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Effectiveness of Opioids-Adjuvant Analgesics Combinations for Pediatric Cancer Pain: A Systematic Review

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ABSTRACT

Background: The pediatric cancer was reported that they got worst pain and 40% weren't managed well. The impact of untreated cancer pain is low quality of life and poor pain experienced. Therefore, it is important to know the best analgesic for improving the clinical outcome of pain.

Objectives: This study aims to determine the effectiveness of using opioid combined with adjuvant analgesics based on WHO analgesic ladder in pediatric cancer pain.

Methods: PubMed and Science Direct were searched for randomized controlled trials and retrospective studies by the keyword's "opioid", "adjuvant analgesic", "pediatric", "cancer" within 2014-2024. The primary outcome was using Faces Pain Scale, or visual analog scale (VAS), or numerical rating scale (NRS).

Results: A result of 556 studies were reviewed. After further inspection of collected studies, only 5 studies achieved all inclusion criteria. The final studies consist of two prospective studies with randomized trial and three retrospective studies. Combination gabapentin or pregabalin as adjuvant analgesic with opioids was better reduced pain intensity and less adverse events than other combinations.

Conclusion: This study supports the increased effectiveness of analgesic opioid combined with adjuvant analgesics, compared with single opioid, in the treatment of pediatric cancer pain. Further study inspires researchers to conduct studies using the randomized trial method and continue meta-analysis study especially in pediatric population and developing countries.

Keywords: Adjuvant analgesic; cancer pain; effectiveness; opioid; pediatric

INTRODUCTION

The global incidence rate of pediatric cancer in United States was 178,3 per 1 million, the rate increased 5% per year during 2003-2019. It was solid and non-solid carcinoma e.g. lymphoma, neoplasm, leukemia, bone tumors, hepatic tumors.[1] Cancer pain occurs in perioperative procedures, nerve damage post-radiation, chemotherapy and mucositis. However, the tumor itself can also cause nerve infiltration, external nerve compression, and other painful inflammatory events.[2] More than 50% of the population in pediatric cancer was reported that they got worst pain and 40% wasn't manage well.[3] The impact of untreated cancer pain is low quality of life and poor pain experienced.[4]

Pain is an impact caused by various treatment procedures for cancer. In treatments for pediatric cancer, the most common chemotherapy was complex regiments and multiple agents. Such as neuropathy pain in patients with leukemia during chemotherapy. Vincristine is suspected to be one of the chemotherapy agents induced neuropathic pain, 33,75% population had neuropathic pain.[5] That agent influenced sensory and motoric nerves, on the whole autonomic nervous system leading to uncontrollable pain.[6] Platinum agents (cisplatin, oxaliplatin, carboplatin) and taxanes (docetaxel, paclitaxel) also have suspected induced neuropathic pain. These were used for treatments solid tumors (brain tumor) by binding DNA leading to cancer cell death and neuronal

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damage caused pain.[6,7] These pain symptoms can persist for months or years after discontinuation chemotherapy treatment, which can worsen the patient's condition. However, we lack a thorough understanding of the underlying mechanism of neuropathic pain in children population, it is critical for developing strategies of effective treatment.

World Health Organization (WHO) analgesic ladder is a strategic to relieve cancer pain. From these guideline, step 2 (weak opioid: tramadol, codeine ± adjuvant therapy) and step 3 (strong opioid: morphine, fentanyl ± adjuvant therapy) are most recommended for cancer patients with moderate-severe pain levels (Numerical Rating Scale score >5/10).[8–10] Opioid analgesics have been shown to significantly improve cancer pain.[11–13] However, inappropriate use of opioids can increase the incidence of adverse events.[14] Adverse events that commonly occur in children with opioid use were nausea, constipation, pruritus, and rash. The incidence of adverse events of opioids was 88,6% from prescriptions, it was increased by age and higher opioid doses.[15]

Adjuvant therapy is an additional analgesic intervention given to patients who show a poor response to opioids. Adjuvant analgesics consist of antidepressants (amitriptyline), anticonvulsants (pregabalin, gabapentin), NMDA receptor antagonist (ketamine, methadone), Na channel blocker (lidocaine).[11,16] Combining these drugs with opioid has resulted significant benefits for cancer pain, enhancing analgesics effect and or reducing the side effects of opioids.[17] In pediatric population, evidence of efficacy adjuvant analgesics is still rare. Lack of research on the use of adjuvant therapy leads to inappropriate medication.[14] It is critical to investigate how to utilize a combination of analgesics to determine effectiveness from the decrease pain relief.

This study aims to determine the effectiveness of opioid-adjuvant analgesics to reduce pain intensity in pediatric cancer pain.

METHODS

Study design

This systematic review focuses on evaluation of effectiveness opioid combined with adjuvant analgesics in pediatric cancer pain. This article research conducted in June 2024, and it used the protocol PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[18]

Search strategy

The search terms were “opioid”, “adjuvant analgesic”, “pediatric”, “cancer” by adding “AND” “OR” between the keywords in the database used. The databased sources were primary literature from PubMed and Science Direct database published between January 2014 - June 2024. English language restriction and available in full text.

Eligibility criteria

Inclusion criteria were adopted PICOS and focused on efficacy opioid combined adjuvant analgesics.

Table I. PICO elements of inclusion criteria

Participants (P)	**0-18 years old**
Intervention (I)	Opioid combined adjuvant analgesics (antidepressants, anticonvulsants, NMDA receptor antagonist, Na channel blocker)
Comparison (C)	Placebo or single opioid analgesic
Outcome (O)	Intensity pain score (Numerical Rating Scale score or Visual Analog Scale)
Study Design (S)	Randomized controlled trials and retrospective studies

Inclusion criteria for screening studies:

Types of study method and interventions: randomized controlled trial and retrospective studies. The content is an evaluation of opioids combined with adjuvant analgesics (antidepressants, anticonvulsants, NMDA receptor antagonist, Na channel blocker. Reviews, case reports, guidelines, opinions were excluded.

Types of patients: Children aged 0-18 years old, diagnoses were solid cancer and nonsolid cancer (including perioperative, postoperative, radiotherapy, chemotherapy, neuropathic pain related to cancer).

Types of outcomes: The primary outcome was intensity pain score using Faces Pain Scale, or visual analog scale (VAS), or numerical rating scale (NRS). The scores of the scales used are between 0-10. The degree of pain was scored as “0” representing no pain, and “10” representing the most severe pain.

Data Extraction

Two independent researchers extracted all studies, including screened titles, full text and English language restrictions based on eligibility criteria. If any discrepancies arise, consult a third researcher (professional reviewer) to resolve the differing arguments. Details of data extraction were study design, countries, patient number, intervention, comparison, clinical outcome measurement (intensity pain score) and the main findings. The data was extracted using standard sheet of Microsoft Excel.

Risk of bias selected studies conducted assessment. Non-randomized studies using the ROBINS-I tool. Assessments were conducted manually by two independent researchers, and results are presented in Table III. For randomized controlled trial study using the Cochrane Risk of Bias tool within RevMan version 5.4.1. The domains evaluated risk of bias include random sequence, allocation concealment, blinding of participant, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential bias.

Data Analysis

Pain intensity score data were collected, analysed, and compared to the single opioid group, as evidenced by the significant p-value in each study. Subsequently, these were subjected to analysis employing validation techniques. In the absence of a p-value, the % decrease in pain scores was utilized. However, this data was only used for descriptive analysis.

RESULTS AND DISCUSSION

Description of selected studies

We searched 556 articles through PubMed and Science Direct using keywords described in our strategies. After screened from title and abstract, 19 studies were selected for next step analysis. However, 6 articles were excluded because they used opioid without adjuvant analgesics and or used single opioid. Then, articles were excluded because the subjects from these studies are over 18 years old. Last time, 1 article was excluded by duplication. Finally, after excluding these studies, our present systematic review studies within January 2014-June 2024. Meta-analytic techniques could not be fully implemented due to the limited number of included studies and heterogeneity in study design. The PRISMA diagram from retrieved this study (figure 1).

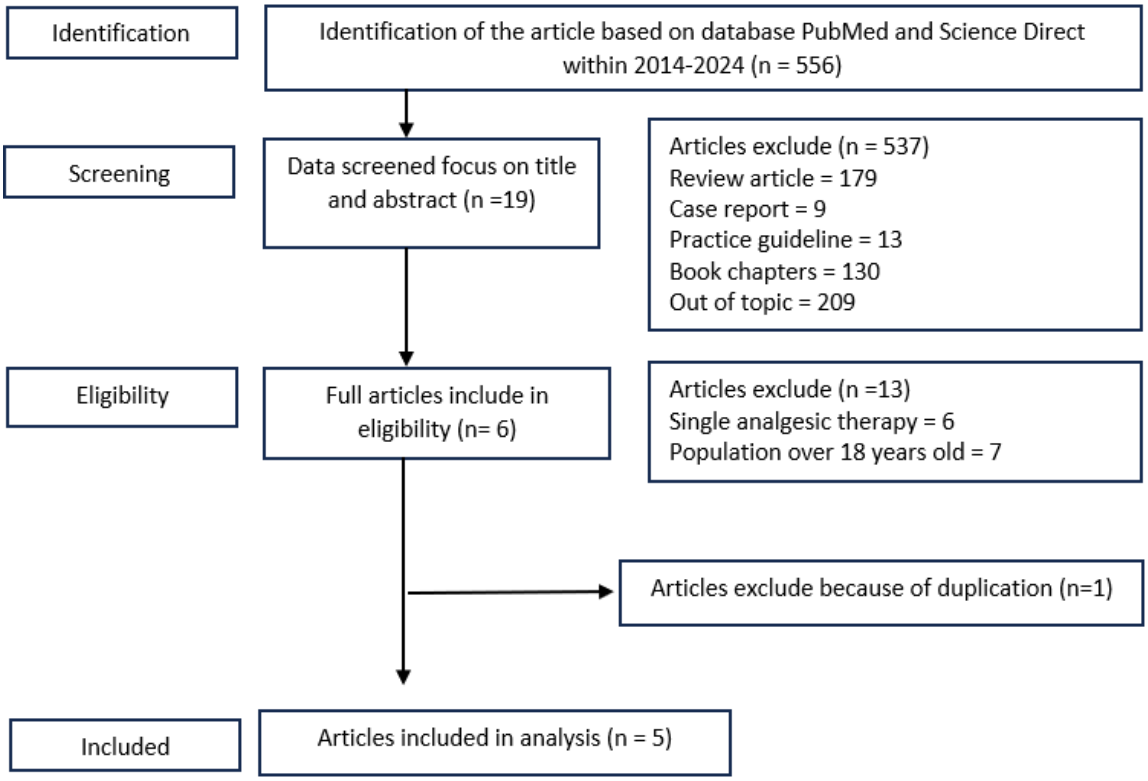

Figure 1. PRISMA Flow Diagram of Retrieves Data

Our systematic review contained five studies, all the studies published 5 years ago, including two randomized controlled trials and three retrospective studies. The most frequent country in this study was Asia (Egypt, China, Turkey, India) and one study from USA.

There were variations in the number of patients; three studies had population between 45-90 patients, two retrospective studies had small population around 8-11 patients. Diagnoses in these randomized controlled trial studies were abdominal cancer surgery and malignant bone tumors. Diagnoses in these retrospective studies were leukemia, lymphoma, sarcoma, neuroblastoma, osteosarcoma, Ewing's sarcoma, Hodgkin lymphoma. Difference studies design, diagnoses and number of patients in two retrospective studies might be major influence of heterogenicity. Details of these studies are shown in Table II.

In these selected studies had two types of cancer pain. First type, neuropathic cancer pain. Etiologies often occur after chemotherapy (chemotherapy induced neuropathic pain), caused by cancer, nerve damage, or radiotherapy. Pain can cause by nerve damage which compressed by tumor, chemotherapy agents cross the blood brain barrier and blocking sensory and motor nerves also can induced pain.[19–21] Neuropathic cancer pain symptoms are burning, tingling and electrical sensation.[21] In Bakir *et al.,* (2023) study, there was a type of neuropathic pain in the pediatric population, the most common diagnosis was leukemia. Vincristine is the one of chemotherapy agents for leukemia's regimen, which is thought to increase the risk of neuropathic pain.[21,22]

Nociceptive pain was another type of cancer pain. The etiologies were caused by tissue damage (non-neural tissue) for example by surgery. Nociceptive cancer pain can be classified into somatic and visceral depending on structure damage.[23] However, cancer pain is often caused by mixed pathophysiology, both nociceptive and neuropathic. In Ghobrial *et al.,* (2019), Wang *et al.,* (2018), and Revuri *et al*., (2022) studies, there was using analgesic intraoperatively and postoperatively. It was type of nociceptive pain and mixed pain (shown from symptoms).[24–26]

Considering the causes and severity of pain in cancer patients, the 2018 ESMO Guidelines on Cancer Pain Management suggest the inclusion of adjuvant analgesics in the treatment of cancer patients.[27] This is also indicated in the 2025 NCCN Guidelines for Adult Cancer Pain Management, which advises combination analgesic therapies to relief pain crises, patient anxiety following surgery or chemotherapy, and additional benefits such as opioid dose reduction.[28] For example combination opioid analgesic with antidepressant agents as adjuvant analgesic, showed effectiveness to reduce intensity pain score. It works to enhance availability monoamine in synaptic nerve pathways; it was reduced pain modulating system. Another mechanism action of antidepressant is norepinephrine reuptake inhibition; serotonergic and dopaminergic actions may also contribute to analgesia.[27,28]

Pain can be measured using many methods. The most frequently used numerating rate scale (NRS) and visual analog scale (VAS) with score range 1-10. Scored as "0" representing no pain, and "10" representing the most severe pain. Differences in score of pain and type of pain in patients are a consideration in selecting analgesics. The data extraction about study objectives and selected studies in this systematic review can be seen in table IV. The clinical outcomes of pain in this study used NRS and VAS scores.

Table II. Characteristics of included studies

First Author	Country	Study Design	Patient Number	Patient Diagnose
Ghobrial [24]	Egypt	Randomized Controlled Pilot Study	90	Abdominal Cancer Surgery
Wang[25]	China	A Prospective Double-Blind Randomized Controlled Trial	45	Malignant Bone Tumor
Bakir[22]	Turkey	A retrospective single center study	90	Leukemia, lymphoma, sarcoma, neuroblastoma
Revuri[26]	USA	Cohort retrospective analysis	8	Osteosarcoma, Ewing's sarcoma
Palat[29]	India	Retrospective study	11	Ewing's sarcoma, Hodgkin lymphoma

Risk of bias in selected studies

Five selected studies were evaluated for potential bias and indicated that most domains were in the low risk of bias category. However, in figure II evaluation using RevMan, the results of one RCT study showed limitations in the randomization procedure, and unclear bias risk was indicated in the blinding of participants domain. It because in the trial, blinding of patient's post-surgery could not be carried out, which could raise the risk of bias.[24] One study also had limitations in the blinding of outcome assessment domain, this was not clearly stated. [25] Overall, the risk of bias can be stated well with limitations in the blinding process.

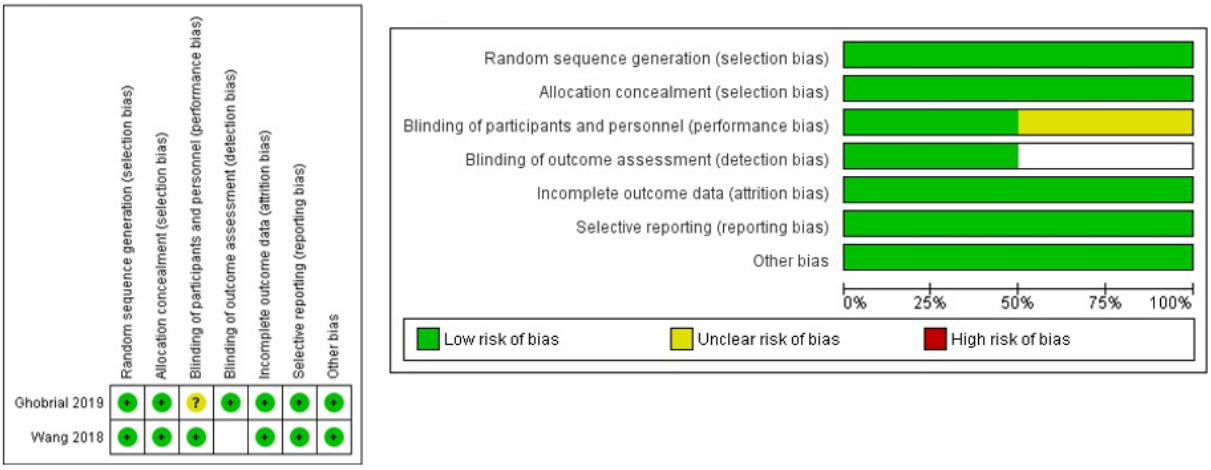

Figure 2. Risk of bias randomized controlled trial using RevMan version 5.4.1

Table III evaluation using ROBIN-I shown in non-randomized studies, many domains exhibit a low potential risk of bias, indicating that the research methodology is acceptable. However, one study demonstrated moderate results in measuring outcomes and reporting results domain, which may impact the analysis and comparison of study groups.[29] Despite of this condition, rating of domain mostly shown low risk of bias and it support to randomized controlled studies.

Table III. Risk of bias non-randomized studies using ROBIN-I tool

Selected study	Study design	Confounding	Classification of interventions	Selection of participant	Deviations from intended intervention	Missing data	Measurement of the outcome	Selection of the reported result
Bakir[22]	A retrospective single center study	Low	Low	Low	Low	Low	Low	Low
Revuri[26]	Cohort retrospective analysis	Low	Low	Low	Low	Low	Low	Low
Palat[29]	Retrospective study	Low	Low	Low	Low	Low	Moderate	Moderate

Analgesics and adjuvant analgesics in cancer pain

Analgesic is a palliative care in cancer populations. Management of using analgesics in patients depends on type and severity of pain. The most common strategies used WHO analgesic step ladder. First step for mild pain (measure from scoring 1-3 NRS or VAS) used analgesic non-opioids such as paracetamol and NSAIDs. Moderate pain in second step (measure from scoring 4-6 NRS or VAS) used combination opioid and non-opioid. Opioids for moderate pain refer to weak opioids such as tramadol. Last step for severe pain (measure from scoring 7-10 NRS or VAS) used combination non-opioid, opioid and adjuvant analgesics.[30] Adjuvants analgesics refer to some drugs were used other than analgesic, but to be potentially useful as analgesics in patients receiving opioid.[16] Adjuvant analgesics administration timing commonly for chronic pain after poorly response with opioid,

cancer survivors with chronic neuropathic pain, minimize dosage and side effects of opioid. Alternative approach used opioid rotation (change other opioid), but it increased aggressive side effects.[16,30,31] Using of adjuvant analgesics is the most recommendation to achieve pain control (figure 1).

Adjuvant analgesics for cancer pain consist of antidepressants, anticonvulsants, NMDA receptor antagonist, sodium channel blocker. Antidepressant agents work to enhance availability monoamine in synaptic nerve pathways; it was reduced pain modulating system. Another mechanism action of antidepressant is norepinephrine reuptake inhibition; serotonergic and dopaminergic actions may also contribute to analgesia. Japanese guideline recommended amitriptyline, duloxetine used in cancer pain based on recently research in adult but still rare in pediatric population because can cause side effect prolong QT and cardiac arrhythmias.[30,32] Combination morphine and amitriptyline also increased sedative effect and delayed morphine clearance.[33] There are also not included study using antidepressant in this systematic review.

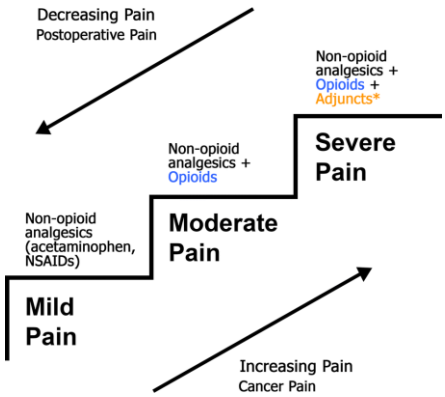

Figure 3. WHO Analgesic step ladder[30]

Anticonvulsant agent recommended by united state guidelines is pregabalin and gabapentin. These mechanism action by binding to the alpha-2-delta protein, which modulates the N-type voltage-gated calcium channel.[34] Binding to this protein lowers calcium influx into the cell, lowering the risk of depolarization. In neuropathic pain unrelated with depressed mood, first line for therapy suggested gabapentin and pregabalin rather than antidepressants.[30]. Difference profile pharmacokinetic of gabapentin and pregabalin can be considered in agent selection. Absorption of gabapentin mediated by saturable transporter in small intestine and central nervous system, so higher dose of gabapentin brings less complete absorption then become non-linear kinetic. These saturable kinetics explain that gabapentin has limits on its pharmacokinetic and pharmacodynamic effects. Otherwise, pregabalin absorption wasn't mediated by saturable transporter then become linear kinetic. Pregabalin has a linear pharmacokinetic profile, making dosage easier than gabapentin.[17,35,36]

The N-methyl-D-aspartate (NMDA) receptor antagonist available is ketamine and methadone, it plays a role in sensitizing central neuron and regulating opioid receptors activity[37]. Subanaesthetic dose of ketamine used in bolus infusion for severe pain or prolonged infusion for refractory pain / advanced illness. Ketamine administration also available in oral, repeated bolus. Short term therapy of ketamine should be monitor for minimize side effect such as delirium and hallucinations.[30,38]

Sodium channel blocker available is lidocaine, it is amide local anesthetic. Lidocaine acts to block nerve conduction through sodium channels on inhibit G protein coupled receptors, sensory neurons and NMDA receptors for analgesic effect and anti-inflammatory.[39] Neural transmission is progressively reduced by increasing lidocaine concentrations, ultimately suppressing motoric and sensory functions to the extent of surgical analgesia and blocking of clinical motor.[16,39] Lidocaine can be taken systemically dose that effectively decrease nociceptive pain sensation without influence sensory and motor function. Due to the high dose-response curve of intravenous lidocaine, minimal dose increased lead to significant improvements in pain relief.[39] Need monitoring for minimize side effect of lidocaine is dizziness, nausea and fatigue.[16]

Effectiveness of opioids combined with adjuvant analgesics in pediatric cancer pain

The assessment of analgesic effectiveness was seen from the mean score pre and post using combined opioids and analgesic adjuvants. All studies compared analgesic effectiveness between control group and test group to see obvious differences. Opioids analgesic intervention given in control group, four study in this

systematic review used morphine as strong opioid. Mechanism action of morphine has an affinity for delta, kappa, and mu-opioid receptors in CNS (central nervous system) and peripheral nervous system.[40] Last studies reported unresponsive to opioids almost 10-15% of population, it can cause disease progression, poor psychological conditions, presence of a neuropathic component, and breakthrough pain.[36,40,41] Increased doses or switching opioid drug is a common practice to achieved clinical outcome cancer pain, but it can increase adverse effects of opioid such as constipation, drowsiness, and nausea.[31,41] WHO recommended adding adjuvant analgesic using analgesic step ladder strategies for better control pain cancer.[30]

Table IV. Effectiveness opioids combined with adjuvant analgesics

Study	Intervention	Comparison (Single Opioid)	Pain Measurement	Main Finding
Ghobrial *et al.,* 2019[24]	Ketamine 0,5 mg/kg bolus	Morphine iv 0,1 mg/kg	VAS	Combination analgesics improve analgesic effect after 24 hours (reduced VAS score) but no statistically significant p=0,546 with control group. The combined approach is more effective than single morphine.
Wang *et al.,*2018[25]	Gabapentin 300mg once daily (D1), 300mg twice daily (D2), 300mg three times daily (D3-30)	Intradermal morphine and oral oxycodone	VAS	Morphine combined with gabapentin reduced phantom limb pain better than single opioid (statistically significant p=0,033). In D4-D9 post operative, this combination showed steady decreased in pain intensity (p<0,05).
Bakir *et al.,* 2023[22]	Pregabalin 3-5 mg/kg/day	Tramadol 52,2%, morphine 43,3%, fentanyl patch 13,3%	NRS and VAS	These combination analgesics decreased pain intensity from 5.2±1.7 to 1.5±0.7 with a statistically significant (p<0.001).
Revuri *et al*., 2022[26]	Gabapentin (post-operatively)	Fentanyl	NRS	The mean pain score was highest on post-operative day 0 at 3 ± 3.75 and lowest on day of discharge at 0.75 ± 1.09 (p=0.002). Effectiveness of the analgesic combination was successful significant in 75% of patients.
Palat *et al*., 2021[29]	Oral methadone	Oral morphine equivalent daily dose 15-240mg	NRS	The addition of methadone had shown increased analgesic effect in 50% of population. Side effects of methadone are nausea (3 patients) and tachycardia (1 patient).

In Ghobrial *et al.,* (2019) study, adjuvant analgesics used ketamine.[24] Ketamine is NMDA receptor antagonist as anesthesia agent; it works to maintain respiratory activity.[37] Furthermore, recent study of systematic review, ketamine has been reported as analgesic in chronic pain and perioperative pain. Active metabolites ketamine such as nor-ketamine which had pain relieve activity.[38,42,43] In Ghobrial *et al.,* (2019) study, effectiveness of combined analgesics hadn't shown differences than control group using single morphine with value p=0,521. Another study Sleigh *et al*., (2014) also reported delayed effects of ketamine and hadn't long effect of analgesic.[37] It can cause combined analgesics (opioid and ketamine) which aren't better than single opioid for reducing pain. Benefit results of these combined analgesics reduced total morphine consumption with value p<0,001.[24] Low total morphine consumption gives benefit to reduces the risk of morphine adverse events such as constipation, nausea, vomiting.[14]

Three selected studies in this systematic review used gabapentin, pregabalin as adjuvant analgesic and morphine, fentanyl as opioid analgesic.[22,25,26] In Wang *et al*., (2018) study, patients in morphine intradermal combined gabapentin group had reduced VAS score better than single opioid group (77,27% versus 43,84% in day 60 after amputation malignant bone tumors surgery) with value p<0,05. Gabapentin oral dose 300 mg once

daily (day 1), 300 mg twice daily (day 2), 300 mg three times daily (day 3 until day 30). There were no significant adverse events in both groups.[25] Revuri *et al* (2022) study in pediatric pelvic and bone sarcoma patients, given chemotherapy: doxorubicin, ifosfamide, cisplatin, methotrexate before operative and chemotherapy: doxorubicin, ifosfamide, etoposide after operative. It also reported that transdermal fentanyl combined gabapentin could reduce NRS score in 75% population at day of discharge. On post-operative day 0, NRS mean score was 3 ± 3.75 and 0.75 ± 1.09 on day of discharge (post-operative day 60).[26] Bakir *et al* (2023) study in pediatric population with commonly diagnosed leukemia and lymphoma. This used morphine, fentanyl patch combined pregabalin. Dose of pregabalin was 75-300 per day (5 mg/kg). These combinations decreased pain intensity using VAS score and NRS score from 5.2±1.7 to 1.5±0.7 with a statistically significant ($p<0.001$). Complication of this pain management was nausea-vomiting (4,4%) and itching (2,2%).[22]

Meta-analysis studies have explored the combination of opioid with gabapentin and pregabalin in adult cancer patients, but lack of study in pediatric population. Gabapentin was known as an antiepileptic drug but recently gabapentin has been used to treat neuropathic pain combined with other analgesics.[34,35] Gabapentin proved can decrease pain intensity especially neuropathic pain type.[34] Mechanism action of gabapentin as adjuvant analgesic is specifically targeting the α-2-δ subunit of voltage-gated calcium channels (Ca^{2+}) lead to reduce Ca^{2+} and releases neurotransmitters glutamate that influence pain perception and reduce neuropathic pain.[34] Gabapentin has different mechanism action with opioid. Recently, the combination of gabapentin with opioids has improved the effectiveness of pain and another benefit can reduce morphine consumption.[36] Most common side effect of gabapentin is drowsiness. Strategies to reduce side effect, started low initial dose gabapentin and then titrated upward. Oral loading dose 5 mg/kg once daily, then increase twice daily on day 2, three times daily on day 3.[30] This strategy has been carried out appropriately in research included in this systematic review and show effectively pain control without seriously side effect.[25,26]

Pregabalin in study Bakir *et al* (2023) administrated one dose 3-5 mg/kg/day, it is different with gabapentin that administrated in titrate doses. Because pregabalin absorption wasn't mediated by saturable transporters in nervous system, pregabalin has a linear pharmacokinetic. In that profile pharmacokinetic doesn't need titrate dose administration of pregabalin to give effectiveness of pain control.[17,22,36] In others study, meta-analysis of efficacy gabapentinoids show better outcomes of pregabalin than gabapentin. Pregabalin reduced ≥50% pain intensity in many patients compared with gabapentin, other superiority of pregabalin give bigger patients impression of clinical change than gabapentin. The most common adverse events of gabapentinoids were related to cognition and coordination such as dizziness and somnolence.[34,44]

In Palat *et al* (2021) study, adjuvant analgesic used oral methadone and morphine as opioid. These combinations had shown increased analgesic effect in 50% of population.[29,45] Loading daily dose of methadone was 3-15mg, give in oral (commonly liquid formulation and a few in pills). Previous decades, methadone used for treatment of refractory pain. In systematic review study, methadone reported effective for both types of pain: nociceptive and neuropathy. In the central nervous system (CNS), methadone acts as a moderate antagonist at the NMDA receptor and powerfully inhibits serotonin and noradrenalin reuptake, therefore inhibiting pain sensation through and attenuating neuropathic pain from the periphery or central nervous system.[46,47]

Weakness of methadone in pharmacokinetic profile, it is highly lipophilic drug with large distribution volume. Methadone metabolizes in liver by cytochrome P450 enzyme, methadone is also substrate for P-glycoprotein, inductor or inhibitor P-glycoprotein can change methadone concentration in blood. it leads to potential drugs interaction such as prolonged QT interval that increased risk for ventricular arrythmia.[45] That cardiotoxicity will be seriously adverse drug reaction if the patients got anthracycline agents for chemotherapy such as doxorubicin, epirubicin.[48] It shown in 1 patient of subject studies got tachycardia during treatment.[29] Another effect of drug interaction was depression respiratory, sedative and gastrointestinal; it comes from interaction of methadone and opioid drug (codeine, morphine, fentanyl). In this study using combination of methadone and morphine leads to increase depression respiratory, sedative effect and gastrointestinal, it shown in 3 patients of subject studies got nausea during treatment.[29]

There was some treatment combinations based on our review, including morphine-ketamine, morphine oxycodone-gabapentin, tramadol morphine fentanyl-pregabalin, fentanyl-gabapentin, morphine-methadone. Combination opioids with gabapentinoids agent (gabapentin and pregabalin) were the most used in pediatrics, also decreased pain intensity and less adverse events in populations than other combinations. Benefit this combination was also low risk of opioid side effects (constipation). Challenging of using this combination need titrate dose administration of gabapentin, started low initial dose gabapentin and then titrated upward for reduced drowsiness side effects.[30] Another studies, combination morphine-ketamine shown reduced pain intensity but reported delayed effects of ketamine and hadn't long effect of analgesic.[24,37] Combination

morphine-oxycodone can decrease pain intensity, but subjects study experienced some adverse effects (nausea and tachycardia), that weakness was associated with drug interaction opioids and methadone.[29] We strongly recommend gabapentin or pregabalin as adjuvant analgesic to combine with opioids.

Potential limitations must be considered when interpreting this review, including heterogeneity method of included studies was challenging to create in this systematic review. In our finding, this research was dominating from developing countries, there were 3 included studies can represent issue in this region. Another finding, study about effectiveness of using opioid combined with adjuvant analgesic for paediatric cancer pain was still limited. Especially study in paediatric populations 0-18 years old, possibly due to ethical considerations in considering the risks of treatment and the side effects that will occur in children.[13] Therefore, we are suggesting more prospective studies (randomized trial method) of opioid and adjuvant analgesic in paediatric population for homogeneous subject and minimize bias especially in developing countries.

CONCLUSION

This systematic review supports the increased effectiveness of analgesic opioid combined with adjuvant analgesics, compared with single opioid, in the treatment of pediatric cancer pain. Despite limitations of small sample sizes, intervention heterogeneity and lack of standardized outcome measures across studies. Therefore, our research could provide more guidance management of pediatric cancer pain to improve pain control in cancer patients and to inspire researchers to conduct studies using the randomized trial method and continue meta-analysis study especially in pediatric population and developing countries.

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