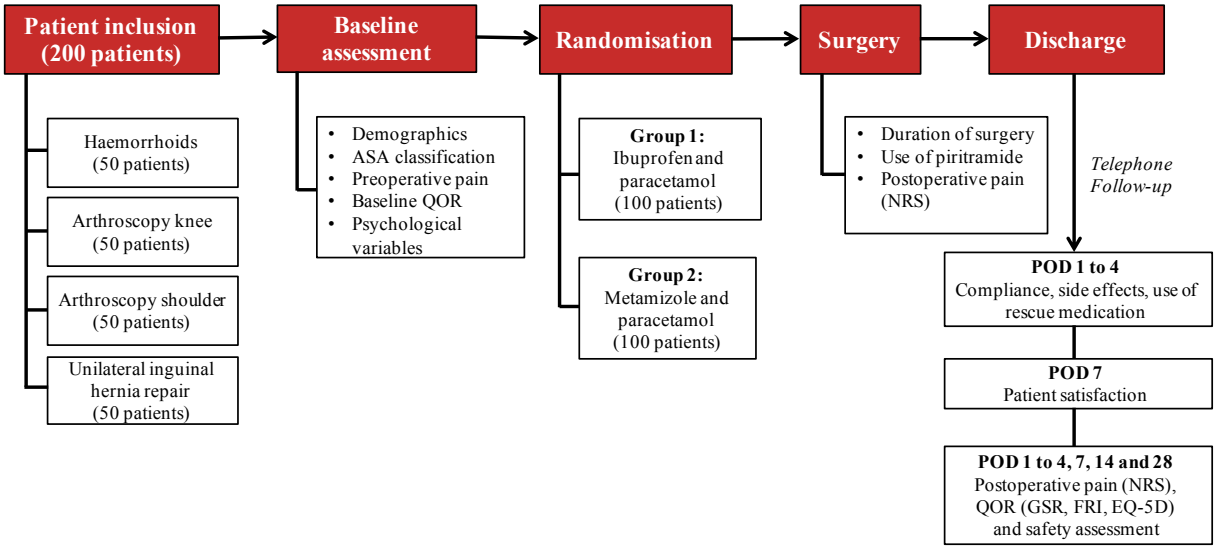


Figure 5: Study procedure. *QOR: quality of recovery, POD: postoperative day; NRS: Numerical rating scale, GSR: global surgical recovery, FRI: functional recovery index, EQ-5D: 5-dimensional European Quality of Life questionnaire.*

2.4 Baseline questionnaire

The baseline questionnaire included questions about demographics (age, gender, body mass index (BMI), work status, highest level of education), ASA physical status and the history of (related) surgery. Furthermore, it assessed fear of the surgical procedure measured by a validated 8-item surgical fear questionnaire (36), preoperative and expected pain measured by an 11-point NRS (0 means no pain and 10 means worst pain imaginable) and baseline QOR measured by the global surgical recovery index (GSR) (37), the functional recovery index (32) and the 5-dimensional European Quality of Life (EQ-5D) questionnaire (38).

2.5 Perioperative procedure

During the perioperative procedure, all patients scheduled for an arthroscopic shoulder procedure received an interscalene block preoperatively. General anaesthesia was induced with IV alfentanil (10 mcg/kg), IV propofol (2 mg/kg) and IV sufentanil (0.15 mcg/kg). After inserting a laryngeal mask airway (or a tracheal intubation facilitated by rocuronium (0.5 mg/kg) in case of an arthroscopic shoulder surgery or laparoscopic inguinal hernia repair) anaesthesia was maintained with sevoflurane and a mixture 50:50 air/oxygen. Furthermore, wound infiltration with local anaesthesia (bupivacaine 0.5 %) was performed in all patients except those receiving an interscalene block. In case of acute postoperative pain in the Post-Anaesthesia Care Unit (PACU), patients were additionally treated with IV piritramide until a NRS score equal or less than three was reached. The duration of the surgery and the total IV piritramide consumption at the PACU were written down.

2.6 Follow-up

A follow-up questionnaire package was used to evaluate the primary and secondary outcome measures. The primary outcome measures of this trial were the average postoperative pain intensity measured by an NRS score and QOR measured by three different questionnaires: GSR index, FRI and EQ-5D questionnaire. The validated 1-item GSR index scored the degree to which patients considered themselves to be recovered from the medical procedure (0-100%) (37). The FRI evaluated the functional QOR of 14-items, grouped under 3 categories (pain and social activity, lower limb activity and general physical activity) (32) and the EQ-5D measured the health outcome on 5 different dimensions (mobility, self-care, usual activity, pain/discomfort and anxiety/depression) (38). POD 1 was chosen as primary day to analyse the primary outcome measures, notwithstanding they were measured during all follow-up days to gather additional information. The secondary outcome measures evaluated on days 1 to 4 were pain relief received by the pain treatment (0-100%), adherence to the study medication, self-reported side effects (e.g. nausea, pyrosis and constipation) and the use of rescue medication. Furthermore, on day 7 patient satisfaction with surgery and hospital care, pain treatment and telephone follow-up were evaluated with an NRS and before discharge and on every follow-up day the pain intensity scores at movement and at rest were measured by an NRS in addition to the average pain intensity scores (figure 5).

2.7 Safety assessment

During the follow-up, patients were also specifically questioned about anaphylaxis, fever or chills, mouth ulcers, sore throat or signs of infection, petechiae, bleeding diathesis and complications related to the surgery. Patients with moderate to severe signs of infection or bleeding diathesis were asked to contact their general practitioner and advised to do a complete blood count to exclude serious adverse events (agranulocytosis, anaemia and thrombocytopenia).

2.8 Statistical analysis

All collected data was depersonalized and entered in a web-based questionnaire (Questback) and exported to the SPSS 24.0 (IBM® SPSS® Inc, Chicago, Illinois, USA) to analyse the primary and secondary outcome measures.

2.8.1 Sample size

The calculations of the sample size were only based on the predicted postoperative pain intensity, because the primary outcome measure average postoperative pain intensity also influences the second primary outcome measure QOR. To conclude non-inferiority of paracetamol and metamizole versus paracetamol and ibuprofen with a power of at least 80% at a non-inferiority margin of 1, 78 patients needed to be included in each treatment group. To bear in mind the eventuality of drop-outs and loss to follow-up due to voicemails, the sample size was inflated to 100 patients per treatment group.

2.8.2 Primary and secondary outcome measures

The primary outcome measures are analysed on a per protocol (PP) basis. Furthermore, these results are compared to the results analysed on an intention-to-treat (ITT) basis to test for sensitivity. Secondary outcome measures are only assessed on an ITT basis. Continuous data is shown as mean (standard deviation) (SD) or median (25^{th} - 75^{th} percentile) and categorical data as numbers (%). Missing values of primary outcome measures and baseline values were imputed using the predictive mean model with multiple imputations. The number of imputations was set to 10, to obtain 10 complete datasets.

The main objective of this trial was to investigate whether a combination of metamizole and paracetamol is non-inferior to the combination of ibuprofen and paracetamol in the treatment of postoperative pain at home after day surgery. To test this objective, 95% confidence

intervals (CI) were computed for the difference in mean average pain intensity scores. The analgesic efficacy of metamizole and paracetamol was considered non-inferior to the gold standard as a difference in mean average pain intensity scores was less than the predefined non-inferiority margin that was set to one and the 95% CI did not include this non-inferiority margin. Between-treatment differences for QOR and secondary outcome measures were analysed using the Student's t test for parametric data, the Mann-Whitney U test for nonparametric data and the Pearson's $\chi 2$ test or the Fisher's exact test (in case of an observed count < 10) for categorical data. Furthermore, the Wilcoxon signed-rank test and a Bonferroni adjustment were used to compare postoperative QOR scores with baseline. Values of $p \leq 0.05$ were considered statistically significant. Graphs were made using Prism 7.0 (Prism®, GraphPad Software, Inc, La Jolla, California, USA).

3 Results

3.1 Participants

During the study period, between 28 January 2016 and 31 March 2017, 200 patients were enrolled in this trial. The flow of participants is presented in a flow diagram constructed following the Consolidated Standards of Reporting Trials (CONSORT) statement (figure 6). Four hundred and two patients were screened for eligibility, of which 202 patients were excluded due to refusal to participate (n= 57), not meeting the inclusion criteria (n= 137) or undergoing spinal anaesthesia (n= 8). Enrolled patients were randomly allocated to the experimental group (metamizole + paracetamol, n= 100) or the control group (ibuprofen + paracetamol, n= 100) and administered at least one dose of the study medication. Two patients of the experimental group and 5 patients of the control group were hospitalized the day of surgery, respectively due to pain (n= 2) and nausea (n= 3), a request to stay one night (n= 1) or a recommended stay to control possible bleeding (n= 1).

Despite the enrolment of 200 patients, only 196 patients were included in the ITT analysis due to logistic errors. More specific, three patients underwent a bilateral inguinal hernia repair instead of the scheduled unilateral procedure and one patient was immediately excluded by the surgeon due to excessive preoperative opioid use. Therefore, the latter patients did not belong in the ITT population and were excluded from all analyses. Hundred sixty-five patients completed all follow-up questionnaires and 149 participants followed the treatment schedule for three days postoperatively. The PP population consisted of 142 patients (n= 65 for the experimental group; n= 77 for the control group) that confirmed to follow the complete treatment schedule as prescribed for three days postoperatively and were not readmitted to the hospital during the first four postoperative days.

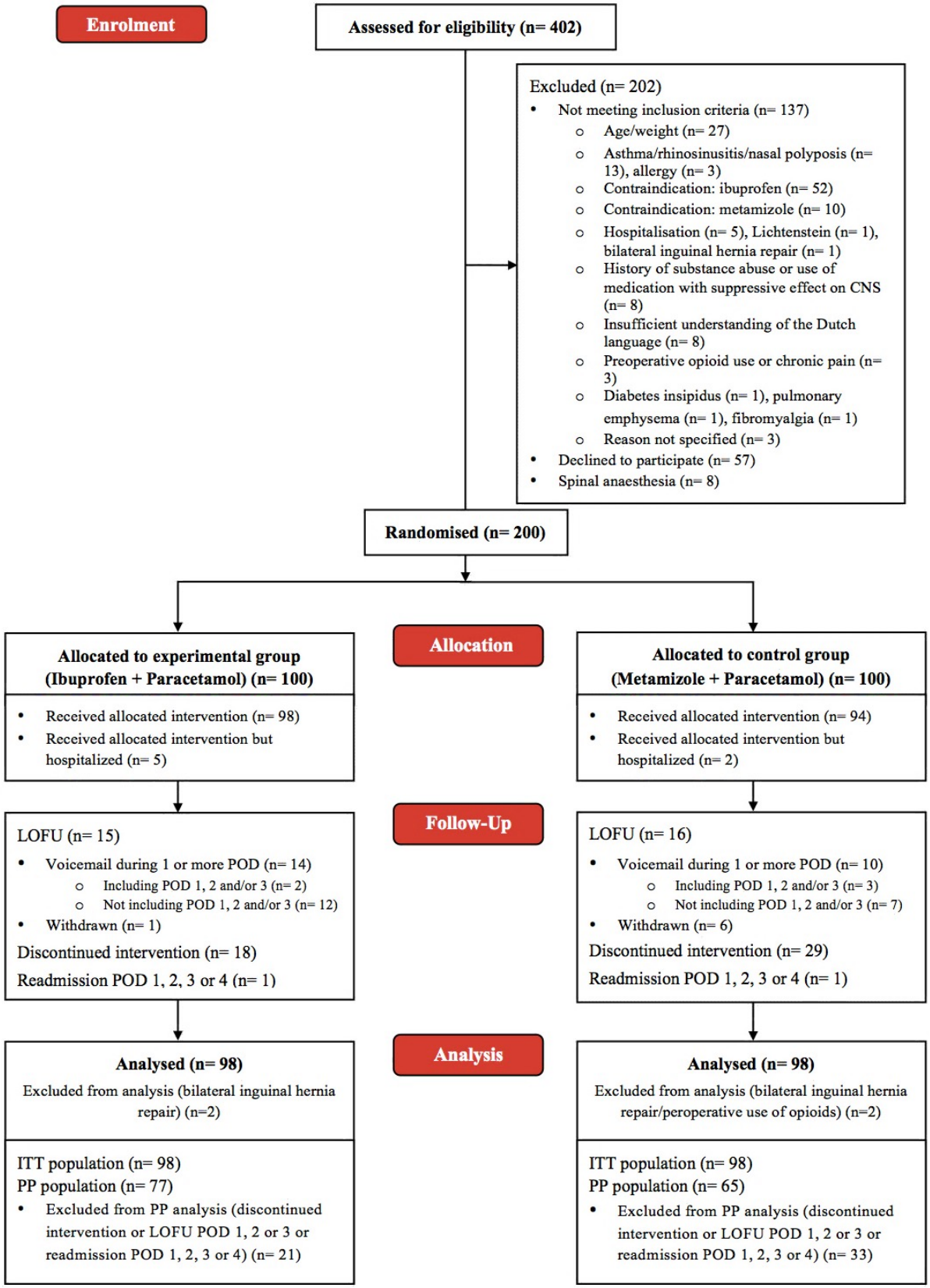


Figure 6: Study flow diagram. *LOFU: Loss to follow-up, POD: postoperative days, ITT: intention-to-treat, PP: per protocol.*

3.2 Baseline characteristics

During the study period, all patients were instructed to complete a baseline questionnaire before surgery. Nevertheless, 62 participants (31,62%) overlooked, forgot or skipped one or more questions and consequently returned an incomplete questionnaire. Baseline patient characteristics for both treatment groups, including demographics, psychological parameters, preoperative quality of life and preoperative pain characteristics are shown in table 1.

Table 1: Baseline characteristics. *Data are presented as mean (SD), median (25^{th} - 75^{th} percentile) or as absolute numbers (%). BMI: body mass index, ASA: American Society of Anaesthesiologists, GSR: global surgical recovery, FRI: functional recovery index, EQ-5D: 5-dimensional European Quality of Life questionnaire.*

	Ibuprofen + Paracetamol (n= 98)	**Metamizole + Paracetamol (n= 98)**
Demographic data		
Age (years)	50.70 (11.71)	49.10 (11.35)
BMI (kg/m^2)	26.25 (3.91)	25.98 (3.39)
Gender (male/female)	68/30 (69.39/30.61)	63/35 (64.29/35.71)
Work situation		
Not working	30 (30.61)	30 (30.61)
Paid work	67 (68.37)	68 (69.39)
Missing data	1 (1.02)	0 (0.00)
Educational background		
Primary/junior secondary education	19 (19.39)	26 (26.53)
Upper secondary education	48 (48.98)	38 (38.78)
Higher education	30 (30.61)	34 (34.69)
Missing data	1 (1.02)	0 (0.00)
Preoperative information		
ASA-classification		
ASA I	40 (40.82)	31 (31.63)
ASA II	50 (51.02)	53 (54.08)
ASA III	2 (2.04)	5 (5.10)
Missing data	6 (6.12)	9 (9.18)

Table 1: Continued.

	Ibuprofen + Paracetamol (n= 98)	Metamizole + Paracetamol (n= 98)
Operation last year (yes/no)?	20/78 (20.41/79.59)	17/81 (17.35/82.65)
Related to surgery (yes/no)?	3/17 (15.00/85.00)	6/11 (35.29/64.71)
Last week: pain associated with the condition (yes/no/missing)?	61/31/6 (62.24/31.63/6.12)	68/25/5 (69.39/25.51/5.10)
Average pain	5.48 (2.11)	5.01 (2.24)
Influence pain on daily activities	5.23 (2.72)	4.60 (2.36)
Short-term surgical fear (0-40)	11.50 (5.00-20.00) [a]	11.00 (5.00-21.25) [b]
Long-term surgical fear (0-40)	8.00 (3.00-15.50) [a]	6.00 (3.00-12.00) [c]
Baseline GSR (0-100)	80.00 (70.00-90.00) [a]	80.00 (70.00-90.00) [d]
Baseline FRI		
Pain and social activity (0-70)	16.50 (4.00-31.00) [e]	13.00 (5.00-27.00) [f]
Lower limb activity (0-40)	4.00 (0.00-14.00) [g]	7.00 (0.00-14.50) [c]
General physical activity (0-30)	1.00 (0.00-7.00) [h]	3.00 (0.00-8.00) [i]
Baseline EQ-5D (-0.59-1.00)	0.76 (0.66-1.00) [h]	0.76 (0.69-0.80) [b]
Expected pain (0-10)	5.44 (2.40) [h]	5.02 (2.46) [i]

[a]n= 92, [b]n= 94, [c]n= 93, [d]n= 89, [e]n= 80, [f]n= 75, [g]n= 90, [h]n= 91, [i]n= 95

3.3 Perioperative characteristics

After enrolment, 2 patients that underwent an arthroscopy knee surgery requested spinal anaesthesia and consequently did not receive the predefined protocol of general anaesthesia. The number of patients that received IV piritramide in the PACU for additional pain relief was rather low. In total, 128 patients (65.31%) received 0 mg, 42 patients (21.43%) received 2 to 4 mg and 26 patients (13.27%) received a higher amount ranging between 5 and 12 mg IV piritramide. Moreover, there was no significant difference found between treatment groups for the amount of IV piritramide administration (p= 0.724). These perioperative patient characteristics are also shown in table 2, stratified by treatment.

Table 2: Perioperative characteristics. *Data are presented as median (25^{th} - 75^{th} percentile) or as absolute numbers (%). PACU: Post-Anaesthesia Care Unit.*

	Ibuprofen + Paracetamol (n= 98)	**Metamizole + Paracetamol (n= 98)**
Type of anesthesia		
General	97 (98.98)	97 (98.98)
Spinal	1 (1.02)	1 (1.02)
Piritramide in PACU (mg)	0.00 (0.00-2.50)	0.00 (0.00-3.00)
0 mg	66 (67.35)	62 (63.27)
2-4 mg	18 (18.37)	24 (24.49)
≥ 5 mg	14 (14.29)	12 (11.22)
Duration of Surgery (min)	23.50 (16.75-39.25)	27.00 (17.00-42.00)

3.4 Follow-up data

After the completion of the telephone follow-up on 28 April 2017, the results were analyzed with a primary focus on POD 1, 2 and 3, to determine whether the combination of metamizole and paracetamol is a potential alternative for the gold standard to treat postoperative pain at home after ambulatory surgery. Besides missing baseline values, there were also missing outcome values due to patient withdrawal or voicemails (figure 6). To cope with these missing values an imputation model was used for the analysis of the primary outcome measures (average pain intensity scores and QOR).

3.4.1 Postoperative pain scores

At follow-up, the reported postoperative pain intensity scores were similar between treatment groups (figure S1). The average pain intensity, pain at rest and pain at movement scores of the 4-day treatment period are presented in figure 7. Before discharge, patients reported an average pain intensity median NRS score of 3.0 (IQR 1.0-4.0) in the experimental group and 2.0 (0.5-4.0) in the control group (figure $7A_2$). In total, 75 patients (29.08%) indicated an NRS score higher than three before discharge, of which 28 patients (49.12%) did not receive IV piritramide, notwithstanding the given instructions to administer IV piritramide in the PACU until an NRS score ≤ 3 was reached.

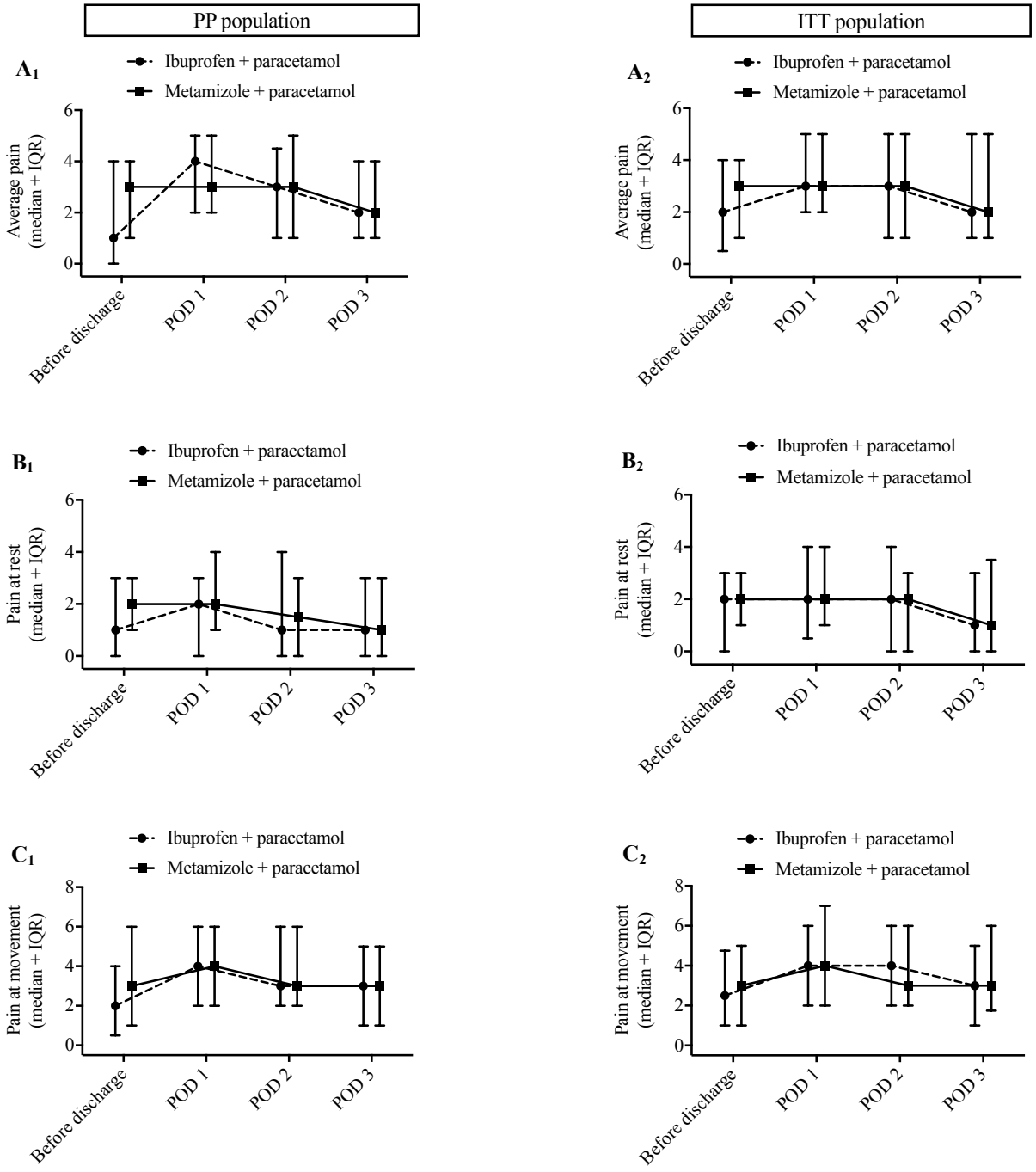


Figure 7: Postoperative pain scores of the per protocol (PP) and intention-to-treat (ITT) population before discharge and during postoperative day (POD) 1, 2 and 3.

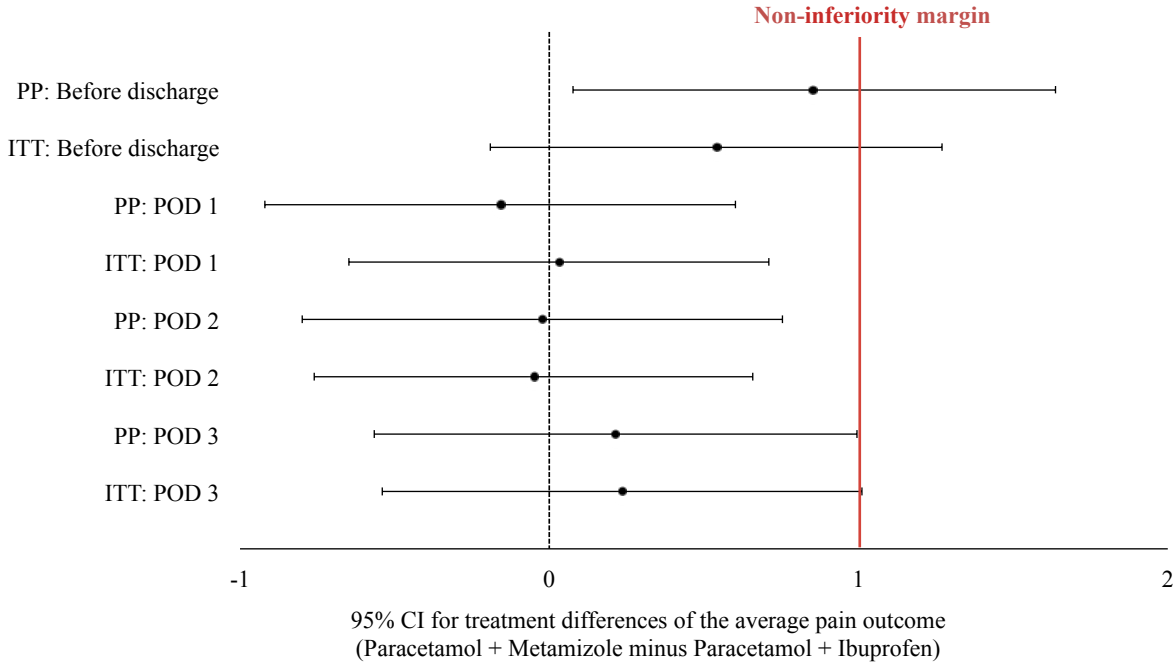
Average pain (A), pain at rest (B) and pain at movement (C) measured by an 11-point numerical rating scale are presented as median and IQR (interquartile range) for both the PP (1) and ITT population (2).

During POD 1, 2 and 3, the PP population administered the study medication at home according to the instructions. However, there were still patients that reported moderate to severe postoperative pain (NRS > 3) during the treatment period. The median values of the average pain intensity scores of the PP population on POD 1, 2 and 3 were similar to the ITT population and respectively 4.0 (2.0-5.0) for the control group and 3.0 (2.0-5.0) for the experimental group, 3.0 (1.0-4.5) for the control group and 3.0 (1.0-5.0) for the experimental group and 2.0 (1.0-4.0) for both treatment groups. At the end of the postoperative pain treatment (POD 3), moderate to severe postoperative pain was still reported by 44 patients (30.99%) of the PP population [21 patients (27.27%) of the control group and 23 patients (35.38%) of the experimental group] and 64 patients (32.65%) of the ITT population [30 patients (30.61%) of the control group and 34 (34.69%) patients of the experimental group].

3.4.2 Treatment efficacy

The primary objective of this trial was to investigate whether a combination of metamizole and paracetamol is non-inferior to the combination of ibuprofen and paracetamol in the treatment of postoperative pain at home after day surgery. To prove non-inferiority of the experimental group against the control group, the upper limit of the 95% CI of the difference in mean NRS of the average postoperative pain intensity scores must be lower than the predefined non-inferiority margin 1. For POD 1, both 95% CI of the PP [-0.913; 0.596] and ITT [-0.647; 0.710] population of the difference in mean NRS (respectively -0.158 and 0.032) were lower than the predefined non-inferiority margin, confirming a non-inferior result. In addition to POD 1, before discharge, POD 2 and POD 3 values of the difference in mean NRS and the related 95% CI are shown in figure 8.

As an additional sensitivity analysis, the same test was performed on the average postoperative pain intensity scores without imputed values (figure S2). The results of the additional sensitivity analysis were comparable to the imputed results. More specific, both analyses proved non-inferiority for POD 1 and 2 and showed an inconclusive result before discharge. However, for POD 3 the PP and ITT population showed respectively a non-inferior and inconclusive result for the primary analysis, while the additional sensitivity analysis concluded non-inferiority for both the PP and ITT population.



Average pain intensity	Mean Metamizole + Paracetamol	Mean Ibuprofen + Paracetamol	Mean difference and 95% CI	Inference
PP analysis				
Before discharge	3.06	2.15	0.852 [0.067; 1.637]	Inconclusive
POD 1	3.40	3.56	-0.158 [-0.913; 0.596]	Non-inferior
POD 2	3.11	3.13	-0.022 [-0.793; 0.749]	Non-inferior
POD 3	2.88	2.66	0.215 [-0.559; 0.988]	Non-inferior
ITT analysis				
Before discharge	3.03	2.49	0.541 [-0.189; 1.270]	Inconclusive
POD 1	3.60	3.57	0.032 [-0.647; 0.710]	Non-inferior
POD 2	3.22	3.27	-0.050 [-0.758; 0.658]	Non-inferior
POD 3	3.18	2.95	0.236 [-0.540; 1.011]	Inconclusive

Figure 8: The evaluation of non-inferiority of the analgesic efficacy of metamizole and paracetamol to ibuprofen and paracetamol. *The difference in mean numerical rating scale (NRS) scores for the imputed average pain intensity values between the two treatment groups (paracetamol and metamizole minus paracetamol and ibuprofen) and the resulting 95% confidence intervals (CI) are shown. A difference in mean NRS of less than 1 point is considered non-inferior, but the 95% CI that include the non-inferiority margin do not allow for a conclusive inference. POD: postoperative day; PP: per protocol; ITT: intention-to-treat.*

Furthermore, the patient reported pain relief scores were not significantly different on POD 1, 2 or 3 ($p > 0.05$). Moreover, the median was equal to 70.00% (IQR 40.00%-80.00%) for both treatment groups.

3.4.3 Quality of recovery

To investigate whether QOR was different between treatment groups, three questionnaires were used: the FRI, the EQ-5D questionnaire and the GSR index. For the FRI, the patient reported values of the 14-items were summated to calculate a total score. In contrast to the EQ-5D and SRI, a higher score indicated greater difficulty with recovery, whereas a lower score indicated better recovery. At follow-up, the calculated total FRI scores showed similar scores for the PP and ITT population and no significant differences between treatment groups (table 3 and figure 9A). Furthermore, the PP and ITT population presented no significant differences between treatment groups during the treatment period (table 3) and at the subsequent follow-up days (figure 9B and C) for both the single index scores of the EQ-5D questionnaire, calculated based on the "MVH_A1 tariff" algorithm (39), and the GSR index scores. Thus, in general no significant differences between treatment groups were found for QOR at follow-up.

Based on the Wilcoxon-signed rank test and Bonferroni adjustment, both treatment groups showed significant higher values on POD 1 to 4 and 7 for the FRI of the ITT population in comparison to the baseline values. On POD 14 no significant differences were found, which indicated the return to baseline values. For the PP population, the FRI compared to baseline showed similar results for the control group, however for the experimental group results were already insignificant on POD 4 and 7 (figure 9A). The EQ-5D index scores were also compared to baseline and showed significant lower scores on POD 1 to 4 and insignificant results on POD 7 and 14 for both treatment groups of the ITT population. However, the results for the PP population are already insignificant on POD 4 for the control group and on POD 3 and 4 for the experimental group (figure 9B). Thus overall, the patients that followed the complete treatment schedule of the experimental group returned earlier to their baseline values than the control group. For the GSR index no comparison was made between baseline (health state before surgery) and postoperative values because the patients were only asked how good they were recovered from the surgery, while normally the GSR index is measured by asking the following question “As 100% recovery means your health is back to the same level as it was before the surgery, what percentage of recovery are you at now?” (figure 9C).

Table 3: Quality of recovery (QOR) during the postoperative pain treatment. *Data are presented as median (25^{th} - 75^{th} percentile). No significant differences between treatment groups were found based on the Mann-Whitney U test. EQ-5D: 5-dimensional European Quality of Life questionnaire, FRI: functional recovery index, GSR: global surgical recovery.*

	Ibuprofen + Paracetamol (PP: n= 77; ITT: n= 98;)	**Metamizole + Paracetamol (PP: n= 65; ITT: n= 98)**	**P-value**
FRI (0-140)			
PP analysis			
POD 1	79.00 (52.50-98.00)	80.00 (60.00-98.00)	0.837
POD 2	60.00 (33.50-81.00)	64.00 (42.00-87.00)	0.656
POD 3	50.00 (22.00-74.00)	52.00 (28.00-87.00)	0.381
ITT analysis			
POD 1	76.00 (52.00-98.00)	80.00 (60.00-98.00)	0.383
POD 2	62.50 (39.00-84.00)	68.00 (48.50-87.00)	0.832
POD 3	54.00 (27.00-77.75)	57.00 (33.50-86.50)	0.263
EQ-5D (-0.59-1.00)			
PP analysis			
POD 1	0.59 (0.26-0.66)	0.59 (0.26-0.69)	0.511
POD 2	0.59 (0.32-0.76)	0.66 (0.59-0.78)	0.448
POD 3	0.66 (0.59-0.79)	0.66 (0.59-0.84)	0.846
ITT analysis			
POD 1	0.59 (0.26-0.69)	0.59 (0.26-0.69)	0.937
POD 2	0.59 (0.32-0.76)	0.65 (0.59-0.78)	0.384
POD 3	0.66 (0.59-0.80)	0.66 (0.48-0.79)	0.707
GSR index (0-100)			
PP analysis			
POD 1	50.00 (20.00-80.00)	50.00 (30.00-70.00)	0.320
POD 2	50.00 (40.00-70.00)	50.00 (30.00-70.00)	0.691
POD 3	60.00 (40.00-80.00)	70.00 (40.00-80.00)	0.987
ITT analysis			
POD 1	50.00 (20.00-77.50)	50.00 (30.00-70.00)	0.682
POD 2	50.00 (40.00-70.00)	50.00 (30.00-70.00)	0.978
POD 3	60.00 (40.00-70.00)	65.00 (40.00-80.00)	0.622

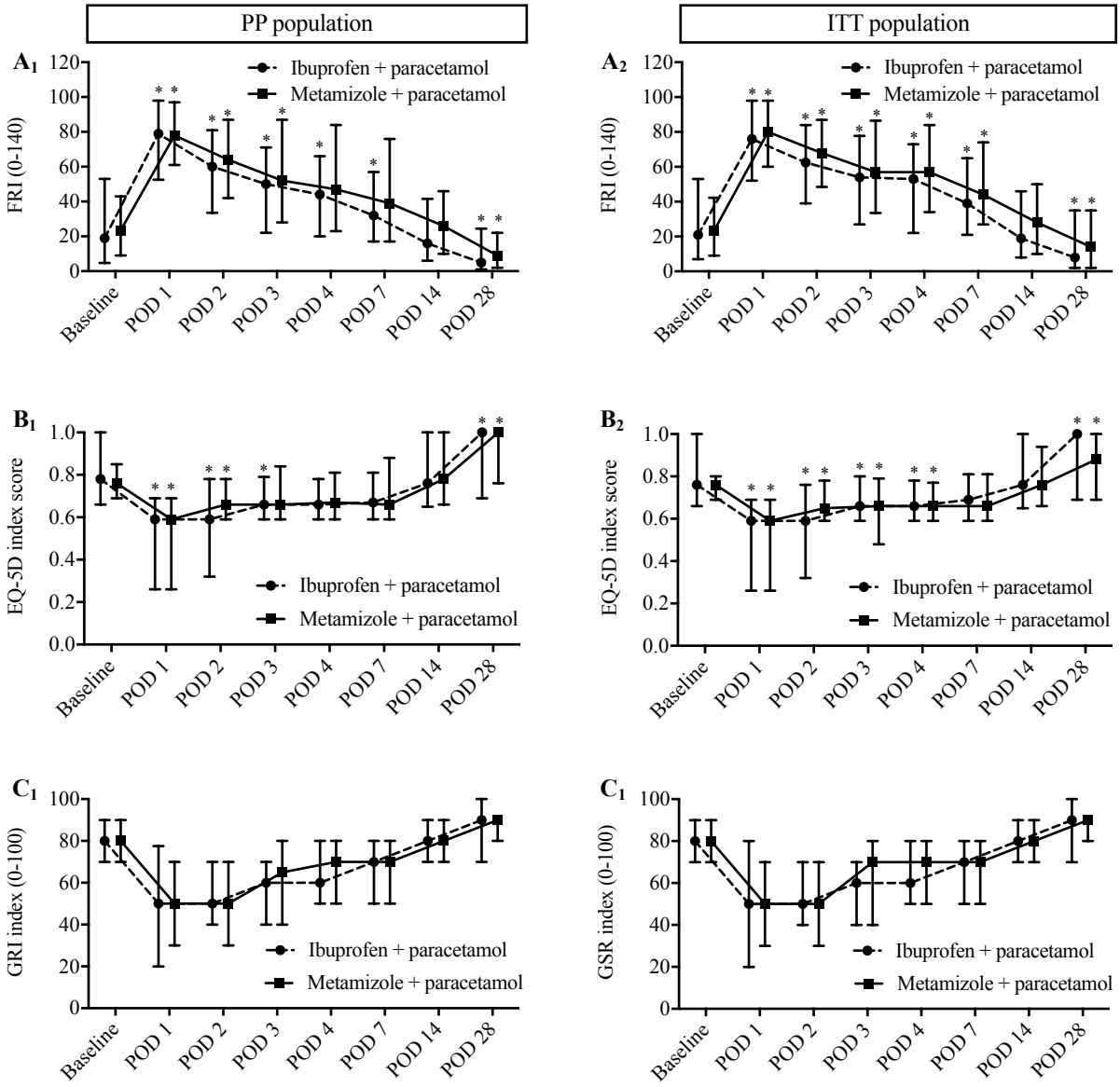


Figure 9: Quality of recovery (QOR) at baseline and during follow-up. *Total functional recovery index (FRI) scores (A), index scores of the 5-demensional European Quality of Life questionnaire (EQ-5D) (B) and global surgical recovery (GSR) index scores (C) are presented as median (25^{th} - 75^{th} percentile) for the PP (1) and ITT (2) population. No significant differences were found between treatment groups based on the Mann-Whitney U test. QOR at follow-up was also compared to baseline for the EQ-5D and FRI scores (based on a Wilcoxon signed-rank test and Bonferroni adjustment). Significant differences from baseline are presented with an asterisk (*).*

3.4.4 Compliance with the study medication

Despite clear written and oral instructions that were given during the informed consent procedure and before discharge, 47 patients (23.98%) did not use the study medication as prescribed. No significant difference was found between treatment groups, notwithstanding the slightly higher number of patients in the experimental group not administering the study medication as instructed (29 patients versus 18 patients of the control group) [χ^2 (1) = 3.569, p= 0.059]. Furthermore, these patients were categorized into a non-adherence group, who never correctly followed the treatment schedule, and a partial adherence group, who did not follow the treatment schedule during one or two PODs. The non-adherence group only consisted out of 11 patients, 4 patients of the control group and 7 patients of the experimental group, while the partial adherence group included 26 patients, 14 patients of the control group and 22 patients of the experimental group (figure 10). The full adherence group significantly differed from the combined non-adherence and partial adherence groups with regard to BMI, sex and the baseline FRI category pain and social activity (table S1). Furthermore, patient satisfaction scores for the pain treatment were significantly higher for the full adherence group in comparison to the combined non-adherence and partial adherence groups (U= 1858.000, p= 0.026).

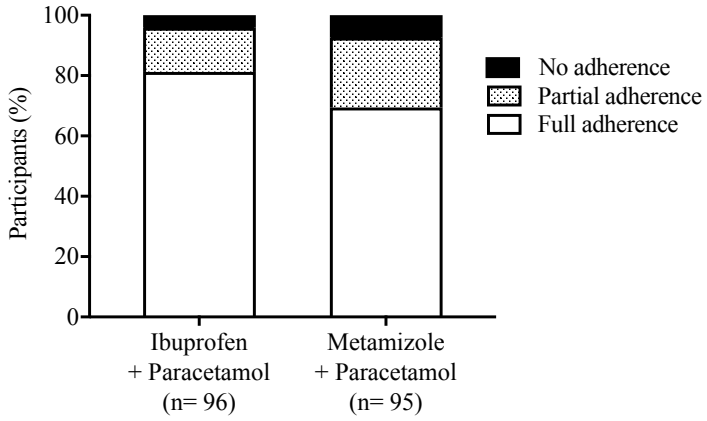


Figure 10: Adherence to the study medication during postoperative day (POD) 1, 2 and 3. *Full adherence means that the patient followed the treatment schedule as prescribed, partial adherence means that the patient did not follow the treatment schedule as prescribed during one or two PODs and no adherence means that the patient did not follow the predefined treatment during any of the PODs. N =196, but due to voicemails data on adherence of 2 patients of the control group and 3 patients of the experimental group are missing and consequently not shown.*

Table 6 presents the reasons for not adhering to the study medication and shows no significant differences between treatment groups. The most frequently reported reason for not following the predefined treatment schedule was the presence of unwanted side effects, such as nausea, pyrosis and fatigue (n= 25). Furthermore, one patient that underwent haemorrhoid surgery, three patients that underwent inguinal hernia repair, six patients that underwent arthroscopy knee surgery and one patient that underwent arthroscopy shoulder surgery discontinued the postoperative pain treatment because they experienced merely no pain during POD 1, 2 and/or 3. Other patient reported reasons for not adhering to the study medication, such as forgetting to take the pain medication (n= 1), thinking that taking medication is unhealthy (n= 1), fear to take too much medication (n= 3), personal reasons (n= 4), excessive pain (n= 2) or admission to the hospital (n= 3) were less common in this trial. Finally, two patients administered one extra dose of ibuprofen or metamizole at night and consequently did not have enough study medication at the end of the treatment period and two patients stopped the treatment as instructed by the surgeon.

Table 6: Patient reported reasons for not adhering to the study medication during POD 1, 2 and/or 3.

Data are presented as numbers (%). No significant differences between treatment groups were found using the Pearson's $\chi 2$ test or the Fisher's exact test (when an observed count < 10 was present).

	Ibuprofen + Paracetamol (n= 98)	**Metamizole + Paracetamol (n= 98)**	**P- value**
Unwanted side effects	10 (10.42)	15 (15.79)	0.283
No pain	5 (5.20)	6 (6.32)	0.767
Afraid of taking too much medication	1 (1.04)	2 (2.11)	1.000
Forgot to take medication	0 (0.00)	1 (1.05)	1.000
Taking medication is unhealthy	1 (1.04)	0 (0.000)	1.000
Other reasons	4 (4.17)	10 (10.53)	0.164

3.4.5 Use of rescue medication

The number of patients that reported the use of rescue medication was not significantly different between treatment groups on POD 1 and 3, while on POD 2 the use of rescue medication was significantly more reported by patients of the experimental group. More specific, the use of rescue medication was reported by 29 patients (29.59%) of the control group and 28 patients (28.57%) of the experimental group on POD 1 [χ^2 (1) = 0.000, p = 0.987], 28 patients (28.75%) of the control group and 14 patients (14.29%) of the experimental group on POD 2 [χ^2 (1) = 5.095, p = 0.024] and 18 patients (18.37%) of the control group and 11 patients (11.22%) of the experimental group on POD 3 [χ^2 (1) = 1.581, p = 0.209]. In addition to the number of patients, the number of administered tablets (tramadol, 50mg) was evaluated and resulted also in a significant difference between treatment groups on POD 2 (U = 3820.500, p = 0.042) (figure 11).

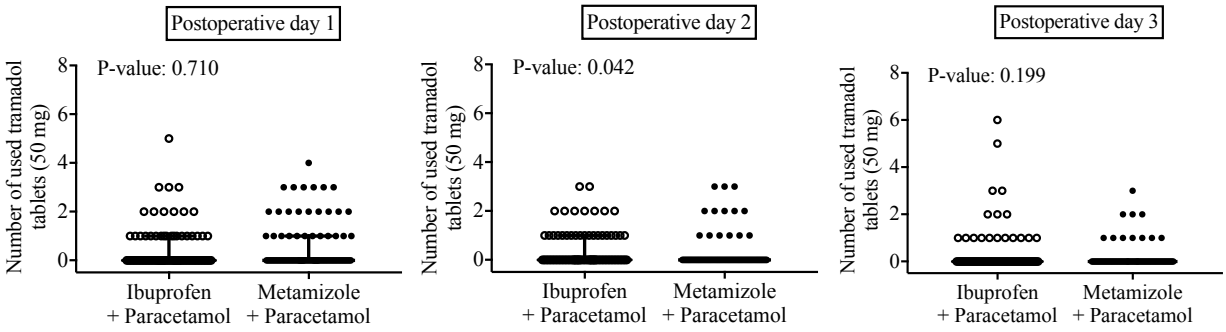


Figure 11: Use of rescue medication (tramadol, 50 mg). *Dots represent the number of administered tablets of rescue medication. Bars present the median and interquartile range (IQR) for each group. Only on POD 2, the group receiving ibuprofen and paracetamol required significantly more rescue medication than the experimental group (metamizole and paracetamol) based on the Mann-Whitney U test (p-value: 0.042).*

3.4.6 Patient reported side effects

Self-reported side effects of the study medication were indicated by 48 patients (48.98%) of the control group and 56 patients (57.14%) of the experimental group during the telephone follow-up of POD 1, 2 and/or 3 and were not significantly different between treatment groups [χ^2 (1) = 1.311, p = 0.252]. Table 7 shows that the numbers of specific self-reported side effects (e.g. nausea, pyrosis and constipation) were also not significantly different between the control group and the experimental group.

Table 7: Patient reported side effects. *Data are presented as numbers (%). No significant differences between treatment groups were found using the Pearson's χ2 test or the Fisher's exact test (when an observed count < 10 was present).*

	Ibuprofen + Paracetamol (n= 98)	**Metamizole + Paracetamol (n= 98)**	**P- value**
Nausea	15 (15.31)	19 (19.39)	0.451
Pyrosis	15 (15.31)	22 (20.45)	0.201
Constipation	8 (8.16)	11 (11.22)	0.630
Other	30 (30.61)	28 (28.57)	0.754
Fatigue	13 (13.27)	10 (10.20)	0.506
Diarrhea	2 (2.04)	2 (2.04)	1.000
Sweating	1 (1.02)	2 (2.04)	1.000
Dizziness	8 (8.16)	10 (10.20)	0.805
Paresthesia	3 (3.06)	0 (0.00)	0.246
Palpitations/high blood pressure	2 (2.04)	1 (1.02)	1.000

Furthermore, there was no significant relationship observed for the use of rescue medication and the presence of pyrosis, constipation or other self-reported side effects during POD 1, 2 and/or 3. However, there was a significant relationship with self-reported nausea [χ^2 (1) = 5.752, p = 0.016]. Fifteen patients (44.12%) reported nausea and did not use rescue medication during POD 1, 2 and/or 3, while 19 patients (55.88%) reported nausea and did use rescue medication. During the study period, also no agranulocytosis or other serious adverse effects of the study medication were reported.

3.4.7 Patient satisfaction

Patient satisfaction with the study medication, median 8.00 (IQR 9.00-10.00) for the experimental group and 8.50 (7.00-10.00) for the control group, was not significantly different between treatment groups (U = 3551.500, p = 0.272) (figure 12). Furthermore, high satisfaction scores, median 9.00 (9.00-10.00), were given by the patients for the surgery and hospital care and the telephone follow-up.

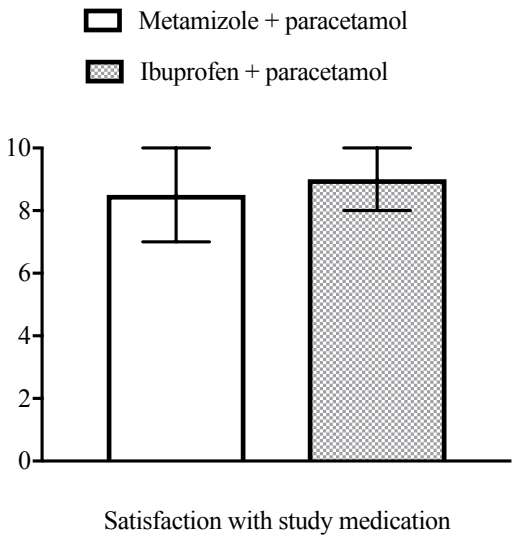


Figure 12: Patient satisfaction with the study medication. *Patient satisfaction measured by an 11-point numerical rating scale is presented as median and interquartile range for both treatment groups. No significant difference was found between groups (p = 0.272), based on the Mann-Whitney U test.*

4 Discussion

Postoperative pain management after ambulatory surgery remains challenging in comparison to the inpatient setting, because the type of analgesics that can be used and the route of administration are limited when patients are recovering at home (5). The gold standard to treat postoperative pain in an ambulatory setting is based on a multimodal analgesic approach and includes the combination of paracetamol and NSAIDs and weak opioids as rescue medication to treat postsurgical pain at home (3). However, this combination cannot be used in 25% of patients, due to the presence of contraindications for NSAIDs (e.g. the presence of gastrointestinal ulcers or bleedings and congestive heart failure) (7). Therefore, it is pivotal to investigate valuable alternatives for the use of oral NSAIDs at home to treat acute postsurgical pain.

In this thesis, the non-opioid analgesic metamizole was investigated as potential alternative because of its favourable gastrointestinal and cardiovascular profile in comparison to NSAIDs (12-14). Nevertheless, to determine whether metamizole is a valuable alternative for NSAIDs in the gold standard, the analgesic efficacy of a combination of paracetamol and metamizole needs to be similar to the analgesic efficacy of the gold standard. Therefore, this master thesis presents the results of the first trial that investigated whether a combination of metamizole and paracetamol is non-inferior to the gold standard in the treatment of postoperative pain at home after painful ambulatory surgery.

Results of the PP analysis, showed that the multimodal analgesic approach consisting of metamizole and paracetamol was non-inferior compared to the combination of ibuprofen and paracetamol in an adult population undergoing ambulatory knee arthroscopy, shoulder arthroscopy, unilateral inguinal hernia repair or haemorrhoid surgery during the postoperative pain treatment at home. Furthermore, these results were confirmed by the ITT analysis for POD 1 and 2, indicating that metamizole is a promising alternative for NSAIDs to treat postoperative pain at home in an ambulatory setting. The results of the non-inferiority analysis of the postoperative pain values that were measured before discharge were inconclusive. However, this inconclusive result is less relevant, because the patients were still in the hospital and the postoperative pain scores could be influenced by the anaesthetic analgesia that they received during surgery and in the PACU. Furthermore, the average pain

intensity scores before discharge were relatively high, notwithstanding the instructions to administer piritramide in the PACU until a NRS ≤ 3 was reached. Therefore, we concluded that the predefined perioperative protocol in the PACU was not strictly followed during the trial, which again emphasizes that the non-inferiority analysis of the results measured before discharge are less relevant in this setting.

Despite the pain treatment, there were still several patients that reported moderate to severe postoperative pain at follow-up. Therefore, additional studies are needed to find a multimodal analgesic treatment that has an additive or even synergistic effect to relief pain in patients with moderate to severe pain after painful ambulatory surgery. This type of research would also be very valuable for the future because there is an increasing trend in the amount of complex and painful surgeries that are performed in an ambulatory setting.

The primary endpoint QOR can be influenced by several dimensions (e.g. psychological, functional and physical dimensions). Because of this, the FRI and EQ-5D questionnaire were used in addition to the GSR index to evaluate QOR during this trial. These questionnaires contain 14 and 5 questions respectively, making it possible to evaluate several domains of QOR after ambulatory surgery by a single questionnaire (32, 38). Because postoperative pain has an influence on all these dimensions, it was expected that the QOR was not significantly different between the treatment groups, as the combination of metamizole and paracetamol was non-inferior in comparison to the gold standard for treating postoperative pain at home after ambulatory surgery. The results confirmed this prediction and showed no significant differences between treatment groups for either the GSR index, the calculated EQ-5D index score or the total score of the FRI. Furthermore, the results showed that the postoperative QOR of the PP population reached similar scores to baseline earlier during follow-up, suggesting that adherence to the study medication can influence the course of the QOR trajectory.

One of our secondary outcomes measures was patient reported compliance to the instructed postoperative pain schedule. Literature, already states that nonadherence is a well-known problem in chronic pain patients that use analgesia (40, 41). Recently, our research group also published the results of a large prospective cohort study (n= 1248) that assessed the prevalence of patient non-adherence to pain therapy at home after day surgery (4). These

results showed that non-adherence and partial adherence to the pain protocol is common after ambulatory surgery with a prevalence of respectively 21.60% and 20.00% of the total study population. However, in our study only 5.60% of the patients were non-adherent to the prescribed pain treatment and 13.20% were partial adherent. In the large prospective cohort study, patients only received a prescription for postoperative analgesics and verbal and written instruction about the pain treatment, while in our study all the pain medication that was needed to follow the postoperative pain protocol was already provided by us and given in the hospital in addition to the verbal and written instructions. Consequently, patients did not need to go the pharmacy to buy the prescribed medication and this could be a potential reason why in our study the prevalence for adherence to the pain medication was higher. Furthermore, BMI, sex, baseline FRI category pain and social activity and patient satisfaction scores for the pain treatment were significantly higher for the full adherence group in comparison to the combined non- and partial adherence groups. In the cohort study, there was also a comparison made between the adherence groups. However, they compared the combined full and partial adherence groups to the non-adherence group and they also found a significant difference between groups for satisfaction with the pain treatment, which was higher in the combined full and partial adherence groups (4).

The number of patients that reported side effects during this trial was relatively high during the pain treatment and was not significantly different between treatment groups. In total, 53.06% of all patients reported one or more side effects during the period of the first three PODs. Consequently, this was also the most common reason for non-adherence to the study medication in our trial. Nausea and pyrosis were most frequently reported in both treatment groups. Thus, despite the favourable gastrointestinal profile of metamizole in comparison to NSAIDs, no significant differences were found between treatment groups for the occurrence of nausea and pyrosis. However, a recent published systematic review that compared metamizole to other analgesics to determine its clinical safety showed no difference in adverse events between metamizole and NSAIDs, including nausea and vomiting (42). This systematic review also showed that metamizole had fewer adverse events compared to opioids, suggesting that it is more appropriate to use as an alternative drug for NSAIDs in the gold standard in comparison to opioids.

Tramadol, was used as a rescue medication in this study and was administered by the patients in case of insufficient pain relief. Studies already showed that NSAIDs have an opioid-sparing effect (43). However, our results presented a significantly lower intake of tramadol on POD 2, suggesting that metamizole has also an opioid-sparing effect when used in a multimodal analgesic treatment to treat postoperative pain at home after ambulatory surgery.

Furthermore, patients indicated high satisfaction scores for the telephone follow-up. In the future of ambulatory surgery, regular telephone follow-up could be an asset to follow-up the patients more carefully after discharge. It could be used to remind them to use their pain medication and to answer their surgical related questions. However, more research is needed to determine whether this could enhance the compliance to the pain medication and QOR.

There were also several limitations to our study. First, secondary outcome measures (occurrence of side effects, compliance, use of rescue medication and patient satisfaction) did not show statistical significant differences between treatment groups, except for the administration of tramadol during POD 2. However, it should be noted that this trial was not powered to find significant differences for secondary outcome measures. Second, patients were allowed to take rescue medication in case of insufficient pain relief. This can lead to an overestimation of the analgesic efficacy of the pain treatments. Nevertheless, use of rescue medication was not significantly different during POD 1, the primary day that was chosen to compare the analgesic efficacy between the treatment groups. Last but not least, there were several missing values, due to voicemails and withdrawal. This can influence the results of a non-inferiority analysis. Therefore, we used an imputation model to predict the missing values and to minimize bias.

5 Conclusion

The primary goal of this thesis was to investigate whether a combination of metamizole and paracetamol is non-inferior to the gold standard in the treatment of postoperative pain at home after painful ambulatory surgery. Our data proved that the combination of metamizole and paracetamol was non-inferior to the combination of ibuprofen and paracetamol for patients that used the study medication as prescribed on POD 1, 2 and 3. At follow-up, there were also no significant differences found between treatment groups for QOR, adherence to the study medication or patient reported side effects. Moreover, the experimental group showed an opioid-sparing effect on POD 2, as significant less participants needed to use rescue medication for extra pain relief. Therefore, acute postoperative pain management with metamizole and paracetamol is a valuable alternative for the gold standard, in particular for patients with a contraindication for NSAIDs. However, future studies are needed to determine whether there are more complex drug-combinations (e.g. the combination of metamizole, parcetamol and NSAIDs) that can have an additive or even synergistic analgesic effect to treat postoperative pain in patients that still experience moderate to severe postoperative pain after ambulatory surgery.

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7 Supplemental information

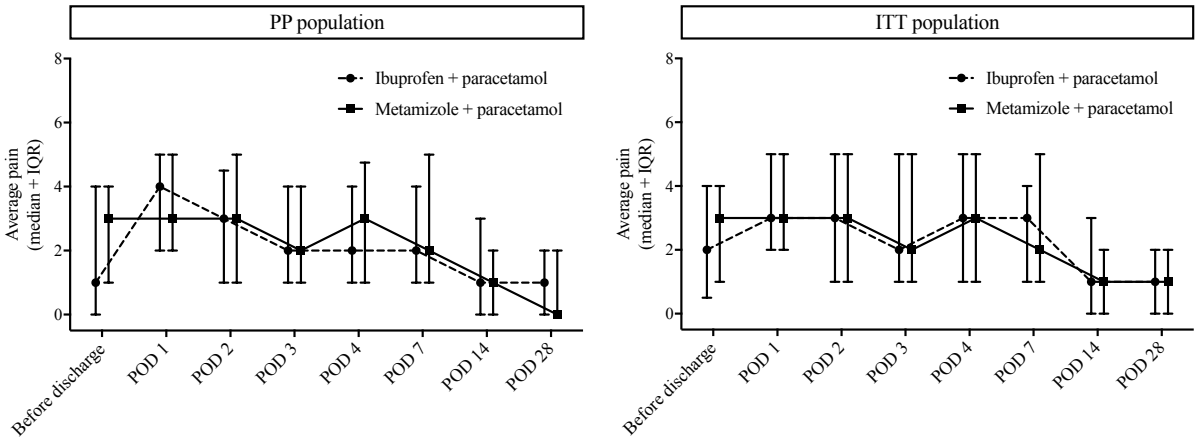
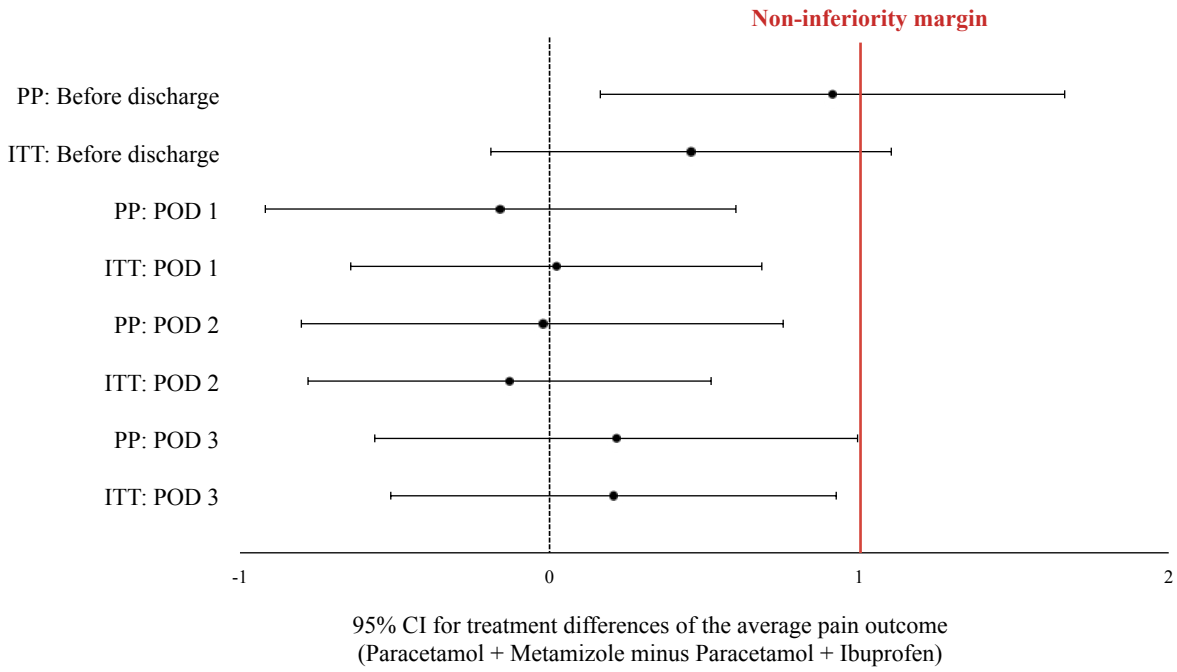


Figure S1: Average pain intensity scores before discharge and at follow-up. *Average pain intensity measured by an 11-point numerical rating scale is presented as median and IQR (interquartile range) for both the PP and ITT population.*



Average pain intensity	Mean Metamizole + Paracetamol	Mean Ibuprofen + Paracetamol	Mean difference (95% CI)	Inference
PP analysis				
Before discharge	3.06	2.15	0.915 [0.166; 1.664]	Inconclusive
POD 1	3.40	3.56	-0.158 [-0.919; 0.602]	Non-inferior
POD 2	3.11	3.13	-0.022 [-0.800; 0.755]	Non-inferior
POD 3	2.88	2.66	0.215 [-0.566; 0.995]	Non-inferior
ITT analysis				
Before discharge	2.78	2.32	0.458 [-0.190; 1.105]	Inconclusive
POD 1	3.56	3.54	0.022 [-0.643; 0.687]	Non-inferior
POD 2	3.14	3.27	-0.130 [-0.781; 0.65]	Non-inferior
POD 3	3.12	2.92	0.206 [-0.513; 0.926]	Non-inferior

Figure S2: The evaluation of non-inferiority of the analgesic efficacy of metamizole and paracetamol to ibuprofen and paracetamol. *The difference in mean numerical rating scale (NRS) scores for not imputed average pain intensity values between the two treatment groups (paracetamol and metamizole minus paracetamol and ibuprofen) and the resulting 95% confidence intervals (CI) are shown for the different time points of the pain treatment. A difference in mean NRS of less than 1 point is considered non-inferior. The 95% CI that include the threshold do not allow for a conclusive inference. Postoperative day: POD, PP: per protocol; ITT: intention-to-treat.*

Table S1: Baseline data for full adherence and partial or no adherence. *Data are presented as mean (standard deviation) median (25^{th} - 75^{th} percentile) or as absolute numbers (%). Full adherence means that the patient followed the treatment schedule as prescribed, partial adherence means that the patient did not follow the treatment schedule as prescribed during one or two postoperative days (PODs) and no adherence means that the patient did not follow the predefined treatment during any of the PODs. Original data on adherence of 5 patients is missing: baseline data is not shown. P-values were calculated using the independent t-test, Mann-Whitney U test, or Pearson's $\chi 2$ test, P-values ≤ 0.05 are considered statistically significant (*).*

Baseline characteristics	**Full adherence (n= 144)**	**Partial or no adherence (n= 47)**	**P-value**
Age (years)	51.00 (43.25-58.00)	48.00 (39.00-53.75)	0.209
BMI (kg/m^2)	25.66 (23.89-28.09)	24.52 (22.34-26.95)	0.005*
Gender (male/female)	105/39 (72.92/27.08)	24/23 (51.06/48.94)	0.005*
Work situation			0.917
Not working	45 (31.25)	14 (29.79)	
Paid work	99 (68.75)	32 (68.09)	
Missing data	0 (0.00)	1 (2.13)	
Educational background			0.351
Primary/junior secondary education	36 (25.00)	9 (19.15)	
Upper secondary education	65 (45.14)	19 (40.43)	
Higher education	42 (29.67)	19 (40.43)	
Missing data	1 (0.69)	0 (0.00)	
ASA-classification			0.780
ASA I	50 (34.72)	18 (39.00)	
ASA II	77 (53.47)	24 (51.06)	
ASA III	5 (3.47)	2 (4.26)	
Missing data	12 (8.33)	3 (6.38)	
Short-term surgical fear (0-40)	11.00 (5.00-19.00)	17.00 (8.00-26.00)	0.108
Long-term surgical fear (0-40)	8.00 (3.00-15.50)	6.00 (3.00-12.00)	0.059
Baseline GSR (0-100)	80.00 (70.00-90.00)	80.00 (60.00-90.00)	0.727
Baseline FRI			
Pain and social activity (0-70)	11.00 (4.00-26.00)	23.00 (10.25-37.50)	0.024*
Lower limb activity (0-40)	4.00 (0.00-12.75)	1.50 (0.00-14.75)	0.139
General physical activity (0-30)	2.00 (0.00-8.00)	0.00 (0.00-7.50)	0.696

Table S1: continued

Baseline characteristics	Full adherence (n= 144)	Partial or no adherence (n= 47)	P-value
Baseline EQ-5D (-0.59-1.00)	0.77 (0.66-1.00)	0.77 (0.73-0.80)	0.531
Preoperative pain (0-10)	3.00 (0.00-6.00)	4.50 (0.25-7.00)	0.085
Influence pain on daily activities (0-10)	2.00 (0.00-6.00)	4.00 (0.00-7.00)	0.221
Expected pain (0-10)	5.22 (2.36)	5.20 (2.68)	0.944

Auteursrechtelijke overeenkomst

Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:
Metamizole versus ibuprofen to treat postoperative pain at home after ambulatory surgery: a randomised controlled non-inferiority trial

Richting: **Master of Biomedical Sciences-Clinical Molecular Sciences**
Jaar: **2017**

in alle mogelijke mediaformaten, - bestaande en in de toekomst te ontwikkelen - , aan de Universiteit Hasselt.

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