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ORIGINAL ARTICLE

Additive or synergistic analgesic effect of metamizole on standard pain treatment at home after arthroscopic shoulder surgery

A randomised controlled superiority trial

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BACKGROUND There is growing evidence that the analgesic effect of metamizole is mediated at least partly by central mechanisms, including the endocannabinoid/endovanilloid system. Consequently, metamizole may have additive or even synergistic analgesic effects with paracetamol and nonsteroidal anti-inflammatory drugs (NSAID).

OBJECTIVE This study aimed to assess if triple therapy with metamizole, ibuprofen and paracetamol (MIP) is superior to double therapy with ibuprofen and paracetamol (i.p.) in treating pain at home after ambulatory arthroscopic shoulder surgery.

DESIGN/SETTING/PATIENTS/INTERVENTION In this double-blind, controlled, high-volume single centre, superiority trial, 110 patients undergoing elective ambulatory arthroscopic shoulder surgery were randomised to receive either MIP ($n = 55$) or i.p. ($n = 55$) orally for 4 days between December 2019 and November 2021. Pain intensity at movement and rest, using a numeric rating scale (NRS), perceived pain relief, use of rescue medication and adverse effects of study medication were recorded at the post-anaesthesia care unit (PACU) and on postoperative day (POD) 1 to 4 and 7. Quality of Recovery (QoR) and satisfaction with study medication were measured at POD 7 with telephone follow-up.

MAIN OUTCOME MEASURE The primary outcome measure was postoperative pain intensity on movement measured by an 11-point NRS (where 0 = no pain and 10 = worst pain imaginable) on POD 1.

RESULTS For the primary outcome, superiority of MIP in reducing postoperative pain at movement on POD 1 was not confirmed: mean difference NRS [95% confidence interval (CI), −0.08 (−1.00 to 0.84)]. For pain on movement and at rest, no significant differences were found between groups in the PACU nor on POD 1 to 4 or day 7. Nausea was reported significantly more frequently in the metamizole group (22.6 vs. 58.5.; $P < 0.001$). Other adverse effects of study medication, rescue opioid consumption, perceived pain relief, QoR at POD 7, and overall patient satisfaction were similar in both groups.

CONCLUSION Clinically, triple oral treatment with metamizole, paracetamol and ibuprofen is not superior to oral paracetamol and ibuprofen in multimodal pain treatment at home after ambulatory arthroscopic shoulder surgery.

TRIAL REGISTRATION European Union Clinical Trials Register 2019-002801-23 and Clinicaltrials.gov NCT04082728.

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KEY POINTS

- Triple oral treatment with metamizole, paracetamol and ibuprofen is not superior to oral paracetamol and ibuprofen in reducing postoperative pain at home after ambulatory surgery.
- Metamizole has no additive or synergistic analgesic effects in combination with paracetamol and NSAID.
- Nausea was reported more frequently in the metamizole group.
- Patients undergoing ambulant arthroscopic shoulder surgery still suffer from moderate-to-severe pain at movement during the first postoperative week despite multimodal analgesic treatment.
- Pain at rest is well treated with a combination of paracetamol, NSAID and rescue tramadol in patients undergoing ambulant arthroscopic shoulder surgery.

Introduction

Adequate postoperative analgesia should be considered to be a primary goal after day surgery, not only because prolonged postoperative pain at home results in patient discomfort but also because it may be associated with poor quality of recovery (QoR).[1]

Despite the implementation of multimodal analgesic regimens combining intra-operative opioids, paracetamol, weak opioids, nonsteroidal anti-inflammatory drugs (NSAID) and local anaesthetics, the prevalence of day surgery patients suffering from moderate-to-severe acute postoperative pain during the first 24 to 48 h at home remains high and varies from 9 to 40%.[2–7] More specifically, patients undergoing ambulatory arthroscopic shoulder surgery are at highest risk of developing moderate-to-severe pain.[8]

Single-shot interscalene block (ISB) of the brachial plexus is considered a gold standard regional anaesthesia technique for shoulder surgery.[9] Regrettably, it provides effective postoperative analgesia for only 6 to 12 h.[10] Thereafter, more than 45% of these patients report moderate-to-severe average pain at home during the entire first postoperative week despite multimodal treatment with paracetamol and ibuprofen or metamizole.[11] More importantly, it has also been demonstrated that a high postoperative pain level at postoperative day (POD) 4 after shoulder surgery is the best predictor for short-term (POD 7) and long-term (POD 28) poor to intermediate QoR.[1]

Clinicians try to avoid prescribing strong opioids at home after day surgery to avoid the risk of side effects and to avoid an opioid addiction.[12,13] Consequently, it is pivotal to expand the arsenal of nonopioid analgesics for pain relief at home after day surgery. Metamizole a nonopioid drug with strong analgesic, antipyretic and spasmolytic effects,[14] was first marketed in Germany in 1922.[15] There is growing evidence that the mechanism related to the analgesic effect of metamizole is complex but may rest on a dual mechanism that includes both the inhibition of cyclo-oxygenase enzyme activity and the stimulation of the endocannabinoid/endovanilloid system.[15–20] Consequently, metamizole may have additive or even synergistic analgesic effects with paracetamol and NSAID, the current gold standard for postoperative pain therapy, at the patient's home after painful ambulatory surgery. The combined analgesic efficacy of paracetamol, an NSAID and metamizole has not yet been studied. Therefore, the aim of this study was to assess if a combination of metamizole, ibuprofen and paracetamol was superior to a combination of ibuprofen and paracetamol in the treatment of acute postoperative pain at home after painful ambulatory arthroscopic shoulder surgery. We hypothesised that patients so treated would achieve better analgesia compared with those treated with paracetamol/ibuprofen because of an additive or even synergistic analgesic effect of metamizole with paracetamol/ibuprofen.

The Consolidated Standards of Reporting Trials (CONSORT) guidelines were followed in this study.

Materials and methods

Study design

This investigator-initiated, double-blind, randomised controlled, superiority trial was approved by the ethical committee of the JESSA Hospital Hasselt, Belgium (registration number 19.74/anesthesie19.01) on 9 September 2019, and by the European Union Drug Regulating Authorities Clinical Trials (EudraCT Number 2019-002801-23). It was registered on clinicaltrials.gov on 9 September 2019 (NCT04082728) and executed according to the Declaration of Helsinki.

After obtaining written informed consent, we recruited 110 consecutive ASA physical status I to III patients, aged 18 to 70 years scheduled for elective ambulatory arthroscopic shoulder surgery in a high volume institution (JESSA hospital, Hasselt, Belgium) between 2 December 2019, and 9 November 2021. Exclusion criteria included inpatient surgery, allergy to or a contraindication to the study medication (paracetamol, metamizole, ibuprofen or another NSAID), pregnancy or lactation, any kind of cognitive impairment or difficulty in understanding the Dutch language, chronic preoperative pharmacologic pain treatment and/or a history of chronic pain, a history of substance abuse or use of medication with a suppressive effect on the central nervous system, fever or other signs of infection and refusal of an interscalene nerve block. Patients undergoing Bankert shoulder repair or Superior Labrum, Anterior to Posterior (SLAP) tear

surgery were excluded because treatment with NSAID may negatively affect early tendon healing.

Interventions, blinding and randomisation

Patients were randomly assigned in a 1 : 1 ratio to either of the two study groups: an experimental group treated with a combination of metamizole, ibuprofen and paracetamol and a control group treated with standard pain treatment, ibuprofen and paracetamol. Depending on the study group, patients were instructed to take metamizole 1000 mg orally or a placebo three times a day for 4 days. All patients were instructed to take ibuprofen 600 mg orally three times a day for 4 days and paracetamol 1 g orally four times a day during the entire study period. The first dose of study medication, metamizole, ibuprofen, paracetamol (MIP), or placebo, ibuprofen and paracetamol (IP), was given 30 min before surgery. Rescue medication consisted of tramadol 50 mg orally up to three times a day if pain relief was not satisfactory. Patients were instructed to take their trial medication as prescribed and were provided with a detailed medication schedule. Furthermore, they were called by telephone daily and asked if they took their trial medication as prescribed.

A computer-generated random allocation sequence was performed by the study statistician to create the randomisation list. Each patient received a unique randomised test number corresponding to the specified drug, according to the group allocation. The randomisation list remained with the study statistician and the hospital pharmacy for the duration of the study. Hence, the patients participating in the trial, the researchers dispensing the medication and assessing outcomes (three study nurses), the treating physicians and the data managers were blinded for group allocation. The hospital pharmacy repackaged the study medication (Metamizole or placebo) into identical blister containers. Each container was numbered according to the randomisation list.

Peri-operative procedure

Before surgery, all study patients received an interscalene block. Following local practice, general anaesthesia was induced with i.v. alfentanil 10 $\mu g\,kg^{-1}$, sufentanil 0.15 $\mu g\,kg^{-1}$, propofol 2 $mg\,kg^{-1}$ and rocuronium 0.3 to 0.6 $mg\,kg^{-1}$. After endotracheal intubation, anaesthesia was maintained with sevoflurane in a mixture of air : oxygen, 50 : 50. Before the end of the surgery, ondansetron 4 mg was given to all patients. Two surgeons performed all arthroscopic shoulder procedures. The duration of surgery was recorded. Postoperatively, all patients were treated with subsequent bolus injections of i.v. piritramide 2 mg until an NRS 3 or less was achieved in the PACU. Before hospital discharge, patients received the study medication and instructions for use. Drop-out criteria included surgical complications leading to re-operation or unanticipated hospital admission.

Outcome measures

The primary outcome measure was postoperative pain intensity on movement measured by an 11-point NRS (where 0 = no pain and 10 = worst pain imaginable) on POD 1. Moderate postoperative pain is generally defined as an NRS greater than 3. A generally accepted cut-off point for severe postoperative pain is an NRS greater than 5.[21,22]

Secondary outcome measures were postoperative pain intensity at rest and on movement measured before discharge and on POD 2, 3, 4 and 7, total postoperative piritramide consumption in the PACU (mg), and the use of rescue medication (tramadol at home) on POD 1, 2, 3 and 4, the percentage of perceived pain relief by analgesic therapy on POD 1, 2, 3 and 4, adverse effects of study medication and adherence to the study medication protocol. These outcome measures were assessed by telephone call on POD 1, 2, 3, 4 and 7. Overall patient satisfaction with the study medication was assessed using an 11-point NRS scale (where 0 = not satisfied at all and 10 = extremely satisfied) by a phone call on POD 7. Quality of recovery was measured by the validated 1-item Global Surgical Recovery (GSR) index, and the EuroQol (EQ5D) questionnaire at baseline and on postoperative day 7. The GSR index represents a single question about the extent to which patients consider themselves to be recovered from the surgery with 0% indicating not recovered at all and 100% indicating a full recovery. Functional recovery of the shoulder was assessed with the simple shoulder test at baseline and on POD 7.[23]

Other baseline assessment measurements included the participants' age, sex, BMI, ASA classification, work status, the highest level of education, fear of the surgical procedure (using an eight-item surgical fear questionnaire),[24,25] expected pain (NRS-score) and the history of (related) surgery.

Safety measures

Possible adverse effects of study medication were explained thoroughly to all patients included in this study. All participants were questioned about adverse events by telephone call on days 1, 2, 3, 4, 7, 14 and 28 postoperatively. Patients were specifically asked whether they experienced postoperative nausea and vomiting, dizziness, headache, fatigue, acid reflux or stomach ache, constipation, anaphylaxis, fever, chills, mouth ulcers, a sore throat or signs of infection, dyspnoea, petechiae and bleeding diathesis. Patients were instructed to immediately contact a research assistant by phone if they experienced any sign of infection and/or a bleeding diathesis. A complete blood count would then be performed to exclude thrombocytopaenia, leucopaenia or anaemia and trial medication would be withdrawn.

Statistical analysis

On the basis of a previous study, we assumed a mean NRS pain score on movement of 5.9 on POD 1 with a

standard deviation of 2.2 in the control group.[11] A difference in mean NRS-score of 1.3 points or more is considered superior.[26] Based on these assumptions, the required sample size to reject the superiority of the experimental treatment was consequently determined to be at least 45 patients for each group to have a power of 80% ($\alpha = 0.05$). The sample size was inflated to 55 participants per group (110 in total) to account for a possible 22% loss-to-follow-up.

All primary and secondary endpoints were analysed on an intention-to-treat (ITT) basis according to a superiority design. To determine superiority for the difference in mean NRS pain score on movement on POD 1, we computed 95% confidence intervals. Secondary outcome measures were analysed with the Student's *t*-test for normally distributed data, the Mann Whitney *U* test in case of nonnormal distributed data, and the Pearson's χ^2 test or the Fisher's exact test (in case of an observed count <10) for categorical data. All analyses were performed using SPSS version 27. Graphs were made using Prism 7.0 (Prism; GraphPad Software, Inc, La Jolla, California, USA).

Results

A Consort flow chart of patient inclusion and exclusion is shown in Fig. 1. In total, 226 patients were screened for eligibility, of which 116 patients were excluded because of refusal to participate ($n = 27$), not meeting the inclusion criteria ($n = 87$) or other reasons ($n = 2$).

The baseline and peri-operative characteristics of all included patients are presented in Table 1. No significant differences were observed between the two groups.

Figure 2a shows the median postoperative pain scores on movement before discharge and on POD 1 to 4 and 7. Figure 2b shows the median postoperative pain scores at rest before discharge and on POD 1 to 4 and 7.

For the primary outcome, superiority of MIP in reducing postoperative pain on movement on POD 1 was not confirmed [mean difference (95% CI), −0.08 (−1.00 to 0.84), Fig. 3]. No significant differences in pain on movement or at rest in the PACU and on POD1 to 4 and POD7 between the control and metamizole groups were found.

Patients in the metamizole group reported similar levels of pain relief from analgesic pain medication on POD1, 70 (32.5%) vs. 70 (20%), $P = 0.19$), POD2, 80 (30%) vs. 80 (20%), $P = 0.67$), POD3, 80 (20%) vs. 80 (35%), $P = 0.58$) and POD4, 80 (20%) vs. 80 (25%) compared with the control group.

Only two patients in the control group and one patient in the metamizole group received 3 to 4 mg of i.v. piritramide in the PACU. There was no significant difference between treatment groups for the amount of piritramide administered ($P = 0.59$).

The use of rescue medication was reported by 22 patients (40.7%) in the metamizole group and 21 patients (38.9%) in the control group on POD 1 ($P = 0.84$), 17 patients (31.5%) in the metamizole group and 19 patients (35.2%) in the control group on POD 2 ($P = 0.68$), 12 patients (22.2%) in the metamizole group and 14 patients (25.4%) in the control group on POD 3 ($P = 0.69$) and 8 patients (14.8%) in the metamizole group and 11 patients (20.0%) in the control group on POD 4 ($P = 0.47$). Patient-reported adverse effects of the study medication are presented in Table 2. Patients in the metamizole group suffered significantly more from nausea compared with the control group, other adverse effects were not significantly different between treatment groups. In addition, no agranulocytosis or other serious adverse effects of the study medication were observed during the study period.

No significant difference was found in the QoR, measured by the GSR index: metamizole group: 78.2 ± 11.7 vs. control group: 77.3 ± 15.8, $P = 0.62$, and the EQ5D: metamizole group: 0.74 [0.66 to 0.82] vs. control group: 0.72 [0.57 to 0.76], $P = 0.06$, between both groups at POD7 nor in the functional recovery of the shoulder at POD 7 measured by the simple shoulder test: metamizole group: 3.0 [1.0 to 3.7] vs. control group: 2.0 [1.0 to 4], $P = 0.82$. The adherence to study medication is presented in Table 3.

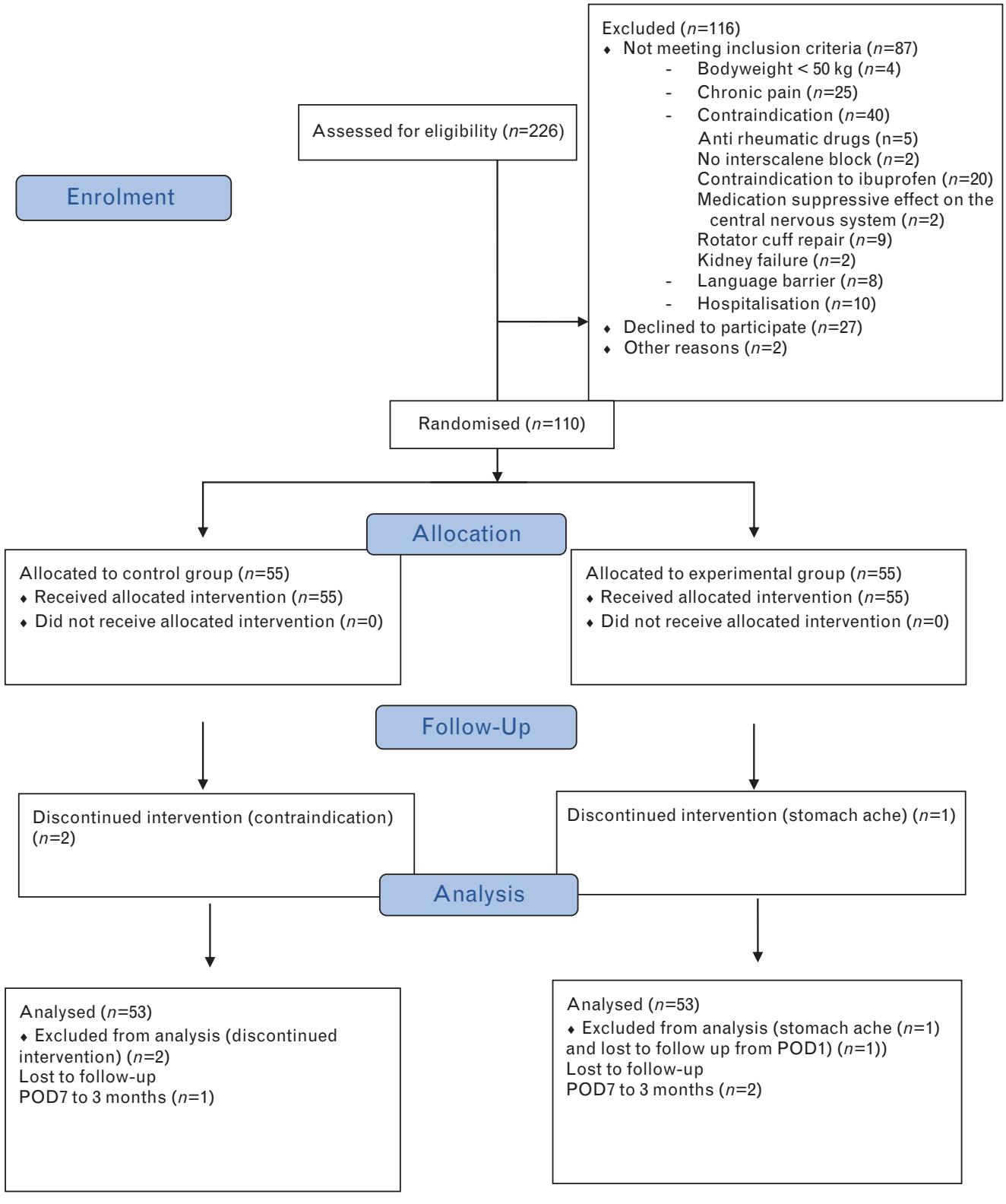
Patient satisfaction with the study medication was not significantly different between treatment groups ($P = 1.00$) with a median score of 9.00 [8 to 10] for the metamizole group and 9.00 [8 to 10] for the control group on POD7.

Discussion

We have failed to demonstrate analgesic superiority of triple oral treatment with metamizole, paracetamol and ibuprofen compared with the standard oral treatment of paracetamol and ibuprofen in the first 4 days at home after ambulatory arthroscopic shoulder surgery. Similarly, intake of oral rescue analgesics at home on POD 1 to 4 and the level of perceived pain relief by analgesic medication was not significantly different between treatment groups. Adherence to study medication and overall patient satisfaction were high and comparable in both groups. Nausea was reported more frequently in the metamizole group. Other patient-reported adverse effects of study medication and QoR measured by the 1-item Global Surgical Recovery (GSR) index, the EuroQol (EQ5D) questionnaire and the simple shoulder test on POD 7 were not significantly different between the two groups. No serious adverse effects of the study medication were reported during the study duration of 3 months.

Combined use of analgesics with different modes of action may result in an additive or even a synergistic analgesic effect [27] and forms the basis of the success of multimodal analgesic strategies in the opioid-sparing

Fig. 1 CONSORT flow chart.



POD, postoperative day.

Table 1 Baseline and perioperative characteristics

	Control group ($n = 55$)	Metamizole group ($n = 55$)	*P*
Age (years)	50.7 ± 11.0	51.1 ± 11.3	0.88
BMI (kg m^{-2})	27.4 ± 3.8	26.8 ± 5.2	0.49
Gender (male/female)	28 (50.9) /27(49.1)	20 (36.4) / 35 (63.6)	0.12
ASA classification			1.00
I	50 (90.9)	50 (90.9)	
II	5 (9.1)	5 (9.1)	
Work status			0.40
Paid work	39 (70.9)	38 (69.1)	
Volunteer	1 (1.8)	2 (3.6)	
Unemployed	1 (1.8)	2 (3.6)	
Sick leave	6 (10.9)	5 (9.1)	
Retired	7 (12.8)	8 (14.6)	
Student	1 (1.8)	0 (0.0)	
Education			0.49
Elementary school	1 (1.8)	2 (3.6)	
Junior Secondary school	2 (3.6)	2 (3.6)	
Upper secondary education	33 (61.1)	35 (63.7)	
Higher education	15 (26.2)	16 (29.1)	
University	3 (5.5)	0 (0.0)	
Missing data	1 (1.8)	0 (0.0)	
Operation last year? (yes/no)	11/43	13/42	0.68
Related?	4/50	5/50	
Missing data	1 (1.8)	0 (0.0)	
Short term Surgical Fear	14.0 [5.0 to 24.0]	10.0 [3.0 to 18.0]	0.26
Long term Surgical Fear	9.5 [2.0 to 16.0]	8 [4.0 to 13.0]	0.62
GSR	78.0 ± 10.3	76.5 ± 12.0	0.48
EQ5D index	0.80 [0.65 to 0.84]	0.74 [0.62 to 0.82]	0.36
Missing data	0 (0.0)	1 (1.8)	
Pain (NRS)			
Preoperative pain	7.0 [5.0 to 8.0]	7.0 [5.7 to 8.0]	0.57
Influence pain daily activities	6.0 [5.0 to 8.0]	7.0 [5.0 to 8.0]	0.22
Expected pain after surgery	6.0 [3.0 to 8.0]	5.0 [2.0 to 7.0]	0.65
Missing data	0 (0.0)	1 (1.8)	
Simple Shoulder Test	5.0 [3.0 to 8.0]	5.0 [3.0 to 7.0]	0.36
Duration of surgery (minutes)	53.0 [46.0 to 62.0]	57.0 [45.7 to 70.2]	0.27

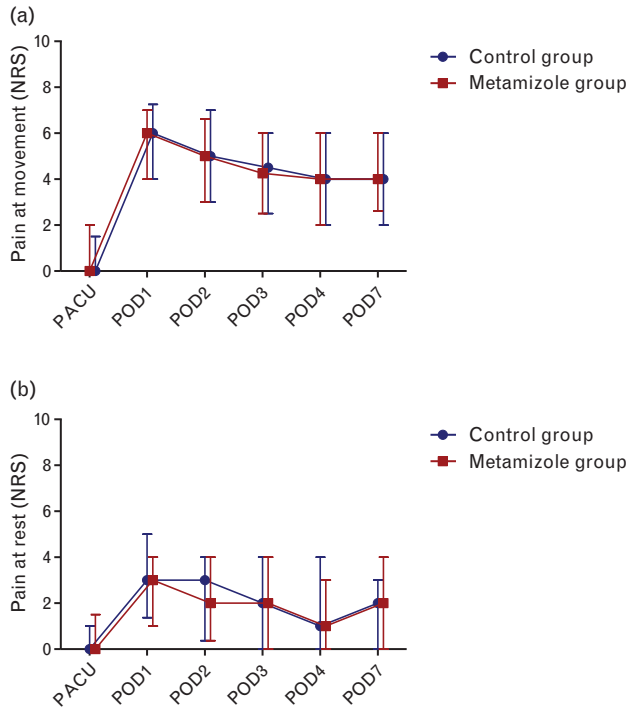
Data are expressed as mean ± SD, median [IQR], number, or number (%). A difference between the groups was analysed with a Student *t* test or a Mann Whitney U test as appropriate. $P < 0.05$ was considered statistically significant. BMI, Body Mass Index; ASA, American Society of Anesthesiologists; GSR, Global Surgical Recovery; NRS, Numerical Rating Scale, EQ5D, Euro Quality of Life

treatment of acute postoperative pain.[28] Despite its widespread use over more than a century, the mechanisms mediating the analgesic effects of metamizole have not been fully elucidated.[29] Metamizole is a pyrazoline derivate and a prodrug characterised by immediate metabolism after oral administration to its active metabolites 4-methyl-amino-antipyrine (MAA) and 4-amino-antipyrine (AA).[18,19] In animal studies, both metabolites were positively tested for cyclo-oxygenase inhibition (COX-1 and COX-2) and cannabis receptor binding (CB1 and CB2) suggesting a dual mechanism of analgesic action.[15] In contrast, another animal study found that concomitant administration of a CB1 receptor antagonist did not alter the antinociceptive effect of metamizole suggesting that cannabinoid CB1 receptors do not participate in its antinociceptive action.[30] The absence of an observable additive analgesic effect of metamizole in combination with paracetamol and ibuprofen in this study also contradicts the current view that central mechanisms including the endocannabinoid/endovanilloid system play a significant role in the analgesic action of metamizole in humans. The results of our study may be explained by the proposition that a major portion of the analgesic action of metamizole is because of peripheral COX suppression in humans. Indeed, assessment of ex-vivo COX inhibition revealed profound COX-1 and COX-2 inhibition in the whole blood of human volunteers.[31]

We found median pain levels on movement and at rest were zero in both treatment groups on POD 0 in the PACU because of the excellent analgesic effect provided by the single-shot ISB. After the ISB wore off, median pain levels on movement rose and remained moderate-to-severe during the entire first postoperative week despite the multimodal oral analgesic approach for pain relief at home. Median pain levels at rest were within acceptable limits in both groups during the whole study period.

These results are in agreement with recent reports. A secondary analysis of data from a large randomised trial comparing the analgesic efficacy of metamizole and ibuprofen orally at home in patients undergoing ambulatory haemorrhoid surgery, arthroscopic shoulder or knee surgery, or inguinal hernia repair,[32] showed that mean pain scores on movement were highest during the first 3 POD after shoulder arthroscopy (NRS >5, indicating severe pain).[11] This study also noted that mean pain

Fig. 2 Display of the median, 25th and 75th percentiles of numerical pain scores on movement (a) and at rest (b) in the post-anaesthesia care unit (PACU) and on POD1 to 4 and POD7.

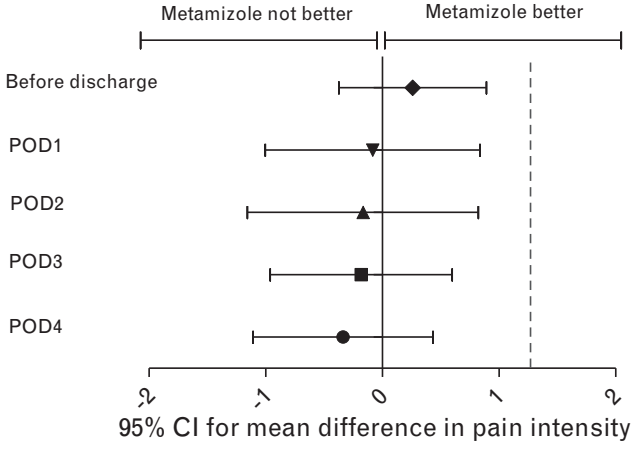


levels at rest were NRS less than 3 during the whole study period.[11]

Rebound pain after peripheral nerve block for ambulatory surgery is defined as the transition from well controlled pain (NRS <3) while the block is working to severe pain (NRS >5) within 24 h of block performance.[33] In a large retrospective cohort study, rebound pain was reported by almost 50% of ambulatory patients treated with peripheral nerve block.[33] Nonetheless, there were high rates of patient satisfaction (83.2%) and return to daily activities (96.6%), indicating a rather limited impact on quality of life.[33] Therefore, we speculate that high rebound pain levels reported in the former study mainly reflect pain intensity at movement in contrast to pain at rest.

This study has some limitations. First, the study was not powered for secondary outcomes including adverse effects. Hence, no firm conclusions can be drawn on medication safety. Second, due to strict exclusion criteria, only 50% of patients screened for eligibility were included in the study. Furthermore, only one type of painful ambulatory surgery was selected in this study to create more homogeneous groups because every type of surgery has its own unique postoperative pain profile, which may influence the study outcome. The downside of these strict inclusion and exclusion criteria is that the

Fig. 3 Evaluation of the superiority of analgesic efficacy of the metamizole group vs. control group.



The difference in mean average numerical rating scores for pain at movement between the metamizole group vs control group and the resulting 95% confidence intervals (CI) are shown for the different time points. A difference in mean numerical rating score (NRS) of 1.3 point or more is considered superior.

Table 2 Patient-reported adverse effects of study medication

	Control group ($n = 53$)	Metamizole group ($n = 53$)	*P*
Nausea	12 (22.6%)	31 (58.5%)	**<0.001**
Vomiting	1 (1.8%)	2 (3.7%)	0.56
Stomach ache	15 (28.3%)	22 (41.5%)	0.10
Constipation	7 (13.2%)	9 (17.0%)	0.78
Dizziness	2 (3.7%)	2 (3.7%)	1.00
Headache	2 (3.7%)	0 (0.0%)	0.56
Fatigue	1 (1.8%)	0 (0.0%)	0.32
Fever	0 (0.0%)	1 (1.8%)	0.32
Dyspnoea	0 (0.0%)	1 (1.8%)	0.32

Data are expressed as number of patients (%). A difference between the groups was analysed with a χ^2 test. A *P* less than 0.05 is considered statistically significant.

Table 3 Adherence to study medication

	Control group ($n = 54$)	Metamizole group ($n = 54$)	*P*
POD1			
Paracetamol	54 (100%)	51 (94.4%)	0.07
Ibuprofen	53 (98.1%)	50 (92.6%)	0.17
Study medication	54 (100%)	51 (94.54%)	0.07
POD2			
Paracetamol	48 (88.9%)	46 (85.2%)	0.56
Ibuprofen	47 (87.0%)	44 (81.5%)	0.43
Study medication	48 (88.9%)	46 (85.2%)	0.57
POD3			
Paracetamol	47 (87.0%)	46 (85.2%)	0.97
Ibuprofen	49 (90.7%)	42 (77.8%)	0.11
Study medication	48 (88.9%)	43 (79.6%)	0.28
POD4			
Paracetamol	44 (81.5%)	43 (79.6%)	0.96
Ibuprofen	46 (85.2%)	43 (79.6%)	0.59
Study medication	47 (87.0%)	43 (79.6%)	0.42

Data are expressed as number of patients (%). A difference between the groups was analysed with a χ^2 test. A *P* less than 0.05 is considered statistically significant. POD, postoperative day.

generalisability of our results can be questioned and is limited to our patient selection and ambulatory arthroscopic shoulder surgery.

Conclusion

In conclusion, triple oral treatment with metamizole, paracetamol and ibuprofen is not clinically superior to standard oral treatment with paracetamol and ibuprofen in multimodal pain treatment at home after ambulatory arthroscopic shoulder surgery. Therefore, we cannot confirm the hypothesis that metamizole has additive or even synergistic analgesic effects when combined with paracetamol and NSAID.

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