REVIEW ARTICLE

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Pre-emptive versus preventive analgesia for postoperative pain: a systematic review and meta-analysis

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ABSTRACT

BACKGROUND

Postoperative pain is a type of nociceptive pain that originates from tissue damage due to trauma caused by surgery. Pre-emptive analgesia is treatment that starts before surgery, to prevent or reduce the establishment of sensitization of dorsal horn neurons caused by tissue injury, the sensitized neurons being supposed to amplify postoperative pain. Pre-emptive analgesia consists of administering analgesic medication before tissue injury, that is, before the reception, transmission, modulation, and nociception of the aggressive stimulus, aiming to prevent hyperalgesia. This review aims to compare the efficacy of pre-emptive analgesia and preventive analgesia in postoperative pain.

METHODS

Article searching was done on five databases (PubMed, ProQuest, Scopus, ScienceDirect, ClinicalKey). Hand-searching was also done to find additional articles. We have only included double-blind, randomized, controlled trials (RCT). A total of fifteen articles were included and all were RCT studies comparing pre-emptive analgesia with preventive analgesia. The quality of the included studies was evaluated with Cochrane risk-of-bias assessment tools. Quantitative analysis was performed by Review Manager 5.4.

RESULTS

Fifteen studies comprising 830 subjects were included in this study. Our analysis revealed that pre-emptive analgesia significantly improved visual analog scale (VAS)/numeric rating scale (NRS)/verbal rating scale (VRS) 4 hours postoperatively [mean difference (MD) = -0.25, 95% CI: [-0.49, -0.02]; I2 = 94%]. Unfortunately, pain scoring at 6, 12 and 24 hours after surgery did not differ significantly between pre-emptive and preventive analgesia. Duration of analgesia was comparable between the two groups. Time to rescue analgesics was similar between the two groups, but the pre-emptive group was associated with less analgesic consumption postoperatively than the preventive group.

CONCLUSION

Pre-emptive analgesia provided better pain relief than preventive analgesia during the short term. Time to rescue analgesics is comparable between both groups, but pre-emptive analgesia is associated with lower amounts of rescue analgesics postoperatively.

Keywords: Pre-emptive analgesia, preventive analgesia, postoperative pain, randomized controlled trial

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INTRODUCTION

Postoperative pain is a form of acute pain caused by surgical trauma accompanied by an inflammatory reaction and initiation of an afferent neuronal barrage.[1] Several factors are associated with effective postoperative pain management, such as a structured acute management team, regular staff training, patient education, regular pain assessment tools, use of balanced analgesia, and adjustment of strategies needed for special patient groups.[2-4] Every surgical procedure needs effective postoperative pain control as it is an essential and humanitarian need of every patient.[5] Poorly controlled acute postoperative pain is linked with increased morbidity, quality-of-life impairment, prolonged duration of opioid use, delayed recovery time, and higher healthcare costs.[6-8] Additionally, the presence of acute pain during or after surgery is associated with the development of chronic pain.[9]

Several concepts have been developed to improve postoperative pain management, such as pre-emptive analgesia and preventive analgesia. Pre-emptive analgesia means the administration of analgesic treatment prior to a tissue injury or surgical insult.[10,11] Meanwhile, preventive analgesia is a wider concept where the timing of analgesic treatment in relation to the surgical insult is not critical.[12-16] Preventive analgesia is an antinociceptive treatment that attenuates pain from high-intensity noxious stimuli before, during, and after the insult.

In the current general consensus, the use of pre-emptive analgesia is not consistent with a better clinical outcome after surgery. Several randomized clinical trials (RCT) provided unclear evidence regarding the benefits of pre-emptive analgesia.[17-20] Theoretically, pre-emptive analgesia suppresses the stimulation of pain receptors and escalates the pain threshold.[21] Pre-emptive analgesia also prevents the establishment of altered afferent processing input, which amplifies pain postoperatively.[22] As promising as it sounds, the results of clinical studies focusing on the value of pre-emptive analgesia are still controversial. A large number of new studies on pre-emptive analgesia were published, but these publications did not significantly change the occurrence ratio between negative and positive outcomes of pre-emptive and preventive treatments. Most of these studies were inconclusive regarding the roles of pre-emptive and preventive analgesia.[2, 23-29] The differences in analgesic techniques, types of surgeries performed, and research settings, all play a significant role in the findings obtained.

However, pre-emptive analgesia and preventive analgesia are still considered essential to reduce inflammatory injury.[30,31] This meta-analysis aims to compare postoperative outcomes, especially pain, between pre-emptive and preventive analgesia.

METHODS

Search strategy

A literature search was conducted on five databases (PubMed, ProQuest, Scopus, ScienceDirect, Clinical Key) on March 8, 2022. Hand-searching was also done to retrieve more studies. The following query search was utilized in all five major databases: pre-emptive AND preventive analgesia AND postoperative pain. The study protocol had been registered with International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY 202360005).

Study selection and data extraction

Articles were included in this study only if they fulfilled the following requirements: adults with a scheduled surgery or intervention (P), patients to whom analgesia was administered before surgical insult (I), patients to whom analgesia was administered after surgical insult (C) and postoperative pain or other postoperative outcomes available in the study (O). Randomized controlled studies (RCT) were included. Exclusion criteria for the articles: the study design is other than RCT, the study has undesirable intervention

or population, and the study is not available in English.

Abstracts, studies, and full articles were selected by three reviewers independently (HA, APN, and MAIM). If there were any discrepancies, these were to be solved with a discussion until an agreement was reached and if not then the articles were to be reviewed by ART independently. Data from included randomized trials were extracted independently by HA.

The following information was extracted from the included randomized trials: first author, year of publication, country of origin, criteria of inclusion, criteria of exclusion, intervention, control, total patients, duration of observation, rate of drop-out, additional rescue analgesic therapy, and outcome data. The outcome measures were defined as follows: (i) visual analogue scale (VAS): a psychometric measuring instrument designed to rate the severity of pain; (ii) verbal rating scale (VRS): adjectives used to describe the severity of pain; (iii) numerical rating scale (NRS): a numeric scale used to rate the severity of pain; (iv) duration of analgesia (DA): time elapsed during analgesia; (v) time to rescue analgesic (TRA): time needed from the postoperative period to the first request for additional analgesic use; (vi) analgesic use (AU): analgesic usage experienced by all patients; and (vii) adverse effects (AEs): total number of patients experiencing adverse effects such as nausea and vomiting. Among all the outcomes, VAS/VRS/NRS was considered the primary outcome. We included these three because each of them has a uniform rating of pain, which starts from 0 (no pain at all) to 10 (maximum imaginable pain).

Bias assessment

The quality of the included studies was assessed with Cochrane risk-of-bias assessment tools. Evaluations were carried out by ART and RF independently. Each study was to be assessed as "low-risk", "high-risk" or "unclear risk" based on seven evidence-based domains, namely: "random sequence generation (selection bias)", "allocation concealment (selection bias)", "blinding of participants and personnel (performance bias)", "blinding of outcome assessment (detection bias)", "incomplete outcome data (attrition bias)", "selective reporting (reporting bias)"; "other bias".

Statistical analysis

Statistical analysis was performed using Review Manager version 5.4. Weighted mean differences (MDs) were used to evaluate continuous data, namely VAS, VRS, NRS, DA, TRA, and AU. Meanwhile, risk ratio (RR) was used to evaluate dichotomous data such as AEs. The Mantel-Haenszel χ^2 test and the I^2 test were used to evaluate the heterogeneity of the study. If the I^2 value was more than 50%, this indicated a high level of heterogeneity.

Ethical Statement

Our study did not require ethical board approval because it did not contain human or animal trials.

RESULTS

Selection of studies and study characteristics

The process of literature selection is based on the "PRISMA 2009 Flow Diagram" as seen in Figure 1. From database searching and other sources, a total of 661 study articles were found. One study was found from manual searching. After the removal of duplicates, 627 articles were left for initial screening. The selection of articles was conducted with a consensus of 3 investigators (RF, APN, and MAIM), and 610 articles were eventually excluded as they did not meet our inclusion criteria based on the title and abstract. Full-text screening was conducted on the remaining 17 articles, among which 2 articles were left out because one article was not available in English and the other study had the pediatric population as the subject of the study. Therefore, we obtained 15 articles eligible to be included in this systematic review and meta-analysis.

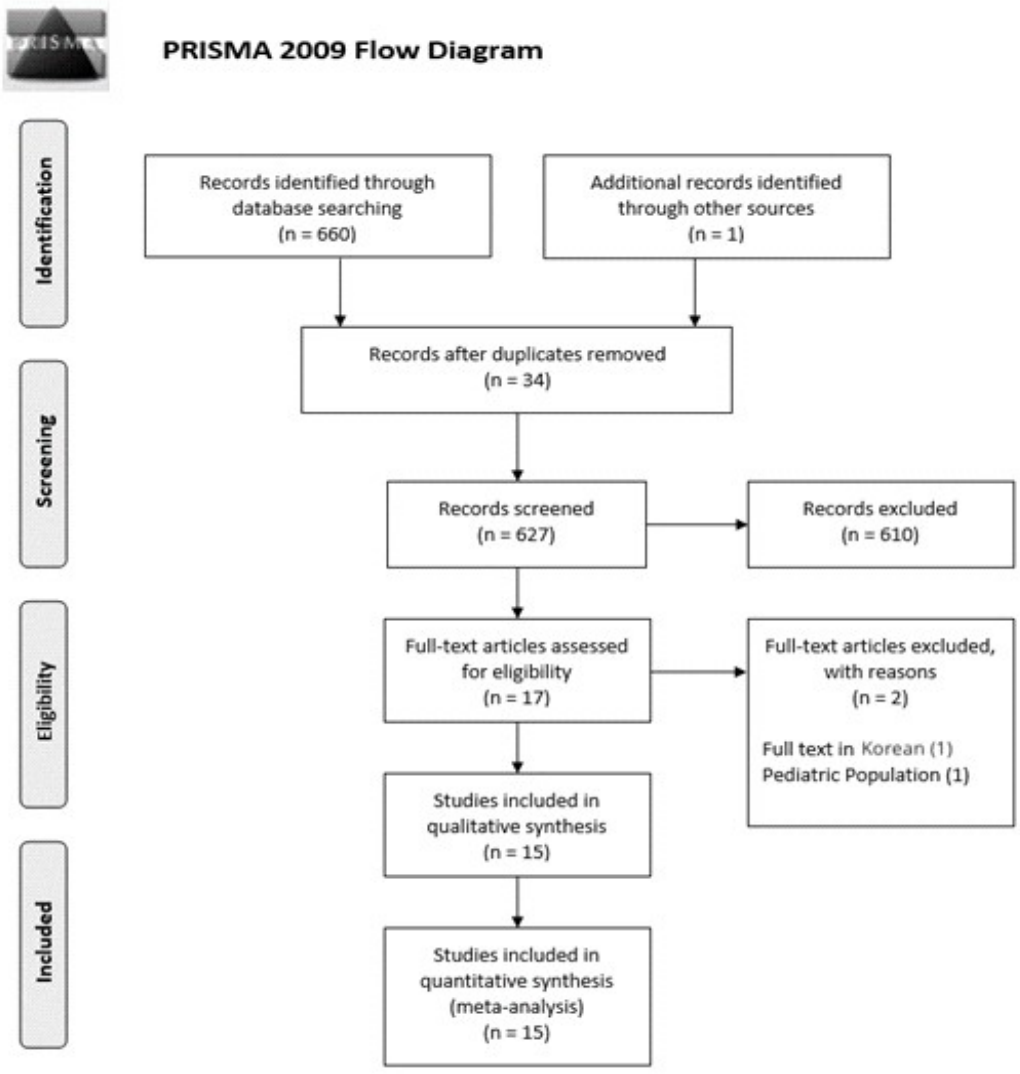

Figure 1. PRISMA flow diagram

Included studies were published between 1993-2015. There were 830 subjects included in all of the studies. The intervention and the control treatment of each study are slightly different. The analgesics used either as pre-emptive or preventive analgesia in the studies comprise morphine, fentanyl, alfentanil, bupivacaine, dextromethorphan, tramadol, lidocaine, lignocaine, gabapentin, acetaminophen, and ropivacaine. The timing of pre-emptive analgesia in each study is also not exactly the same, it varies from an hour before skin incision to exactly before skin incision. The same goes for the timing of preventive analgesia, which varies from exactly after skin incision to before skin closure. The duration of observation is mainly a day after surgery, but some studies extend their observation until 2/3 days after surgery. Rescue analgesics provided for the patients consisted of morphine, meperidine, sodium diclofenac, ibuprofen, paracetamol and fentanyl. A summary of the characteristics of included studies can be seen in Table 1.

Risk of bias

Of all the included studies, one study did not explain the process of randomization of subjects. Therefore, there was an unclear bias risk regarding selection bias. Nine studies did not explain allocation concealment. From five studies that did not explain the blinding of outcome assessment, three studies also did not explain the blinding of participants and personnel. Thus, there was an unclear risk regarding both performance and detection bias. One study had a high risk of

Table 1. Study characteristics and primary outcome

Study	Intervention Group	Number of Patients (Male/Female)	Control Group	Number of Patients (Male/Female)	Duration	Drop-out Rate	Concomitant Therapy	Outcomes
Richmond, et al.[32]	10 mg of morphine (intramuscularly 1 hour before operation or intravenously at induction of anesthesia)	39 (NA)	10 mg of morphine intravenously at closure of the peritoneum	21 (NA)	4-48 hours after operation	0/60	PCA (morphine) on demand	VAS, AU
Fassoulaki, et al.[33]	Fentanyl 10 ug/kg before induction of anesthesia OR sufentanil 1 ug/kg before induction of anesthesia	34 (0/34)	Fentanyl 10 ug/kg either after peritoneal incision or after removal of uterus OR sufentanil 1 ug/kg after peritoneal incision	51 (0/51)	30 minutes-24 hours after surgery	0/85	Propoxyphene 75 mg with paracetamol 600 mg im six hourly supplemented by meperidine 50 mg given im 12 hours postoperatively	VAS, DA
Griffin, et al.[34]	Alfentanil 70 ug/kg 10 minutes before incision	19 (NA)	Alfentanil 70 ug/kg 10 minutes after incision	19 (NA)	6-72 hours after surgery	4/38	PCA (morphine) on demand	VAS at rest, VAS on movement, AEs, AU
Ke, et al.[35]	Local infiltration of 0.5% bupivacaine before incision	20 (0/20)	Local infiltration of 0.5% bupivacaine prior to skin closure	19 (0/19)	30 minutes-24 hours after surgery	0/39	Meperidine on demand	TRA, AU
Helmy, et al.[36]	Dextromethorphan 120 mg intramuscular 30 minutes before skin incision	20 (12/8)	Dextromethorphan 120 mg intramuscular 30 minutes before the end of surgery	20 (13/7)	6-24 hours after surgery	0/40	Ibuprofen on demand	AU, TRA, VAS, AEs
Kilickan, et al.[37]	Morphine 0.15 mg/kg following induction	20 (0/20)	Morphine 0.15 mg/kg during peritoneal closure	20 (0/20)	3 hours-48 hours after surgery	0/40	Morphine on demand	VAS at rest, VAS on movement, AU

Uzunkoy, et al.[38]	Bupivacaine injection at area of skin incision before trocar entry	15 (NA)	Bupivacaine injection at area of skin incision after trocar removal	15 (NA)	1 hour-24 hours after surgery	0/30	Sodium diclofenac on demand	VAS, AU
Wordliczek, et al.[39]	100 mg of tramadol iv before induction of general anesthesia	30 (18/12)	100 mg of tramadol iv immediately after peritoneal closure	30 (16/14)	2 hours-24 hours after surgery	0/60	Patient Controlled Analgesia on demand, 20 mg bolus of tramadol with a lockout time of 5 minutes	VAS, TRA, AU, AEs
Katz, et al.[40]	Epidural lidocaine and fentanyl before incision	49 (NA)	Epidural lidocaine and fentanyl 40 minutes after incision	56 (NA)	3-48 hours after surgery	11/105	PCA (morphine) on demand	VAS, AU
Lam, et al.[41]	10 mL of 1% lignocaine before incision	48 (0/48)	10 mL of 1% lignocaine before closure of incision	48 (0/48)	2-24 hours after surgery	0/96	Paracetamol on demand	VAS, AU
Pandey, et al.[42]	Gabapentin 600 mg 2 hours before surgery	20 (5/15)	Gabapentin 600 mg after surgical incision	20 (8/12)	After surgery-24 hours after surgery	0/40	Fentanyl on demand	VAS, AU, AEs
Karaaslan, et al.[43]	20 mL of 0.5% bupivacaine in the subhepatic area after intubation	16 (6/10)	20 mL of 0.5% bupivacaine in the subhepatic area immediately after creation of pneumoperitoneum AND just before removal of the trocars	34 (13/21)	After surgery-24 hours after surgery	0/50	Diclofenac sodium on demand	VAS, AU
Barczynski, et al. [44]	2 mg/kg of bupivacaine before creation of pneumoperitoneum	30 (3/27)	2 mg/kg of bupivacaine after creation of pneumoperitoneum	30 (4/26)	4 hours-48 hours after surgery	0/60	Ketoprofen on demand	VAS, TRA, AU
Khalili, et al. [45]	15 mg/kg IV acetaminophen 30 minutes before surgery	25 (17/8)	15 mg/kg IV acetaminophen prior to skin closure	25 (21/4)	6 hours-24 hours after surgery	0/50	Meperidine on demand	VRS, TRA, AU
Song, et al. [46]F	Local anesthetic injection containing 0.5% ropivacaine and	25 (17/8)	Local anesthetic injection containing 0.5% ropivacaine and	27 (15/12)	1-24 hours after surgery	8/60	Dexamethasone 10 mg IV, ondansetron 4 mg IV, tramadol 100	NRS, DA

attrition bias, because this study had a dropout rate of 8/60 participants and did not implement an intention-to-treat analysis approach. All studies reported their outcomes based on their proposed design. Accordingly, the risk of reporting bias was low. Additionally, all methods stated in the studies were quite clear to exclude other biases. The risk of bias summary can be seen in Figure 2.

Quantitative analysis

Generally, all fifteen studies, comprising a total of 830 subjects, were included for the purpose of quantitative analysis. Specifically, three studies [41,44,46] were included for assessment of pain 4 hours after surgery, five studies [36,37,42,45,46] were included for assessment of pain 6 hours after surgery, six studies [36,40,42,44-46] were included for assessment of pain 12 hours after surgery and lastly, eight studies [33, 36, 40, 41, 42,44-46] were included to assess pain 24 hours after surgery. Some studies presented their findings in graphs and did not present a table or provided raw data, therefore we did not include their findings in our analysis. As shown in Figure 3, as primary outcome of the study, pre-emptive analgesia resulted in lower VAS/VRS/NRS significantly only up to 4 hours after surgery, with a mean difference (MD) of -0.25 (95% CI [-0.49, -0.02]; p<0.00001) and high level of heterogeneity (I^2=94%) (Figure 3A). There is no significant difference regarding VAS/VRS/NRS during 6, 12 and 24 hours after surgery, with a mean difference of -0.38 (95% CI [- 0.83, -0.06]) (Figure 3B), -0.18 (95% CI [-0.37, -0.00]) (Figure 3C) and 0.03 (95% CI [-0.13, -0.18]) (Figure 3D), respectively. These findings indicated that pre-emptive analgesia might be beneficial in reducing VAS/VRS/NRS only in the short term, but not in the long term.

Three studies [36,39,42] reported adverse effects, with the most common adverse effects reported being nausea and vomiting. The occurrence of nausea and vomiting was similar in both groups, indicating that neither the use of pre-emptive nor preventive analgesia will benefit the patients in terms of side effect occurrences. Regarding rescue analgesic needed, the most common rescue analgesics prescribed are morphine (four studies,[32,34,37,40] meperidine (two

Figure 2. Risk of bias summary

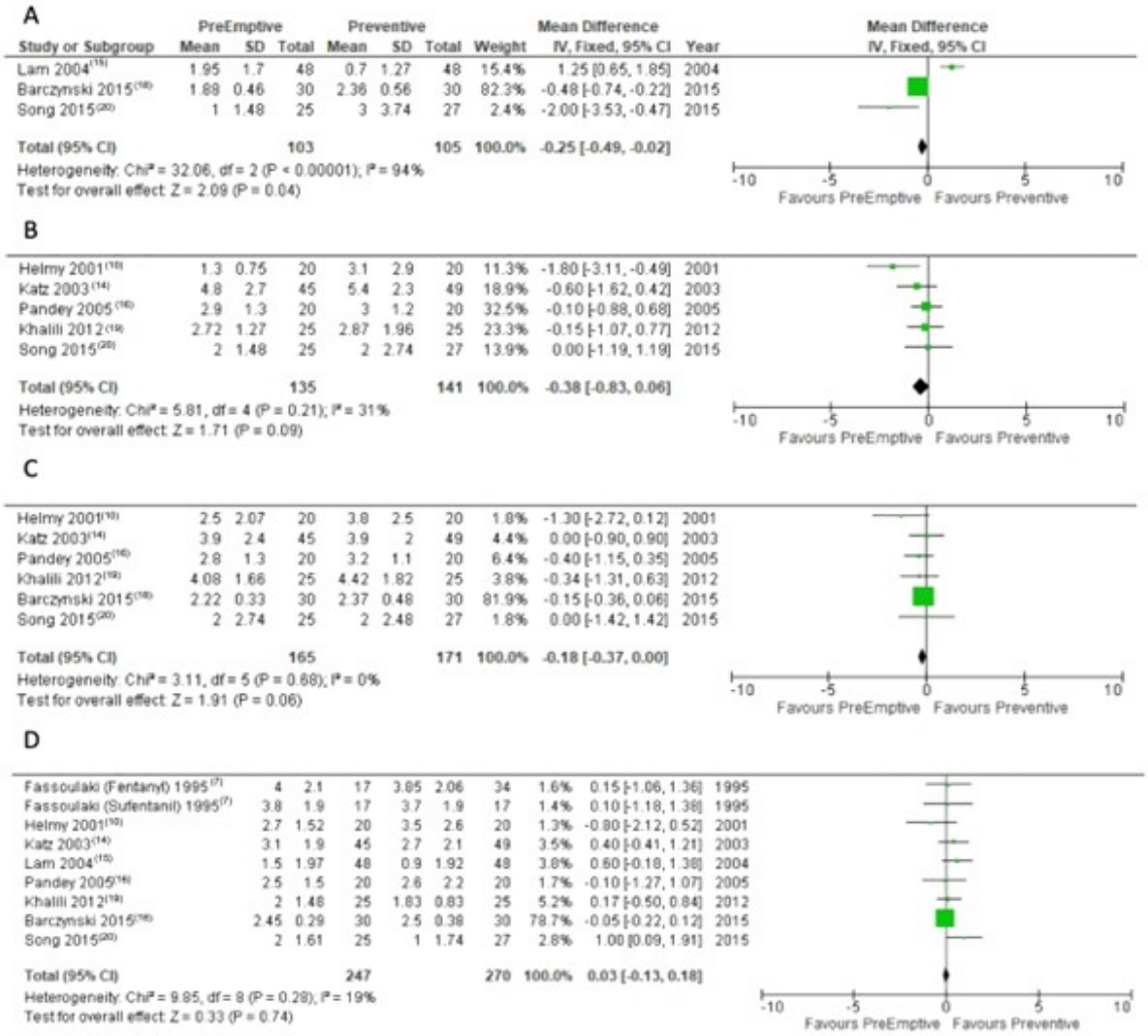

Figure 3. Forest plot analysis of VAS/VRS/NRS. A. 4 Hours, B. 6 hours, C. 12 hours, D. 24 hours after surgery

studies [36,45] and diclofenac sodium (two studies.[38,43] In those studies, similar results had been reported. Consumption of morphine and meperidine (mg) post-surgery reduced the pain significantly in patients given pre-emptive analgesia.

DISCUSSION

Our meta-analysis indicated that pre-emptive analgesia was only beneficial postoperatively for the short-term in terms of pain control. This is shown in the graphs of Fig 3, where VAS/VRS/NRS was only significantly lower during 4 hours after surgery. Unfortunately, the heterogeneity of these results was high (I^2=94%), which might be due to one study with an extremely contradictory result when compared to the other studies. In our findings, VAS/VRS/NRS were similar during 6,12 and 24 hours after surgery, indicating that long-term pain relief is not different between pre-emptive and preventive analgesia. This might be due to the fact that inflammatory injury followed by incisional injury will be reduced over time, [47-50] and that reduced inflammatory injury means reduced pain hypersensitivity. [51-53] However, pre-emptive analgesia was still beneficial during the short term. Pre-emptive analgesia prevents the formation of altered afferent processing input, which will reduce pain post-operatively. This might also explain why the patients receiving pre-emptive analgesia were

taking fewer analgesics postoperatively than did the patients receiving preventive analgesia.

Differences in analgesic effectivity between each study might be related to some factors, such as the half-life of the drugs used and the duration of surgery.[54] Morphine has a half-life of about 2 to 3 hours, while lidocaine has a slightly shorter half-life of about 1.5 to 2 hours.[55, 56] Longer-lasting analgesics are more effective in suppressing pain hypersensitivity than are shorter-lasting analgesics.[31] Therefore, the selection of analgesic agents is important in achieving effective postoperative pain control. A study by Cruz et al.[57] revealed that a shorter duration of surgery correlated with reduced postoperative pain. Duration of surgery is known to be correlated with increased interleukin-6 (IL-6) levels, where IL-6 is a pro-inflammatory cytokine responsible for stimulating C-reactive protein (CRP) and procalcitonin (PCT). Longer periods of surgery might lead to more extensive tissue injury, which might amplify pro-inflammatory responses created by the body.[22] Therefore, the duration of surgery is also an important factor in achieving effective postoperative pain control. The longer the surgery, the more likely it is to result in worse postoperative pain.[58-60]

According to prior studies that included 4-hour postoperative pain outcomes individually, one study had an extremely different outcome compared to the other studies. The study by Lam et al.[41] failed to demonstrate the benefits of pre-emptive analgesia with 1% lignocaine compared to preventive analgesia with the same agent. This might be due to lignocaine belonging to a group called aminoethyl amides and being fast acting after parenteral, oral or topical administration. Its half-life is around 100 minutes and then the lignocaine will be metabolized by the liver.[40,61] This may explain why infiltration of surgical wounds with lignocaine before wound closure would be of more benefit than pre-emptive infiltration of lignocaine.[62-64]

From all the studies that include 6-hour postoperative pain outcomes, Helmy et al.[36] demonstrated the clinical benefits of pre-emptive dextromethorphan injected intramuscularly. The elimination half-life of oral dextromethorphan is around eight hours. Intramuscular injection of dextromethorphan provides higher bioavailability than oral administration of dextromethorphan. A long-acting anesthetic agent administered preoperatively will reduce pain hypersensitivity, thus resulting in a better pain outcome post-operatively.[31,36] Other studies in this group showed similar pain outcomes 6 hours postoperatively between pre-emptive and preventive analgesia.

All studies included for analysis of 12-hour postoperative pain outcomes are consistent, in that they all demonstrated similar pain outcomes between pre-emptive and preventive analgesia. Meanwhile in studies that analyzed 24-hour postoperative pain outcomes, only Song et al.[46] showed better clinical outcomes in preventive analgesia compared to pre-emptive analgesia. This might be explained by their concomitant therapy, where dexamethasone 10 mg IV was administrated before skin closure. This means that the preventive group, which already received a local anesthetic injection containing 0.5% ropivacaine and 1% lidocaine (40 mL) before skin closure, would receive the additional anti-inflammatory effect of dexamethasone, which is a long-acting corticosteroid with a half-life of 36 to 72 hours.[65] Clearly this is an advantage compared to the pre-emptive group, where the patients already received infiltration of ropivacaine and lidocaine before skin incision, therefore reducing the benefits of additional dexamethasone because the agents administrated beforehand might already have been partially metabolized. This might decrease the additive effects of ropivacaine/lidocaine and dexamethasone.

There are some limitations in our study. There are still some studies with unclear risk of bias or high risk of bias in some aspects. Secondly, some studies did not provide mean and standard deviation, but provided median and interquartile ranges instead. Therefore, we had to estimate the mean from the median and also estimate the standard deviation from the range of data. Lastly,

there is still high heterogeneity in some outcomes due to the different methods of each study. Further, we did not consider the influence of variations in surgical procedures since different surgeries may produce differing pain severity and type. Considering our limitations, further prospective studies are needed to support the benefits of pre-emptive analgesia. Postoperative pain is an important part of patient well-being and good postoperative pain control means a better quality of life for the patient.

CONCLUSION

Our analysis demonstrated the benefits of pre-emptive analgesia in achieving better pain relief than those of preventive analgesia during the short term. Furthermore, pre-emptive analgesia is also associated with fewer rescue analgesics taken postoperatively. Further prospective studies with better methods, especially those that include 4, 6, and 12-hour postoperative outcomes, are needed to support the clinical benefits of pre-emptive analgesia.

CONFLICT OF INTEREST

There is no conflict of interest.

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There was no funding for this study.

AUTHOR CONTRIBUTIONS

Conception and design of the case series: ART, RF. Informed consent: HA, APN. Interpretation and analysis of data: ART, HA, RF. Drafting the manuscript: ART, HA, APN, MAIM. Final approval of the manuscript: ART, RF. All authors have read and approved the final manuscripts.

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