Summary in English (Streszczenie w języku angielskim)

PhD dissertation title:

"Comparison of two therapeutic regimens for pain management using metamizole in patients undergoing maxillary sinus surgery under combined anaesthesia".

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Introduction

Contemporary perioperative pain management incorporates the concept of multimodal analgesia, which utilises analgesics and co-analgesics with different mechanisms of action, as well as regional anaesthetic techniques, to increase the effectiveness of therapy and reduce the risk of adverse effects.

Pre-emptive analgesia involves administering an analgesic and/or adjuvant before the onset of a nociceptive stimulus and aims to limit the adverse physiological consequences of surgical injury by preventing the sensitisation of the nervous system. There are controversies regarding the clinical effectiveness of pre-emptive analgesia. Therefore, a broader therapeutic strategy, known as preventive analgesia, has been adopted, prioritising the maintenance of pain control throughout the perioperative period. This broader approach is implemented within the framework of multimodal analgesia as 'preventive multimodal treatment' and represents a more comprehensive approach than pre-emptive analgesia alone. Non-opioid analgesics are commonly used as an adjunct to general anaesthesia with opioids.

Metamizole, a potent non-opioid analgesic, is also included in perioperative analgesia regimens, but the data available in the literature on its use in pre-emptive analgesia are limited and inconsistent.

Monitoring homeostasis in patients under general anaesthesia is a key issue in clinical practice. Accurate assessment of nociception, alongside the control of haemodynamic and respiratory stability during general anaesthesia, represents a significant challenge in modern

anaesthesiology. The introduction of dedicated nociception-monitoring methods into clinical practice offers the potential to optimise intraoperative analgesia, thereby reducing the risk of complications associated with inaccurate dosing of analgesic agents. Numerous commercial prototype devices have been evaluated regarding their utility in nociception monitoring.

The ANI (Analgesia Nociception Index) monitor, developed by a team of French researchers (MetroDoloris, Mdoloris Medical Systems, Lille, France), enables intraoperative indirect measurement of nociception based on a standardised ANI parameter calculated in real time from heart rate variability (HRV) analysis. The ANI is expressed on a dimensionless scale from 0 to 100, with higher values reflecting a predominance of parasympathetic over sympathetic activity, which corresponds to lower levels of nociception.

Aim of the study

This study aimed to evaluate the use of metamizole for acute pain management in patients undergoing maxillary sinus surgery (Caldwell–Luc antrostomy and maxillary reconstructive surgery) under combined general anaesthesia using total intravenous anaesthesia (TIVA-MCI) with remifentanil and propofol, supplemented with lidocaine infiltration anaesthesia at the surgical site.

Research hypotheses

1. The use of metamizole in a pre-emptive analgesia regimen reduces intraoperative nociception.
2. The use of metamizole in a pre-emptive analgesia regimen reduces pain intensity in the immediate postoperative period.

Research objectives

1. Assessment of pre-emptive metamizole administration on the level of analgesia, indirectly measured using the ANI parameter during surgery and anaesthesia.
2. Evaluation of the impact of pre-emptive metamizole administration on haemodynamic parameters: heart rate (HR) and arterial blood pressure (SBP, DBP, MAP) during surgery and anaesthesia.

3. Assessment of the influence of pre-emptive metamizole administration on the depth of anaesthesia, measured indirectly using the Bispectral Index (BIS) parameter.
4. Evaluation of the correlation between the tested parameters (HR, MAP, ANI, BIS) in the study and control groups during surgery and anaesthesia.
5. Comparative assessment of remifentanil and propofol dosing between the study and control groups.
6. Assessment of the correlation between the ANI parameter and the NRS and VAS scores immediately post-operatively in the study and control groups.
7. Evaluation of pre-emptive metamizole administration on the intensity of pain measured using the NRS and VAS scales after surgery.
8. Assessment of the correlation between NRS and VAS scores post-operatively in the study and control groups.

Patients and Methods

After obtaining a positive opinion from the Bioethics Committee of the Medical University of Warsaw (KB/186/2013), a prospective, randomised study was conducted in fifty-nine patients (N = 59) undergoing elective maxillary sinus surgery under combined general anaesthesia using a total intravenous anaesthesia–manual controlled infusion (TIVA–MCI) technique with propofol and remifentanil, combined with local infiltration anaesthesia of the surgical field using lidocaine. According to the randomisation list, patients were allocated to two groups.

The study group (G1, n = 30) comprised patients who received intravenous metamizole 1.0 in 100 ml of saline solution (0.9% NaCl) in a 5-minute infusion as part of a pre-emptive analgesia regimen 10 minutes before surgery, whereas the control group (G2, n = 29) comprised patients who received intravenous metamizole 1.0 in 100 ml of saline solution administered as a 5-minute infusion after the completion of general anaesthesia.

In this study, nociception during anaesthesia and surgery was assessed indirectly using the Analgesia Nociception Index (ANI) monitor (MetroDoloris, Lille, France). Patients' haemodynamic status was monitored using heart rate (HR) derived from electrocardiogram recordings, as well as values of blood pressure (SBP, DBP, and MAP) measured using a non-invasive intermittent method. The depth of anaesthesia was evaluated based on the

bioelectrical activity of the brain using the bispectral index (BIS™). Postoperative pain was assessed using two scales: the Numerical Rating Scale (NRS) and the Visual Analogue Scale (VAS). The study was conducted over a period of 25 months.

Statistical analysis was performed on data from 58 patients (N = 58; G1 n = 30; G2, n = 28) using SPSS v.29 and Statistica v.13.3. Comparisons of the studied parameters and analyses of their correlations within the groups were conducted using tests appropriate for the data type. The significance level was set at $\alpha = 0.05$. Results were considered statistically significant if the p-value was less than or equal to this threshold. The study evaluated the effects of metamizole administered as part of a pre-emptive analgesia regimen on the parameters outlined in the research questions.

Results

Statistical analysis was performed on the results obtained from 58 patients. No significant differences were observed between the groups with respect to sex, age, height, weight, BMI, or ASA physical status classification. Similarly, there were no differences between the groups in terms of the duration of anaesthesia and surgery, or the type of surgical procedure.

The most significant results are summarised below:

1. Intravenously administered metamizole within a pre-emptive analgesia regimen reduced ANI values by 6-7 points during surgery in the study group. No statistically significant differences were found between the groups.
2. Intravenously administered metamizole within a pre-emptive analgesia regimen resulted in a decrease of the mean heart rate by approximately 3 beats per minute after mucous incision and reduced arterial blood pressure values (SBP, DBP, MAP) after induction of anaesthesia in the study group. The differences between the groups were approximately 5, 9, and 7 mmHg, respectively. No statistically significant differences were observed between the groups.
3. Intravenously administered metamizole within a pre-emptive analgesia regimen was associated with a smaller decrease in the BIS parameter after induction of anesthesia in the study group. A statistically significant difference of 8 points between the groups was observed (p = 0.008), with a size effect close to large (d = 0.724).

4. Analysis of the time-normalised area under the curve ($AUC_{t\text{-}norm}$) for repeated intraoperative measurements of the studied variables (HR, SBP, DBP, MAP, ANI, BIS) revealed no statistically significant differences between groups.
5. High negative correlations were observed for HR/ANI in the control group and moderate negative correlations in the study group during anaesthesia and surgery. Furthermore, a moderate negative correlation was found for MAP/ANI in the control group and a very weak negative correlation in the study group. No statistically significant differences were found between the groups.
6. Dosing of propofol and remifentanil did not differ between the groups.
7. A moderate correlation between ANI and NRS and a weak correlation between ANI and VAS were found in the study group, along with weak correlations: ANI/NRS and ANI/ VAS in the control group immediately post-operatively. The results were not statistically significant.
8. Pain intensity measured using the NRS and VAS scales immediately after surgery did not decrease in patients receiving metamizole within a pre-emptive analgesia regimen.
9. Intravenously administered metamizole within a post-operative analgesia regimen was associated with a small reduction in pain intensity on the NRS scale immediately after surgery in the control group. The result was not statistically significant.
10. A high correlation between the NRS and VAS scales was found in the post-operative period. No differences were observed between the groups.

Conclusions

1. Administration of metamizole within a pre-emptive analgesia regimen in patients undergoing maxillary sinus surgery in combined general anaesthesia was associated with a decrease in ANI values. However, the lack of significant differences between the groups suggests that the drug had no substantial effect on intraoperative nociception levels. A potential confounding influence of the drug on ANI measurements cannot be excluded.
2. Metamizole, administered intravenously as part of a pre-emptive analgesia regimen, reduced average heart rate values during the operation and anaesthesia and arterial blood pressure following the induction of anaesthesia. Nevertheless, the absence of significant

inter-group differences indicates that this regimen did not significantly impact the patients' haemodynamic stability.

3. The use of metamizole for preemptive analgesia, which led to differences in BIS values after induction of anaesthesia, may have influenced anaesthetic requirements during the initial phase. However, this did not result in differences in total anaesthetic dosage between groups. A confounding effect of the drug on BIS readings cannot be ruled out.
4. The use of metamizole for preemptive analgesia did not significantly affect the course of anaesthesia, as assessed by repeated intraoperative measurements of the parameters across groups ($AUC_{t\text{-}norm}$).
5. In both study groups, correlations were demonstrated between haemodynamic parameters and the ANI, confirming the complex nature of the relationship between nociception and the autonomic nervous system response, despite the lack of significant differences between the analgesia strategies.
6. The use of metamizole within a pre-emptive analgesia regimen did not result in a reduction in propofol and remifentanil requirements during general anaesthesia.
7. The ANI parameter measured immediately post-operatively has limited clinical utility as an indicator of post-operative pain intensity.
8. Administration of metamizole, as part of a pre-emptive analgesia regimen, did not reduce pain intensity, measured with NRS and VAS scales, immediately after surgery in the study group.
9. The reduction in pain severity observed in patients receiving metamizole immediately after surgery may indicate the potential benefits of this therapeutic regimen.
10. A high correlation was demonstrated between the NRS and VAS scales in the post-operative period, confirming their high consistency in post-operative pain assessment and equivalent clinical value within the study population.

Final conclusion

The results obtained do not confirm the proposed hypotheses that metamizole used within a pre-emptive analgesia regimen significantly reduces intraoperative nociception and the intensity of pain in the immediate postoperative period.

Summary

Based on the obtained results, it was not possible to clearly determine the validity of using metamizole as part of a pre-emptive analgesia regimen for maxillary sinus procedures under combined anaesthesia. The nociception measurement method (ANI) indicated a negative correlation between the level of analgesia and the drug's administration as part of the pre-emptive analgesia regimen. Therefore, the assumption that ANI monitoring accurately reflects the effect of metamizole on analgesia is questionable, considering the drug's known analgesic properties.

Furthermore, metamizole administered as part of the pre-emptive analgesia regimen did not reduce pain levels in the immediate postoperative period. However, the reduction in pain intensity observed in patients receiving the drug immediately after surgery indicates the potential benefits of this therapeutic regimen. The decrease in blood pressure observed after metamizole administration following induction of anaesthesia is consistent with previously reported data. To avoid this effect, it may be advisable to reduce the dose of the induction agent or to withhold metamizole when using a preemptive analgesia regimen. The detected weakening of the correlations between ANI and HR, and between ANI and MAP, in the study group suggests that metamizole may alter the natural associations between the studied parameters during the intraoperative period, potentially reflecting the drug's mechanism of action.

The study has several limitations that should be taken into account when interpreting the findings. The collected data do not allow for the clear exclusion of the influence of metamizole on the reliability of intraoperative parameters of monitoring nociception (ANI) and depth of anaesthesia (BIS). The study was conducted on a relatively small sample size of patients, which constitutes a substantial risk factor for bias. The relatively small sample size reduced the statistical power of the study, especially with regard to detecting subtle differences between groups in the parameters assessed. Moreover, the investigation was performed at a single clinical centre, potentially limiting the generalisability of the results to other patient populations undergoing different surgical procedures or anaesthetic techniques. Intraoperative nociception in this study was evaluated indirectly using the ANI parameter, which is not a direct measure of nociception and may be influenced by other factors unrelated to painful stimuli. The use of lidocaine for local infiltration anaesthesia at the surgical site

may have reduced the intensity of nociceptive stimuli, potentially masking differences resulting from pre-emptive analgesia with metamizole. Postoperative pain assessment was based on subjective scales (NRS, VAS), which also represent a potential source of measurement error. In addition, postoperative pain assessment was limited to the immediate postoperative period, preventing conclusions regarding the long-term effects of metamizole on postoperative pain control. The study did not include measurements of metamizole or its metabolites, making it impossible to analyse pharmacokinetic–pharmacodynamic relationships.

The results suggest that routine use of metamizole in a pre-emptive analgesia regimen in patients undergoing maxillary sinus surgery under combined anaesthesia does not provide significant clinical benefits in terms of reducing intraoperative nociception or postoperative pain. Administration of metamizole after the completion of general anaesthesia appears to be comparable in analgesic efficacy to its use before the procedure, which may simplify analgesic protocols. The results indicate that the ANI parameter, despite its usefulness in monitoring autonomic responses, is not a sufficient indicator for assessing postoperative pain intensity, and its interpretation should always be complemented by the patient's subjective assessment. The study highlights the importance of multimodal postoperative analgesia, in which metamizole may serve as an adjunctive agent but not a key component of a pre-emptive analgesia strategy. Further studies are warranted involving larger patient groups, a variety of surgical procedures, and extended follow-up periods to validate these findings, enhance their statistical power, and facilitate generalisation to wider patient populations. Such investigations are necessary to provide a definitive assessment of the potential benefits of pre-emptive analgesia with metamizole.