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Efficacy and safety of multimodal analgesia based on bolus versus continuous infusion of nonsteroidal anti-inflammatory drugs: a meta-analysis of randomized controlled trials

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Abstract

INTRODUCTION: Multimodal analgesia is a key component of enhanced recovery after surgery protocols, with nonsteroidal anti-inflammatory drugs (NSAIDs) playing a central role in pain management. However, the optimal method of administration — bolus versus continuous/prolonged infusion — remains a subject of ongoing debate. **OBJECTIVES:** This meta-analysis aims to compare the efficacy and safety of these two NSAID administration approaches in the postoperative setting. **MATERIALS AND METHODS**: A systematic literature search was conducted in PubMed, Cochrane CENTRAL and other sources up to March 2024. Only randomized controlled trials (RCTs) comparing continuous NSAID infusion (≥ 6 hours) with bolus administration in adult postoperative patients were included. The primary outcome was total opioid consumption; secondary outcomes included pain intensity (6–48 hours), incidence of postoperative nausea and vomiting, respiratory depression, and need for rescue analgesia. Statistical analysis was performed using STATA 18.0, applying a random-effects model with assessment of heterogeneity (I^2) and publication bias (Egger's test). The protocol was registered in INPLASY (INPLASY202550045). **RESULTS**: Of the 343 publications screened, six RCTs (n = 462) met the inclusion criteria. No significant differences were observed between the continuous infusion and bolus administration

Эффективность и безопасность мультимодальной анальгезии на основе болюсного против продленного введения нестероидных противовоспалительных препаратов: метаанализ рандомизированных контролируемых исследований

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Реферат

АКТУАЛЬНОСТЬ: Мультимодальная анальгезия является важным компонентом протоколов ускоренного восстановления после хирургического вмешательства. Нестероидные противовоспалительные препараты (НПВП) играют в ней ключевую роль, однако оптимальный способ их введения (болюсное введение или продленная инфузия [ПИ]) остается предметом дискуссий. **ЦЕЛЬ ИССЛЕДОВАНИЯ:** Цель настоящего метаанализа — сравнить эффективность и безопасность этих двух методов в послеоперационный период. **МАТЕРИАЛЫ И МЕТОДЫ**: Систематический поиск был проведен в базах данных PubMed, Cochrane CENTRAL и других источниках до марта 2024 г. В метаанализ включены только рандомизированные контролируемые исследования (РКИ), сравнивающие ПИ НПВП (≥ 6 ч) и болюсное введение у взрослых пациентов. Основной исход — потребление опиоидов, вторичные исходы — уровень боли (6–48 ч), частота послеоперационной тошноты/рвоты, угнетение дыхания, потребность в дополнительной анальгезии. Анализ проводился в STATA 18.0 с использованием модели случайных эффектов, оценкой гетерогенности (I^2) и смещения публикаций (тест Эггера). Протокол зарегистрирован INPLASY202550045. **РЕЗУЛЬТАТЫ**: Из 343 опубликованных исследований в метаанализ

groups regarding opioid consumption (standardized mean difference [SMD] — –0.35; $p = 0.219$), pain scores, nausea, or respiratory depression. However, the need for additional analgesia was significantly higher in the infusion group (relative risk — RR) — 3.74; $p < 0.001$). Most studies had a moderate to high risk of bias. According to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, the certainty of the evidence was low to very low. **CONCLUSIONS**: Despite theoretical pharmacokinetic advantages, continuous NSAID infusion did not show clinical superiority over bolus administration. Both methods can be used in multimodal analgesia, but the choice should consider individual patient needs and institutional resources. Further high-quality, multicenter RCTs are warranted.

KEYWORDS: anti-inflammatory agents, non-steroidal, pain, postoperative, analgesia, drug administration routes, meta-analysis

REGISTRATION OF THE STUDY: The study protocol is registered with International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY), reference ID: INPLASY202550045

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было включено 6 РКИ ($n = 462$). Не было выявлено значительных различий между группами ПИ и болюсного введения по общему потреблению опиоидов (стандартизированная средняя разница [standardized mean difference — SMD] — –0,35; $p = 0,219$), уровню боли, частоте тошноты или угнетению дыхания. Однако потребность в дополнительной анальгезии была значительно выше в группе с ПИ НПВП (относительный риск [relative risk — RR] — 3,74; $p < 0,001$). У большинства исследований был умеренный или высокий риск систематической ошибки. Согласно подходу Grading of Recommendations Assessment, Development and Evaluation (GRADE), уровень доказательств был оценен как низкий или очень низкий. **ВЫВОДЫ:** Продленная инфузия НПВП не продемонстрировала клинических преимуществ по сравнению с болюсным введением. Оба метода могут быть использованы в рамках мультимодальной анальгезии, однако выбор метода следует делать с учетом индивидуальных характеристик пациента и организационных возможностей учреждения. Для окончательных выводов необходимы новые высококачественные многоцентровые РКИ.

КЛЮЧЕВЫЕ СЛОВА: нестероидные противовоспалительные препараты, послеоперационная анальгезия, продленная инфузия, болюсное введение, мультимодальная анальгезия, метаанализ, рандомизированные контролируемые исследования

РЕГИСТРАЦИЯ ИССЛЕДОВАНИЯ: Протокол зарегистрирован на международной платформе протоколов систематических обзоров и метаанализов (INPLASY), регистрационный номер INPLASY202550045

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Introduction

At present, there is little doubt regarding the efficacy and safety of enhanced recovery after surgery (ERAS) programs, which protocols have been firmly established as an essential component in most clinical guidelines on perioperative patient management [1, 2]. Among other elements, effective, well-controlled multimodal analgesia plays an essential role in ensuring early postoperative mobilization [3]. The disadvantages of opioid-based postoperative analgesia are well recognized [4, 5], and thus the widespread adoption of opioid-sparing multimodal strategies is virtually uncontroversial [6–9]. Within this context, nonsteroidal anti-inflammatory drugs (NSAIDs) occupy a central role, particularly in the management of postoperative visceral pain, forming the cornerstone of multimodal analgesic regimens [10–12].

The antinociceptive effects of NSAIDs are mediated through inhibition of cyclooxygenase activity, resulting in reduced synthesis of prostaglandin — key mediators of inflammation and nociceptor sensitization [13]. NSAIDs have both peripheral and central analgesic effects, rendering them highly effective in the setting of surgical trauma. Certain agents, such as ketorolac, demonstrate multiple mechanisms of action, including inhibition of both cyclooxygenase and lipoxygenase pathways, thereby reducing prostaglandin and leukotriene synthesis, as well as stimulating the release of endogenous opioids, which further enhances their analgesic effect [14, 15].

The efficacy of NSAIDs as part of postoperative pain management appears to vary by type of surgical intervention: while consistent benefits have been demonstrated in orthopedic procedures [16, 17], the effectiveness in abdominal surgery seems less pronounced [18].

The postoperative clinical efficacy of NSAIDs may be determined not only by the type of surgery, but also by the method of administration: bolus administration is associated with a rapid but short-term effect, while continuous infusion provides a more stable level of analgesia by maintaining a constant concentration of the active agent [19, 20]. These theoretical considerations require clinical validation. To date, however, studies addressing this issue have been limited to single-center trials with relatively small sample sizes [21, 22].

Objective

To evaluate the effect of continuous infusion of nonsteroidal anti-inflammatory drugs compared with bolus administration on postoperative pain intensity, opioid analgesia requirements, and the incidence of adverse events in adult patients undergoing surgery under general anesthesia.

Materials and methods

This meta-analysis was conducted in accordance with the recommendations of the Cochrane Collaboration and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [23]. The study protocol was registered on the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) under registration number INPLASY202550045 (DOI: 10.37766/inplasy2025.5.0045). The completed PRISMA checklist is provided in Table D1 of the Supplementary Material, available at the following link: (https://data.mendeley.com/datasets/cfwd-5j7dm9/1).

Search strategy

The two researchers have independently conducted a systematic literature search for studies published up to and including March 2024. All available studies at the time of the search comparing bolus versus continuous infusion of NSAIDs were considered for inclusion in the meta-analysis. The following databases were searched: PubMed (Medline) and Cochrane CENTRAL. The PubMed query was the following: (“continuous” [tiab] OR “infusion” [tiab]) AND (“bolus” [tiab]) AND (“nonsteroidal anti-inflammatory drug” [tiab] OR “NSAID” [tiab] OR “NSAIDs” [tiab] OR “diclofenac” [tiab] OR “ibuprofen” [tiab] OR “indomethacin” [tiab] OR “ketoprofen” [tiab] OR “ketorolac” [tiab])

Table 1. PICOS criteria

PICOS	Inclusion criteria
Population	Adult patients
Intervention	Continuous infusion of NSAIDs (> 6 hours) for postoperative analgesia
Comparison	Bolus administration of NSAIDs for postoperative analgesia
Outcomes	Opioid consumption; postoperative nausea and/or vomiting; respiratory depression; need for rescue analgesia; pain intensity (6, 12, 24, 48 hours)
Study design	Randomized controlled trials (RCTs)

Note: NSAIDs — nonsteroidal anti-inflammatory drugs; RCT — randomized controlled trials.

AND ("surgery" [tiab] OR "postoperative" [tiab] OR "operation" [tiab]). The Cochrane CENTRAL query: ("continuous infusion":ti,ab) AND bolus:ti,ab AND (NSAID* OR diclofenac OR ibuprofen OR indomethacin OR ketoprofen OR ketorolac):ti,ab AND (surgery OR postoperative):ti,ab, restricted to records in Trials with publication dates up to March 2024. In addition, reference lists of the included studies were screened (backward snowballing), and citation tracking was performed (forward snowballing) using the Litmaps tool [24]. The search was conducted without language restrictions.

Eligibility criteria and study selection

Abstracts of the retrieved publications were reviewed by five independent researches, who assessed the studies for eligibility according to the predefined inclusion criteria for the meta-analysis (Table 1).

Decisions regarding study inclusion were made after a thorough review of the full-text articles, supplementary materials, and study protocols. Publications were excluded if they met any of the following criteria:

1) systematic reviews, meta-analyses, letters to the editor, or similar (not randomized controlled trials);
2) use of multimodal analgesic combinations as the intervention under investigation;
3) absence of data on the outcomes of interest.

Any disagreements were resolved through discussion with the involvement of an additional expert until consensus was reached.

Data extraction and outcome assessment

Five independent investigators extracted the following data:

- general study characteristics (first author, year of publication, journal, sample size);
- patient characteristics (mean age, mean weight, sex distribution);
- details on surgical procedures, anesthesia, and postoperative analgesia regimen (type and duration of surgery, type of anesthesia, duration of postoperative analgesia, drugs used and mode of administration);
- outcomes, including total reported opioid consumption during hospitalization; incidence of postoperative nausea and/or vomiting; incidence of respiratory depression; and pain intensity at 6, 12, 24, and 48 hours postoperatively, assessed by visual analogue scale (VAS) and numerical rating scale (NRS).

In cases where pain scores were not reported for the prespecified time points, the following rules were applied:

- pain assessment between 4–8 hours or at 8 hours was considered equivalent to the 6-hour time point;
- assessments within 12–16 hours were considered equivalent to the 12-hour time point.

Discrepancies between investigators were discussed, and consensus was reached on all extracted values.

In line with Cochrane recommendations [25], quantitative data were standardized to means and standard deviations (SD) using established methods [26, 27]. Missing SD values were imputed based on sample size, mean values, and available SDs for the given outcome, using multiple imputation. Values were taken from the third iteration; and when the data were insufficient, the missing SD was replaced by the largest SD reported for the respective outcome within the group. Imputation was performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA).

The primary endpoint of this meta-analysis was total opioid consumption.

Secondary endpoints included:

- pain intensity at 6, 12, 24, and 48 hours postoperatively;
- need for rescue analgesia (opioids or NSAIDs);
- incidence of respiratory depression;
- incidence of postoperative nausea and vomiting.

Risk of bias assessment

Risk of bias for included studies was assessed independently by three investigators using the Risk of Bias 2 tool [28]. Disagreements were resolved through discussion with the study supervisor. Publication bias and small-study effects were evaluated using Egger's test and funnel plot analysis [29]. The certainty of evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [30].

Statistical analysis

The meta-analysis was conducted using STATA 18.0 (StataCorp LLC, College Station, TX, USA). Opioid doses were converted to intravenous morphine equivalents (mg) [31], and pain scores were standardized to centimeters. For continuous outcomes (opioid consumption, pain scores), pooled effect sizes were calculated as standardized mean differences (SMD, Hedges's g) with 95% confidence intervals (CIs) between the continuous infusion and bolus groups. Mean differences were also analyzed. For binary outcomes, risk ratios (RR) with 95% CIs were calculated. Random-effects modeling was applied using the restricted maximum likelihood (REML) method [32].

Between-study heterogeneity was assessed with Cochran's Q-test and the I^2 statistic. Heterogeneity was considered significant at $p < 0.05$ and/or $I^2 > 50\%$.

A two-sided p-value < 0.05 was considered statistically significant.

Results

Study characteristics

The initial search identified 240 publications matching the query, with additional 216 retrieved through snowballing. After abstract screening, 334 studies were excluded. Of the remaining 99 articles, 93 were excluded at the stage of full-text assessing for various reasons (Table D2), and 6 studies were included in the meta-analysis. The study selection process is summarized in the PRISMA flow diagram (Figure 1).

A total of 462 patients were included in the meta-analysis, with a mean age of 38.7 years (range: 31.0–48.1). Most studies were conducted in the context of perioperative abdominal surgery [21, 22, 33–35], while one study involved a mixed cohort of non-cardiac surgical procedures [36]. General anesthesia was used in four studies [21, 33–35], spinal anesthesia in one [22], and combined anesthesia in another [36]. Intravenous administration of NSAIDs in both groups was studied in half of the publications [33, 34, 36], intramuscular administration was studied in one work [21], and infusion/injection into the suprafascial space was studied in another one [22]. In one study, the continuous infusion was administered intravenously, whereas bolus doses were delivered intramuscularly [35]. The follow-up duration of 24 hours was described in four publications [33–36] and 48 hours in two publications [21, 22]. A more detailed overview of the included studies is presented in Tables 2 and 3.

Meta-analysis

No statistically significant differences were observed in opioid consumption between the groups of continuous infusion and bolus administration of NSAIDs (p = 0.219) (Table 4, Figure 2). Statistical heterogeneity was 83.88% (p = 0.001). Among the secondary endpoints, a statistically significant difference was found for the need for rescue analgesia (p < 0.001). The effect size of 3.739 (95% CI: 2.013–6.945) indicated a lower frequency of additional analgesic use in the bolus administration group. Heterogeneity for this outcome was lower than 0.01% (p = 0.888) (Table 4, Figure 2).

Differences in the incidence of postoperative nausea and/or vomiting, respiratory depression, as well as pain scores at 6, 12, 24, and 48 hours after surgery were not statistically significant (Table 4, Figures 2, 3). High statistical heterogeneity was observed for pain scores at 6, 12, and 24 hours.

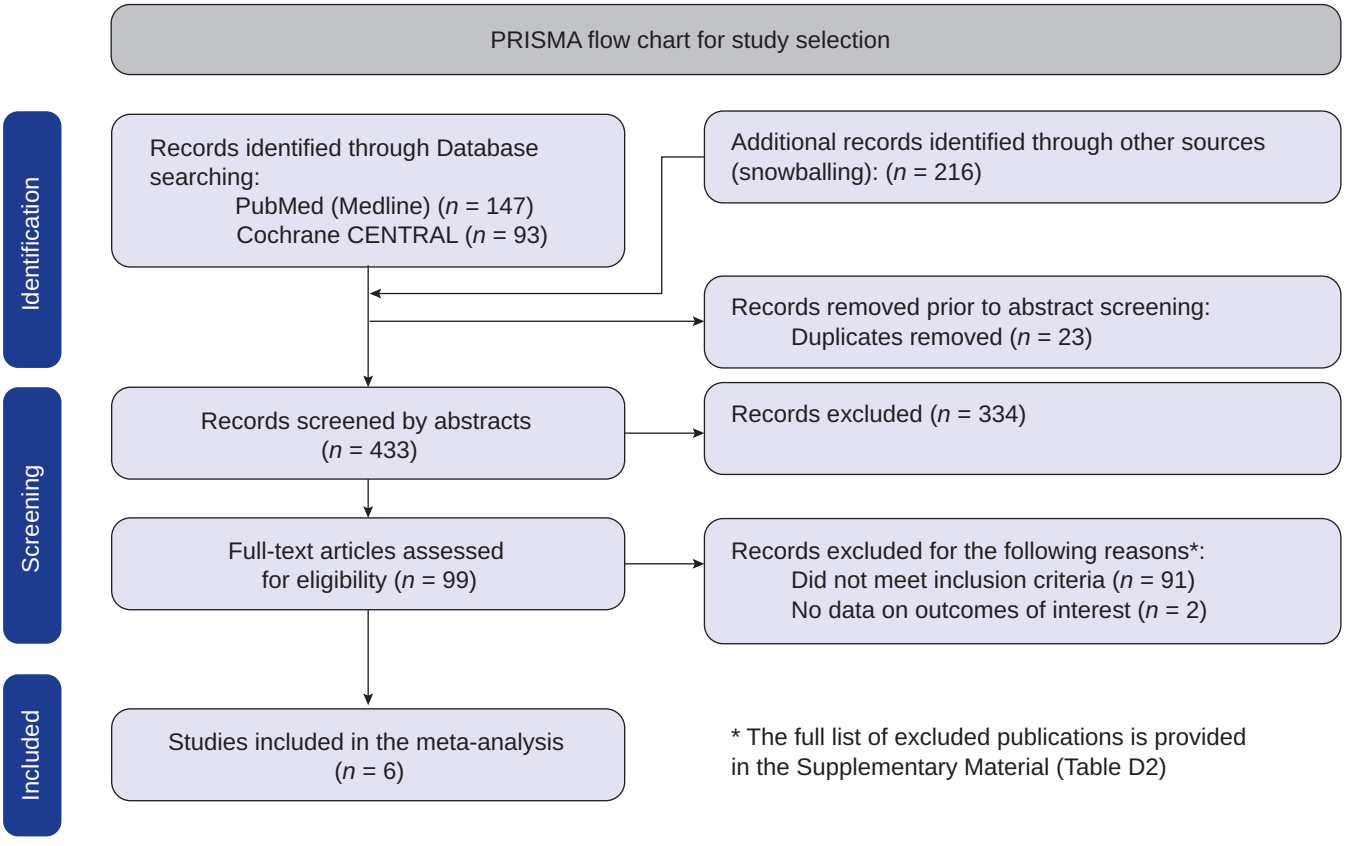

Fig. 1. PRISMA flow chart for study selection

Table 2. Characteristics of studies included in the meta-analysis: inclusion criteria, anesthesia and postoperative analgesia protocols

Study	Inclusion criteria	Anesthesia protocol	Postoperative analgesia protocol	
			Group CI	Group Bolus
Burns J.W., 1991 [21]	Patients aged 18–75 years, body weight 40–95 kg, elective upper abdominal surgery	**GA:** all patients were premedicated with temazepam 20–40 mg orally; anaesthesia was induced with thiopentone 3–6 mg/kg and maintained with nitrous oxide and enflurane in oxygen, with supplements of alfentanil as required	**CI:** a continuous i.m. infusion of ketorolac at a loading dose of 12.5 mg/h for 30 minutes and at 2.5 mg/h for the remainder of the study. **Bolus:** they also received intermittent intramuscular injections of saline every 4 hours under automatic computer control. **Additional:** the PCA device was configured to allow patients to receive a bolus dose of morphine at 0.02 mg/kg, with a lock-out period of 2 minutes between doses to control the total amount administered	**CI**: for continuous infusion, patients received sodium chloride (0.9 %) infusion (placebo). **Bolus**: bolus intramuscular injections of ketorolac at a dose of 10 mg every 4 hours using an automatic computerized injector. **Additional**: a patient-controlled analgesia device set to boluses of morphine (0.02 mg/kg) with a lockout interval of 2 minutes
Lavand'homme P.M., 2007 [22]	ASA I–II parturients, elective cesarean delivery	**Spinal anesthesia**: all parturients were premedicated with 50 mg intravenous ranitidine; 10 mg metoclopramide; and 30 ml oral sodium citrate, 0.3 M. After a 500-ml intravenous preload with balanced salt solution, a standardized intrathecal injection was performed in all parturients. With the patient in the sitting position, a 25-gauge pencil-point spinal needle was inserted at the L3–L4 interspace, and 1.8–2 ml of a mixture of 0.5 % hyperbaric bupivacaine with sufentanil (final dilution: 4 mg/ml bupivacaine and 1 μg/ml sufentanil) was injected	**CI:** catheter was connected to an elastomeric pump set to deliver 5 ml/h for 48 hours with 300 mg diclofenac in 240 ml. **Additional**: immediately after recovery from spinal analgesia, an intravenous PCA device was started, set to deliver 1 mg morphine per demand with a 5-min lockout time and a maximum allowed dose of 25 mg per 4 hours. If necessary, patients were allowed to receive 1 g acetaminophen per 6 hours	**CI**: the catheter was connected to an elastomeric pump with 240 ml of sodium chloride (0.9 %) to deliver 5 ml/h for 48 hours. **Bolus**: every 12 hours, 75 mg of diclofenac diluted in 50 ml of sodium chloride (0.9 %) was administered over 20 minutes. **Additional**: immediately after recovery from spinal anesthesia, a patient-controlled analgesia device was started, set to 1 mg of morphine on demand, with a lockout interval of 5 minutes and a maximum dose of 25 mg over 4 hours. If necessary, 1 g of acetaminophen was administered every 6 hours
O'Hara D.A., 1997 [33]	Patients age over 18 years, weight over 40 kg, with moderate-to-severe baseline postoperative pain on a categorical scale	**GA**: all patients received inhalation anesthesia without concomitant epidural anesthesia. No premedication was given. Fentanyl or morphine, midazolam, and up to 0.625 mg of droperidol were allowed during anesthesia	**CI**: ketorolac 30 mg IV loading dose, then 2.5 mg/h continuous infusion. **Bolus**: cartridge of a patient-controlled analgesia device with a concentration of ketorolac 2 mg/ml. Maximum permissible dose (per 24 hours): 150 mg of ketorolac. **Additionally**: morphine at a dose of 5–10 mg intramuscularly was permitted upon the patient's request after evaluation by a physician	**CI**: placebo. **Bolus**: loading bolus dose of ketorolac 30 mg; patient-controlled analgesia, ketorolac 4 mg/ml. Maximum permissible dose (per 24 hours): 150 mg ketorolac. **Additionally**: intramuscular injection of 5–10 mg of morphine was permitted upon the patient's request after evaluation by a physician

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Study	Inclusion criteria	Anesthesia protocol	Postoperative analgesia protocol	
			Group CI	Group Bolus
Ready L.B., 1994 [36]	Patients undergoing major orthopedic, gynecologic, or general surgery, English-speaking, weight over 40 kg, able to take intravenous drugs and capable of using PCA, enrolled within 18 hours post-surgery; baseline pain on a categorical scale moderate or greater; no postoperative PCA use prior t enrollment	All patients received anesthetics as judged appropriate by their anesthesiologists. 203 general anesthetics (9 of which were combined with a regional anesthetic technique, i.e., epidural or spinal) and 4 spinal anesthetics	**CI:** initial intravenous bolus dose of ketorolac 30 mg, intravenous infusion of ketorolac 5 mg/h. **Bolus**: placebo intravenously every 3 hours. **Additionally**: a patient-controlled analgesia device administered morphine at a dose of 1 mg with a lockout interval of 6 minutes, limited to 30 mg/h for 4 hours or 10 mg/hour for 1 hour	**CI**: initial loading dose intravenously: placebo; intravenous infusion of placebo; **Bolus**: 15 mg of ketorolac intravenously every 3 hours. **Additionally**: patient-controlled analgesia, 1 mg morphine, 6-minute lockout, limit 30 mg/hour for 4 hours or 10 mg/hour for 1 hour.
Russo A., 2012 [34]	ASA I women, age 30–50 years, elective open hysterectomy	**GA**: During induction, patients received Fentanyl (4 µg/kg), Propofol (2 mg/kg), and Vecuronium (0.1 mg/kg). After intubation, anaesthesia was maintained with a mixture of oxygen (40 % O_2), air and sevoflurane (2–2.2 %)	**CI**: 24 hours analgesic infusor (2 ml/h) containing morphine (0.02 mg/kg/h) and ketorolac (90 mg). **Additionally:** tramadol on demand	**CI**: 24-hour infusion pump (2 ml/h) containing morphine (0.02 mg/kg/h). **Bolus**: ketorolac was administered in boluses every 8 hours **Additionally**: tramadol on demand
Testa G., 1994 [35]	Patients age 20–70 years, ASA I–II, elective non-oncologic abdominal surgery, expected duration ~120 minutes	**GA**: premedication with atropine sulfate (0.01 mg/kg) and diazepam (0.2 mg/kg) intramuscularly 30 minutes before surgery; induction with TPS (5 mg/kg), IOT after succinylcholine administration (1 mg/kg); maintenance with fentanyl and droperidol, N_2O and O_2 at 60 and 40 % respectively; muscle relaxation was achieved with vecuronium bromide (0.08 mg/kg). At the end of surgery, a decurarizing mixture of prostigmine (2.5 mg) and atropine sulfate (1.5 mg) was administered	**CI+bolus**: ketorolac tromethamine (30 mg) was used. Method of administration: intravenous infusion using a patient-controlled analgesia system. Dosing strategy: initial dose — 120 mg of ketorolac diluted in 30 ml of 0.9 % NaCl solution (with a concentration of 4 mg/ml). Loading dose — 20 mg (5 ml), bolus dose — 2 mg (0.5 ml) administered at the patient's request. Blocking interval: the minimum interval between boluses was 5 minutes to prevent overdose. Prolonged infusion: 4 mg/h (1 ml/h). Maximum dose over 4 hours: 48 mg (12 mL) excluding the loading dose. The patient-controlled analgesia device allowed patients to self-administer additional boluses as needed, ensuring safety through locking mechanisms and total dose limits over 4 hours	**Bolus**: ketorolac tromethamine (30 mg) was used, administered intramuscularly. Dosing strategy: the first dose was 30 mg intramuscularly immediately after the patient came out of anesthesia. Doses were repeated every 6 hours for 24 hours after surgery. A gastroprotective agent (ranitidine) was additionally administered to protect the gastrointestinal tract

Note: ASA — American Society of Anesthesiologists; CI — continuous infusion; GA — general anesthesia; PCA — patient-controlled analgesia; VAS — Visual Analog Scale.

Table 3. General characteristics of studies included in the meta-analysis

№	Parameter	Group	Burns J.W., 1991 [21]	Lavand'homme P.M., 2007 [22]	O'Hara D.A., 1997 [33]	Ready L.B., 1994 [36]	Russo A, 2012 [34]	Testa G., 1994 [35]
1	Journal		Br J Anaesth	Anesthesiology	Pharmacotherapy	Anesthesiology	Eur Rev Med Pharmacol Sci	Minerva Chir
2	Country		United Kingdom	Belgium	USA	USA, New Zealand	Italy	Italy
3	Study design		RCT	RCT	RCT	RCT	RCT	RCT
4	Sample size	CI	19	30	61	65	38	14
		Bolus	23	30	63	68	37	14
5	Type of surgery		Abdominal	Abdominal	Abdominal	Mixed	Abdominal	Abdominal
6	Centers		Single-center	Single-center	Multicenter	Multicenter	Single-center	Single-center
7	Blinding		Double-blind	Double-blind	Double-blind	Double-blind	ND	ND
8	Funding		Yes	Not reported	Yes	Not reported	Not reported	Not reported
9	Age, years, mean (SD)	CI	48.1 (11.9)	31.0 (5.0)	43.0 (10.0)	43.9 (11.8)	38.4 (4.2)	ND
		Bolus	47.1 (11.7)	31.0 (6.0)	43.0 (10.0)	44.3 (14.2)	37 (3.5)	ND
10	Sex, male (%)	CI	47.4	0.0	ND	35.4	0.0	0.0
		Bolus	43.5	0.0	ND	26.5	0.0	0.0
11	Weight, kg, mean (SD)	CI	63.5 (9.6)	71.0 (16.0)	78.0 (21.0)	73.0 (12.8)	56.8 (8.7)	ND
		Bolus	62.7 (12.1)	75.0 (14.0)	76.0 (23.0)	74.0 (16.3)	60.3 (9.5)	ND
12	Anesthesia type		General	Spinal	General	Combined	General	General
13	Duration of surgery, min, mean (SD)	CI	ND	48 (9)	ND	114 (66)	67 (12)	ND
		Bolus	ND	57 (8)	ND	156 (162)	69 (10)	ND
14	Analgesic used	CI	Ketorolac, morphine	Diclofenac, morphine	Ketorolac, morphine	Ketorolac, morphine	Ketorolac, morphine, tramadol	Ketorolac
		Bolus	Ketorolac, morphine	Diclofenac, morphine	Ketorolac, morphine	Ketorolac, morphine	Ketorolac, morphine, tramadol	Ketorolac
15	Administration	CI	IM (morphine IV)	Into supra-fascial space (diclofenac IV, morphine IV)	IV (additional morphine IM)	IV	IV	IV
		Bolus	IM (morphine IV)	Into supra-fascial space (diclofenac IV, morphine IV)	IV (additional morphine IM)	IV	IV	IV

End of the tabl. 3

№	Parameter	Group	Burns J.W., 1991 [21]	Lavand'homme P.M., 2007 [22]	O'Hara D.A., 1997 [33]	Ready L.B., 1994 [36]	Russo A, 2012 [34]	Testa G., 1994 [35]
16	Duration of per-protocol analgesia, h	CI	48	48	24	24	24	24
		Bolus	48	48	24	24	24	24
17	Total opioid consumption, mg, mean (SD)	CI	100.5 (45.0)	18.0 (12.7)	6.0 (6.8)	33.0 (28.0)	ND	ND
		Bolus	118.5 (47.5)	38.0 (20.0)	6.2 (5.7)	31.0 (18.0)	ND	ND
18	Additional analgesia, N	CI	ND	ND	ND	ND	31	1
		Bolus	ND	ND	ND	ND	8	0
19	Postoperative nausea and vomiting, N	CI	3	ND	26	44	ND	ND
		Bolus	5	ND	26	42	ND	ND
20	Respiratory depression, N	CI	ND	ND	0	3	0	ND
		Bolus	ND	ND	0	4	0	ND
21	Pain score, 6 h	CI	4.25 (2.30)	ND	ND	2.00 (1.67)	6.00 (2.99)	2.07 (1.03)
		Bolus	3.75 (2.02)	ND	ND	1.52 (1.82)	3.00 (2.02)	2.89 (1.45)
22	Pain score, 12 h	CI	ND	3.00 (1.90)	ND	ND	4.00 (2.44)	ND
		Bolus	ND	5.00 (2.00)	ND	ND	4.00 (2.00)	ND
23	Pain score, 24 h	CI	3.30 (1.98)	1.00 (1.00)	ND	1.30 (1.20)	4.00 (1.48)	1.93 (1.03)
		Bolus	2.62 (1.53)	2.00 (2.00)	ND	1.30 (1.60)	3.00 (3.29)	1.00 (0.71)
24	Pain score, 48 h	CI	1.60 (0.98)	1.00 (1.00)	ND	ND	ND	ND
		Bolus	2.25 (1.35)	1.00 (2.00)	ND	ND	ND	ND

Note: CI — continuous infusion; IM — intramuscular; IV — intravenous; ND — no data; RCT — randomized controlled trial; SD — standard deviation.

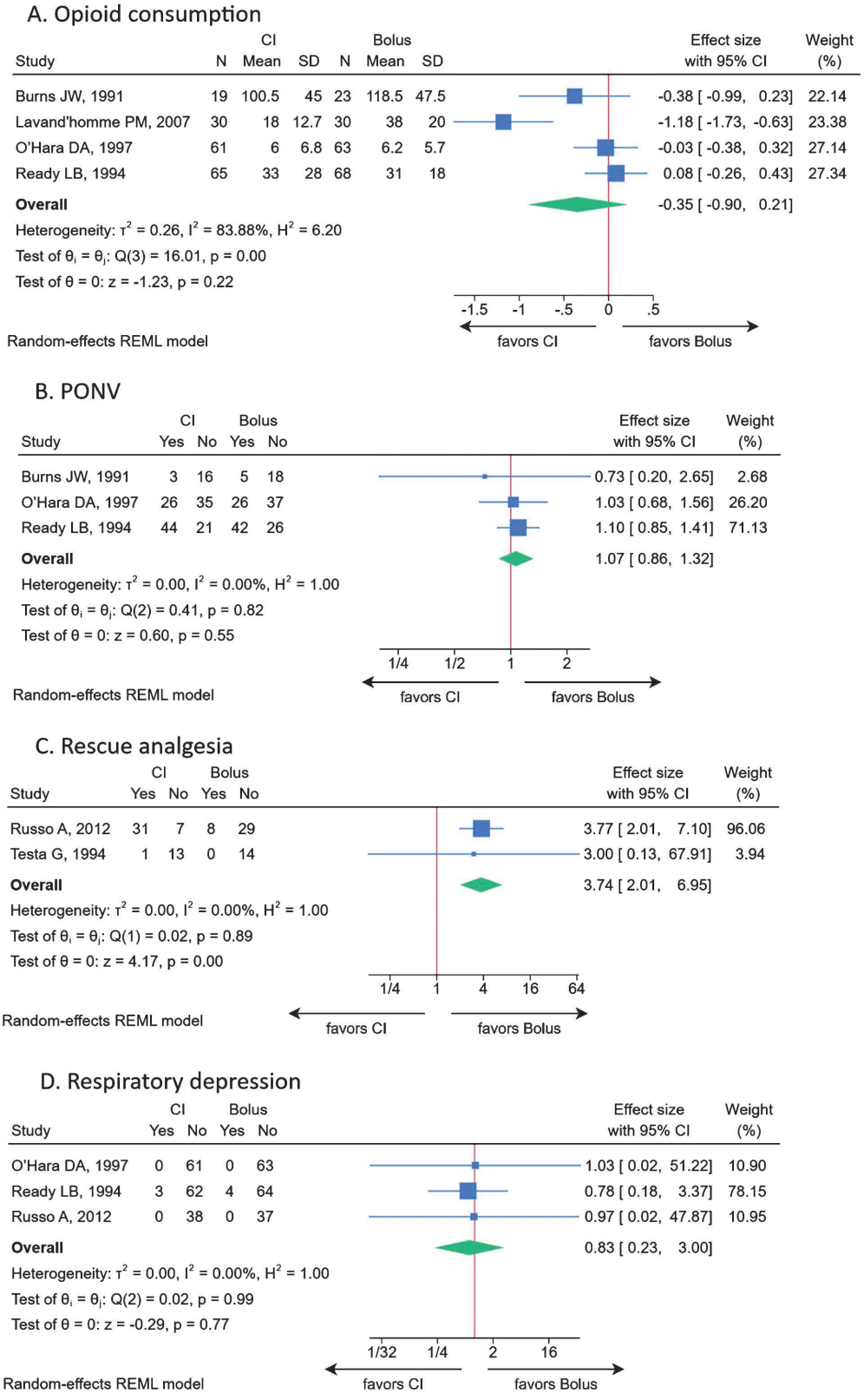

Fig. 2. Forest plots representing the standardized mean difference in opioid consumption (A) and risk ratio for postoperative nausea and/or vomiting (B), respiratory depression (D), and need for additional analgesia (C) in the CI (continuous infusion) group and the Bolus group

95% CI — 95% confidence interval; CI — continuous infusion; REML — restricted maximum likelihood; SD — standard deviation.

Note: The line of no effect was set at 0 for opioid consumption and at 1 for all other outcomes.

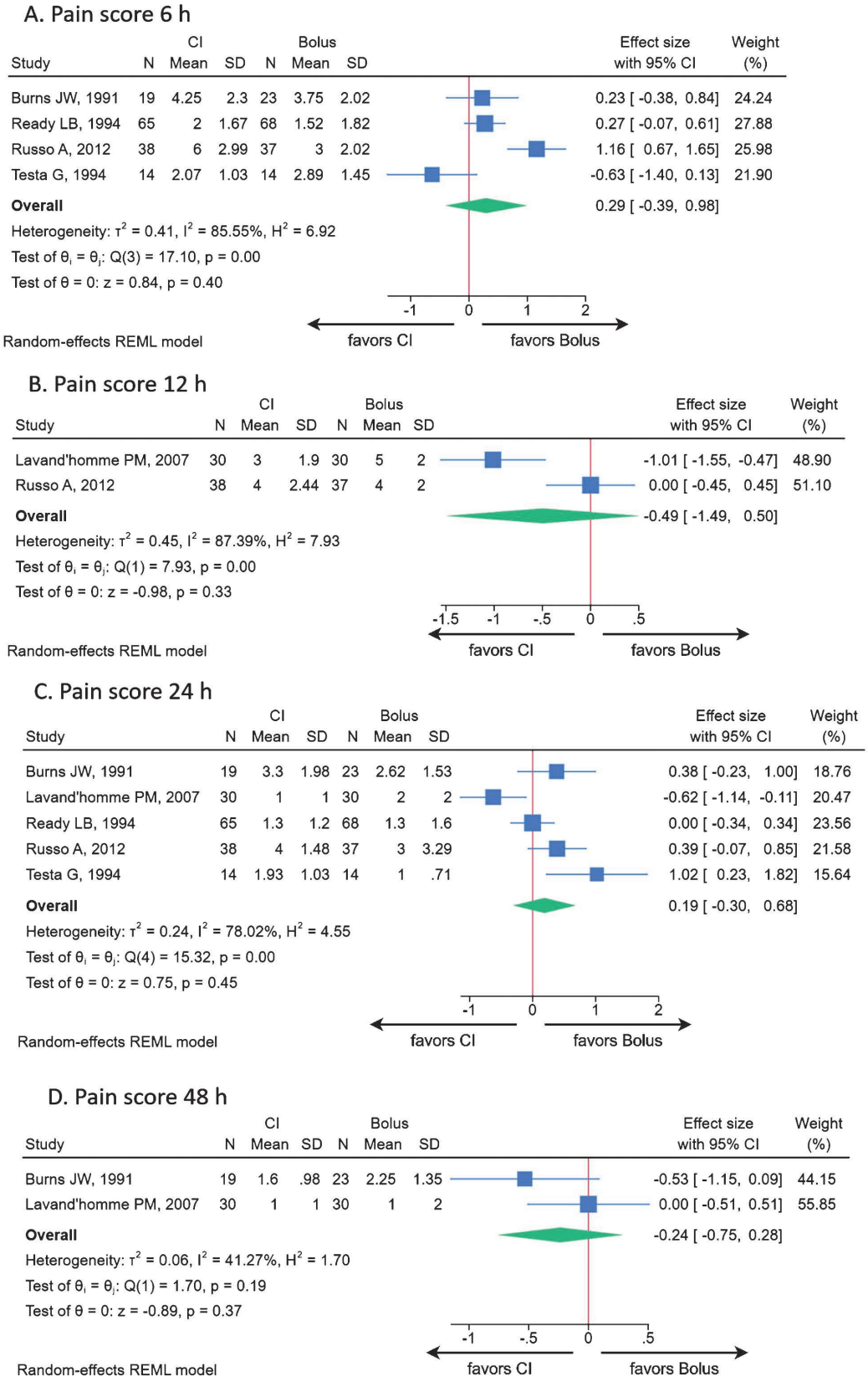

Fig. 3. Forest plots representing the standardized mean difference in pain level at 6 h (A), 12 h (B), 24 h (C), and 48 h (D) after the end of surgery in the CI (continuous infusion) group and the Bolus group

95% CI — 95% confidence interval; CI — continuous infusion; REML — restricted maximum likelihood; SD — standard deviation.

Note: The line of no effect was set at 0.

Table 4. Main results of the meta-analysis

Outcome		*n* studies	*n* patients	Effect size (95% CI)		*p*-value (SMD, RR)	I^2, %	*p*-value (I^2)	Egger's test (*p*-value)
				SMD	MD				
Opioid consumption, mg		4	359	–0.35 (–0.90; 0.21)	–7.15 (–18.93; 4.64)	0.219	83.88	0.001	0.095
Postoperative nausea and/or vomiting, N		3	299	RR: 1.07 (0.86; 1.32)		0.547	< 0.01	0.816	0.524
Respiratory depression, N		3	332	RR: 0.83 (0.23; 3.00)		0.774	< 0.01	0.988	0.877
Need for additional analgesia, N		2	103	**RR: 3.74 (2.01; 6.95)**		**< 0.001**	< 0.01	0.888	NA
Pain score, cm	6 h	4	278	0.29 (–0.39; 0.98)	0.77 (–0.78; 2.31)	0.402	85.55	0.001	0.309
	12 h	2	135	–0.50 (–1.49; 0.50)	–1.00 (–2.96; 0.96)	0.328	87.39	0.005	NA
	24 h	5	338	0.19 (–0.30; 0.68)	0.28 (–0.46; 1.02)	0.453	78.02	0.004	0.220
	48 h	2	102	–0.24 (–0.75; 0.28)	–0.35 (–0.99; 0.28)	0.374	41.27	0.192	NA

Note: CI — confidence interval; MD — mean difference; NA — not applicable; RR — risk ratio; SMD — standardized mean difference.

Risk of bias assessment

No evidence of publication bias was detected; *p*-values for Egger's test exceeded 0.05 in all analyses (Table 4). Funnel plots are presented in the Supplementary Material (Figures D1, D2).

Of the six studies included in the meta-analysis, one was assessed as having a low risk of bias, one a moderate risk, and four a high risk of bias.

In accordance with the GRADE approach, the following statements were formulated:

1. Continuous infusion of NSAIDs is comparable to bolus administration with respect to postoperative opioid consumption (certainty of evidence — very low).
2. Continuous infusion and bolus administration of NSAIDs do not differ in the incidence of postoperative nausea and/or vomiting (certainty of evidence — low).
3. Continuous infusion and bolus administration of NSAIDs do not differ in the incidence of respiratory depression (certainty of evidence — low).
4. The need for rescue analgesia is higher with continuous infusion compared with bolus administration of NSAIDs (certainty of evidence — low).
5. Continuous infusion and bolus administration of NSAIDs do not differ in postoperative pain scores at 6, 12, 24, and 48 hours after surgery (certainty of evidence — very low).

Discussion

This meta-analysis is the first to synthesize data from randomized controlled trials comparing continuous infusion versus bolus administration of NSAIDs for postoperative analgesia.

Key findings

The results demonstrated no statistically significant differences between the two approaches in terms of total opioid consumption, postoperative pain intensity at various time points, incidence of postoperative nausea and vomiting, or respiratory depression. However, the requirement for rescue analgesia was significantly higher in the continuous infusion group. This result seems somewhat unexpected and counterintuitive, unless one takes into account the psychological aspect: pain is subjective, and the patient may experience apparent relief after each repeated bolus of NSAIDs. Continuous infusion does not appear to have this effect.

Relation to previous studies

This meta-analysis did not reveal any statistically significant differences between continuous infusion and bolus administration of NSAIDs in terms of key clinical outcomes. This contradicts another study evaluating the efficacy of ketorolac as part of multimodal analgesia in combination with opioids, which showed that prophylactic administration of ketorolac followed by continuous infusion in patients undergoing abdominal surgery was associated with improved pain relief, a decrease in plasma cortisol levels, and a significant reduction in the incidence of side effects compared to the control group. Although the difference in morphine consumption between the groups did not reach statistical significance, the authors noted a "marked clinically significant morphine-saving effect" as well as no adverse effects on hemostasis and renal function [37]. These data confirm the safety and potential clinical benefit of using ketorolac in a prolonged infusion regimen as part of multimodal analgesia after abdominal surgery.

A 2025 narrative review on the intravenous use of nonsteroidal anti-inflammatory drugs in clinical practice identi-

fied the presumed pharmacokinetic and pharmacodynamic advantages of continuous infusion regimens, including maintaining stable plasma drug concentrations, potentially enhancing the analgesic effect, and reducing the risk of adverse reactions [20]. It should be noted that narrative reviews may reflect the subjective position of the authors, as the selection of sources is often based on their own views. The results of this meta-analysis did not confirm the clinical significance of these theoretical assumptions. The identified advantage of bolus administration in terms of the need for additional analgesia may reflect a more pronounced peak of the drug's action at the time of administration or individual characteristics of pain perception in the first hours of the postoperative period. Continuous infusion provides a stable concentration of the drug in plasma, which in theory should lead to a more even and prolonged analgesic effect. However, in the absence of pronounced peak concentrations, the subjective sensation of pain relief may decrease. In contrast, bolus administration provides a faster and more noticeable effect, which may be particularly important in conditions of postoperative variable intensity pain syndrome.

The results of this study differ from the conclusions of the meta-analysis by Howard M.L. et al. [38], which compared continuous infusion of NSAIDs with placebo and opioids. Most studies demonstrated a reduction in the need for opioids when continuous infusion of NSAIDs was used. However, differences in pain scores often did not reach statistical significance, indicating that despite the theoretical advantages of continuous NSAIDs infusion, such as more stable plasma drug concentrations, the clinical efficacy of this method of postoperative analgesia remains a subject to discussion. Unlike the above-mentioned meta-analysis, this study focused on comparing bolus administration of NSAIDs with continuous infusion, while the study by Howard M.L. et al. examined different dosages of continuous NSAIDs infusion and its comparison with opioid analgesics or placebo. In addition, this meta-analysis did not include studies involving children. These differences in sample selection and methodology may explain the discrepancies in the results obtained.

Significance of the results

The significance of the obtained findings is supported by the following conclusions:

1. **Comparability of NSAIDs administration methods.**

The results obtained are important for the practice of postoperative analgesia, as they emphasize that despite the theoretical advantages of continuous NSAIDs infusion, such as maintaining stable plasma concentrations, the clinical efficacy of this approach is comparable to that of bolus administration of NSAIDs. However, in terms of the need for additional analgesia, prolonged NSAIDs infusion demonstrated worse results compared to bolus administration. One possible explanation for the observed results is the pharmacokinetic feature of continuous infusion, which maintains a stable but relatively low concentration of the drug. Unlike bolus administration, which achieves high peak concentrations, this regimen may reduce the intensity of the antinociceptive effect in the acute postoperative period, which in turn may lead to an increased need for additional analgesia. It should be noted that the level of evidence for all statements is "low" and "very low," indicating the need for further research.

2. **Lack of standardized continuous NSAIDs infusion protocols and limited generalizability across NSAIDs variety.**

The most studied drug among the NSAIDs included in the analysis was ketorolac, which was used in both study regimens — continuous infusion and bolus administration. The range of doses used varied: infusion regimens provided for an administration rate of 2.5 to 5 mg/h, often with a preliminary loading dose, while bolus administration was performed intravenously or intramuscularly every 4–8 hours in doses ranging from 10 to 30 mg. This variability in dosing approaches reflects the lack of standardization in the infusion regimen for NSAIDs, which makes it difficult to develop generalized clinical recommendations and highlights the need to standardize prescribing protocols, taking into account the pharmacokinetics of a particular drug and the clinical and biological characteristics of the patient, such as age, body weight, functional status of the liver and kidneys, and comorbidity.

Unlike bolus administration, for which official dosage guidelines are provided in most cases, continuous infusion is often carried out on the basis of empirically adapted regimens. This creates risks of both insufficient analgesia and an increase in adverse effects incidence. At the same time, for some drugs, such as ibuprofen, the manufacturing instructions already contain restrictions on the maximum daily dose and duration of infusion, which emphasizes the need for strict compliance.

Strengths and limitations

The strengths of this meta-analysis include a rigorous study protocol with pre-registration, inclusion of only randomized controlled trials, and a standardized process for data extraction and analysis.

The limitations of the study include significant heterogeneity among the included studies in terms of types of surgical procedures, NSAIDs dosing regimens, and pain assessment criteria, which limits the possibility of direct comparison and reduces the internal validity of the results obtained. Some studies demonstrated the advantages of continuous NSAIDs infusion only when patient-controlled analgesia was available, indicating that the potential morphine-saving effect depends on organizational and technical factors. It is also worth noting that all studies have small sample sizes, and some studies are characterized by a short observation period (≤ 24 hours). Meta-regression was also impossible due to the small number of studies.

An additional limitation is the high risk of bias in a number of the studies analyzed. The prevalence of studies conducted in abdominal surgery settings limits the possibility of extrapolating the results to other types of surgical interventions.

In addition, most of the studies included in the analysis used fixed infusion rates and dosages that were not always adapted to the individual characteristics of patients, while bolus administration provided more flexible and rapid control of pain. It should also be noted that in one study, continuous infusion of NSAIDs was performed into the suprafascial space, which differs significantly from systemic intravenous administration and may affect the clinical effect.

The meta-analysis included RCTs from 20–30 years ago due to the lack of more recent studies. Much has changed since then: new NSAIDs have appeared, some rules for conducting RCTs have been modified, all of which reduces the quality of the evidence obtained but confirms the conclusion that further studies are needed.

Further research directions

The obtained data emphasize the need for large multicenter RCTs with a unified design, standardized NSAIDs administration, and uniform outcome assessment. Special attention should be paid to analyzing subgroups of patients depending on the type of surgery and multimodal analgesia strategy.

Conclusions

Despite pharmacological considerations, prolonged infusion of NSAIDs did not demonstrate clinical advantages over bolus administration for most of the analyzed indicators. In the context of multimodal analgesia, both approaches can be considered comparably effective; however, the choice of method should take into account organizational capabilities and individual patient needs.

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