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# The Effectiveness of Analgesics in Pain Treatment in Critically Ill Children: a Literature Review



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## ABSTRACT

Adequate pain management is an important and common requirement in health care in pediatric intensive care units. There are many pain assessment scales in children based on the literature, but the guidelines for using pain scales as a guide in pain management have not been widely discussed. One of the most common pain interventions is to provide opioid or non-opioid analgesics. Analgesic drugs given to critically ill children can provide different anti-pain outcomes when measured by a pain scale. Therefore, this literature review will compare the effectiveness of analgesics in pain management in critically ill children.

**Keywords:** Analgesics, opioid, non-opioid, pain measurement, PICU.

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## INTRODUCTION

Pain management is important in the pediatric intensive care unit. Critically ill children tend to experience more severe pain due to their illness as well as procedures to be performed in both surgical and medical nursing units.<sup>1</sup> When compared to pain in children in general medical surgical floors, critically ill children have significantly more cases of moderate to severe pain and have higher pain scores.<sup>2</sup> Patients with critical illness often experience uncontrolled pain and the use of analgesic drugs can actually prevent this. Pain can elicit an immediate physiological response, including an increase in intracranial pressure, heart rate, respiratory rate, blood pressure, blood glucose, and hormonal stress as well as a decrease in oxygen saturation. Furthermore, pain experienced by children is often associated with changes in sensory perception, stress response, cognition, and immune function which can later increase the risk of diseases of the nervous system and affective disorders in the future.<sup>1,3</sup> The perception of pain becomes highly subjective depending on a person's emotional state and emotional experience.<sup>3,4</sup> Therefore, minimizing pain in pediatric intensive care units can improve the quality of a child's health in

both the short and long term.<sup>1,3</sup>

The scale of pain assessment in children based on literature is quite a lot, but the guidelines for using the pain scale as a guide in pain management have not been widely discussed, because the population in the Pediatric Intensive Care Unit (PICU) is so complex, ranging from diverse ages, different levels of cognitive development of children, and the number of diagnoses of diseases that each child may be able to suffer from.<sup>3,5</sup> One way to deal with pain is to give opioid or non-opioid analgesics. Opioids are currently an option that has long been used to treat pain, and has proven to be more effective than non-opioids. A meta-analysis examining various opioid drugs (compared to placebo and nonsteroidal anti-inflammatory drugs [NSAIDs]) in chronic non-cancerous pain found that, all patients with Chronic Non-Cancer Pain (CNCP) did not respond to opioids, only 30-50% of screened subjects reported experiencing a decrease in pain with opioids.<sup>6,7</sup>

Based on the above review, a literature review is needed that discusses the effectiveness of analgesic drugs used in critically ill children in intensive care unit, including the relationship between pain scores and analgesic administration in critically ill children, length of ventilator

use, length of hospitalization, and extubation time.

## METHOD

This study is a literature review without statistical analysis and process of literature review method. The search is done using AND to search for literature containing all keywords and OR to search for literature that contains alternative keywords. The search strategy is carried out with search keywords namely (Analgesics OR Opioid OR Non-Narcotic OR Pain management) AND (Pediatric Intensive Care Unit) AND (Length of stay OR Pain Measurement OR intubation OR mechanical ventilation). This research database comes from a literature search in :

1. PubMed
2. The Cochrane Library

The limitation of literature search in this study is only the English literature used and the limit of the last 10 years, children aged >1 month and <18 years of publication from literature. From the literature search, 1302 articles were obtained, of which 10 articles were identified as relevant to the topic and met the inclusion criteria. The article consists of retrospective, observational and RCT research in 2012-2022. In this study, the outputs that are often reported

are the length of ventilator use, length of hospitalization, extubation time, and pain score.

### Pain assessment in children

Pain assessment in children is the most important component of pain management, sometimes difficult to do, because there is no one standard method that can measure pain in children in various conditions. Self-report by children is a reliable indicator in measuring the scale of pain in children.<sup>3</sup> However, this only applies to children with good cognitive and communication skills, but cannot be applied to all age groups. In infants and children with cognitive and communication abilities that are not optimal in their development, self-report is not possible, so pain observation can be based on observations of physiology and behavior in children. One way to assess pain is to use the QUESTT method, which is: Question the child, Use a pain rating scale, Evaluate the patient's behavior and physiologic changes (secure the parent's involvement), Take the cause of pain into account, and Take action and evaluate results.<sup>3,6</sup>

#### a. Measurement pain by giving questions to children

The statement and description of pain is an important factor in assessing pain. Children aged less than 2 years can convey and localize pain, although at this age the child has not been able to describe the quantity of the intensity of the pain he feels. When giving questions to the child should be patient and use words that are commonly used daily in the family. One of the difficulties in identifying pain in a child is that if the examiner is an unknown person, the child tends to deny the pain, or the child feels afraid to express the pain.<sup>8</sup>

#### b. Measurement pain by using a pain scale

Pain assessment is important to know the intensity and determine which therapy is effective. The intensity of pain should be assessed as early as possible and good communication with the patient is needed. Some of the scales that can be done to assess the degree of pain in a child are:

- *Visual analog scale (VAS)*  
This scale is ideally used in children aged >8 years. The VAS scale is a scale in the form of a linear line that visually describes the degree of pain that a person may experience. The pain range is represented as a line 10 cm long, with one end representing no pain, while the other end representing the heaviest pain. Usage is very easy and simple. However, VAS has a disadvantage, namely in postoperative cases, VAS is difficult to apply because VAS requires visual and motor coordination and concentration ability. There are studies that state that the use of VAS can be done in younger children, namely the age of  $\geq 3$  years when combined with FPS (Faces Pain Scale).<sup>9</sup>
- *Numeric Rating Scale (NRS)*  
This scale can be applied to children aged  $\geq 8$  years. This scale uses the numbers 0 to 10 to describe the degree of pain. The use of NRS is better than VAS especially when assessing acute pain, as it is considered simple and easy to understand. However, NRS has limited word options to describe the taste of pain that can be represented. The use of NRS to assess the degree of pain can only be used in children who are able to count at least up to 10 and understand the sequence of numbers.<sup>10</sup>
- *Verbal Rating Scale (VRS)*  
The Verbal Rating Scale (VRS) is more beneficial for assessing pain in surgical patients since verbal/wording does not rely on visual and motor coordination. VRS uses words to assess the degree of pain, not lines, or numbers in assessing pain, so VRS can be used in children aged  $\geq 5$  years, who in general the child can already speak and understand oral speech, but it also depends on the child's cognitive ability to describe the degree of pain.<sup>11</sup>
- *Wong Baker Pain Rating Scale*  
This scale is used in children aged >3 years who cannot describe the intensity of their pain with

numbers. On this scale the degree of pain is represented by an image of facial expressions that the child can choose from when assessing the pain he feels. The advantages of using this scale are Ease of administration (fast and easy to use, requires minimal instruction) and cost-effectiveness). Research conducted by stinson et al, found that children at the age of 4-5 years showed a tendency to choose the face on a more extreme scale in pain associated with medical procedures.<sup>9</sup>

#### c. Measurement of pain by evaluating behavioral and physiological changes

The stress that occurs in children can be described through changes in voice, facial expressions and body movements. This is often related to pain and can be used to evaluate pain, especially in children who have limitations in communication. Changes in behavior in children as a way to assess pain have weakness, which is difficult to distinguish from other causes, such as hunger, thirst and anxiety. This is in line with research conducted by Dorfman et al, where in critically ill infant patients there are limitations in evaluating facial expressions for pain and normal infant behavior, such as the baby's discomfort to change diapers.<sup>12</sup> The FLACC scale (face, legs, activity, cry and consolability) is a scale that is often used to assess changes in behavior in children. The FLACC scale was originally used to assess postoperative pain in children aged 2 months - 12 years. This scale was created as a simple method that nurses use to identify, document, and evaluate pain in children who are unable to verbally express pain and intensitas of pain. A review conducted by maria beatz in 2019 stated that, this scale is good for use in children aged 2 months - 7 years. The study also found that this scale can be used in children with disabilities or special needs, but there is a lack of evidence to apply to all age groups of children.<sup>13</sup> This scale includes face, legs, activity, cry and consolability assessments. Each such component is assigned a value of 0-2, so the total value is 0-10 (Table 1).<sup>8</sup>

In chronic pain such as postoperative pain, the scale for assessing the degree of pain based on behavioral changes used is

**Table 1. FLACC Scale (face, legs, activity, cry dan consolability)**

Categories	Scoring		
	0	1	2
Face	No particular expression or smile	Occasional grimace/frown; withdrawn or disinterested; <i>appears sad or worried</i>	Consistent grimace or frown; frequent/constant quivering chin, clenched jaw; <i>distressed-looking face; expression of fright or panic</i>
Legs	Normal position or relaxed; <i>usual tone and motion to limbs</i>	Uneasy, restless, tense; <i>occasional tremors</i>	Kicking, or legs drawn up; <i>marked increase in spasticity, constant tremors or jerking</i>
Activity	Lying quietly, normal position, moves easily; <i>Regular, rhythmic respirations</i>	Squirming, shifting back and forth; <i>tense or guarded movements; mildly agitated (eg. head back and forth, aggression); shallow, splinting respirations, intermittent sighs</i>	Arched, rigid, or jerking; <i>severe agitation, head banging, shivering (not rigors); breath-holding, gasping or sharp intake of breaths; severe splinting</i>
Cry	No cry/verbalisation	Moans or whimpers; occasional complaint; <i>occasional verbal outburst or grunt</i>	Crying steadily, screams or sobs, frequent complaints; <i>repeated outbursts, constant grunting</i>
Consolability	Content and relaxed	Reassured by occasional touching, hugging, or being talked to; distractible	Difficult to console or comfort; <i>pushing away caregiver, resisting care or comfort measures</i>

Each category is scored on the 0-2 scale, which results in a total score of 0-10

0 = Relaxed and comfortable

1-3 = Mild discomfort

4-6 = Moderate pain

7-10 = Severe discomfort / pain

**Table 2. Modified Children Hospital of Eastern Ontario Pain Scale (CHEOPS)**

Score	0	1	2
Cry	No cry	Crying, moaning	Scream
Facial	Smiling	Composed	Grimace
Verbal	Positive	None or other complaints	Pain complaint
Torso	Neutral	Shifting, tense, upright	Restrained
Legs	Neutral	Kicks, squirm, drawn up	Restrained
Touch	Not touching	Reach, touch, grab	Restrained

the Modified Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) (Table 2). On this scale, the examiner observed 6 types of behavior changes, namely crying, facial expressions, verbal expressions, body position, reactions to touch and limb position. The disadvantage of this scale is that its application in a narrow age group, can only be used in children aged 1 – 5 years, but has the advantage of a simple and fast application.<sup>14</sup> The CHEOPS pain score is the sum of the values of the six parameters of behavior change. If the total score of 8 or more indicates that the child is in a state of pain / pain.

Assessment of pain can also be carried out by observing the physiological changes of the child. The difficulty of assessing pain based on a child's physiological changes is that it is difficult to distinguish

physiological changes due to pain or other forms of stress. In some studies, pain assessment based on physiological changes is more widely used and more effective for assessing acute pain than persistent pain. In patients with intensive care, the COMFORT pain scale is a pain scale that is often used to assess the degree of pain and sedation given to pediatric patients treated in intensive rooms that cannot be assessed using the Visual Analog Scale. The administration of sedation aims to reduce agitation, eliminate anxiety and align breathing with a mechanical ventilator. This scale is used at various ages, there are several studies conducted using this scale with different age ranges, namely, research by Lauren et al in the age range of 12 months – 3 years, Maria beatz research in the neonatal age range –

3 years, research Here et al at the age of 0-10 years and research of Harris et al in the range of 0-16 years, of the four studies concluded that, this scale is validated for postoperative settings and is suitable for anesthetized or unconscious patients. This scale has the disadvantage that the assessment takes a long time, which is 2 to 3 minutes of observation and accuracy is not proven for conscious patients.<sup>13,15-17</sup>

On the COMFORT Behavior scale (Figure 1), there are 7 categories that are assessed, with each category having a score of 1-5 so that the total score is 35. The interpretation on the COMFORT scale is: <12 value: deep sedation, value 13-18: adequate sedation and analgesia, value >18: inadept sedation.

Ceeli et al's study using the Randomized Controlled Trial method in 71 infants

under the age of 1 year who underwent major thoracic surgery (non-cardiac) or abdominal obtained COMFORT-B scores with pain scores of 13 and 13.2 included in the category of optimally working analgesics.<sup>18</sup> Another study conducted by Neunhoeffler F et al using pre- and post-implementation standard therapy consisting of continuous IV infusion of opioids and fentanyl obtained an average COMFORT-B score of 14.72 including the category of analgesics worked optimally with a percentage of 70% of all observations, while 12% had oversedation and undersedation of 18% with the same dose of morphine analgesics.<sup>19</sup>

Research conducted by Hanser A et al in 2020 obtained a median COMFORT-B score of 13.8 showing analgesics and sedation working optimally at 71% of all observations, oversedation occurred at 25% and undersedation at 4%.<sup>20</sup> In a study conducted by Dreyfus et al in 2017 with the Randomized Controlled Trial method on 200 children aged 2 - 3 years using opioid sufentanil the average COMFORT-B score per patient was 8 during the period preimplementation and 9.5 during the post-implementation period. Both periods of <12 scores showed oversedation with a value of  $p=0.002$  indicating the number of scores increased significantly after implementation.<sup>21</sup>

Optimal sedation is described as a patient under sedation who can be easily awakened and can undergo medical treatments and procedures. On both sides of this optimal state are the states of "oversedation" and "undersedation". Excessive sedation is associated with a poor prognosis such as prolonged mechanical ventilation, longer hospitalizations, nosocomial infections, and more frequent withdrawal symptoms. Inadequate sedation involves the risk of agitation and complications, such as unplanned extubation.<sup>21</sup>

Pain measurements using the FLACC scale were performed by Barnes T.A et al in 2020 with a retrospective study of 140 postoperative heart patients getting higher maximum FLACC scores in the postoperative period of 2017 compared to 2018 (5 to 3 each), but the rate of decline in FLACC scores in 2017 was statistically faster and significantly compared to 2018

( $P < 0.001$ ).<sup>22</sup> Honarmand et al in 2012 with the Randomized Clinical Trial method obtained pain scores Using the CHEOPS scale in tonsillectomy surgery patients, it was significantly lower in the group whose combined use provided a better and longer analgesic effect compared to the use of each drug alone.<sup>23</sup>

## Analgesics used in pediatric intensive care rooms

### Opioid analgesics

#### a. Morphine

Morphine was discovered more than 200 years ago. Morphine is the oldest opioid and the only hydrophilic opioid that is still commonly used. Bolus administration of morphine can reach the peak effect in 10-20 minutes and has a working duration of about 2-4 hours. Morphine is metabolized by the liver through glucuronidation and its metabolites are excreted through the kidneys. The dose of morphine should be carefully titrated to avoid excessive sedation and the occurrence of respiratory depression. Morphine doses are administered taking into account the age, physiology and medical condition of the child, since the pharmacokinetics of morphine differs from premature babies to childhood. Initial administration of morphine in children with intermittent doses was 0.03-0.2 mg / kg intravenously and 0.01-0.04 mg / kg / hour in continuous intravenous infusion. Morphine doses for neonates aged <10 days are less than half the dose of morphine for children.<sup>17</sup> Morphine is still the most commonly used opioid in intensive care rooms and has risks and side effects such as vasodilation, hypotension, bronchospasm, and pruritus, but is usually not clinically significant.<sup>24</sup>

#### b. Fentanyl

Fentanyl is a synthetic morphine that is highly lipophilic and fat-soluble. Fentanyl has an anti-pain effect a hundred times stronger than morphine and shows a very fast onset (<1 to 2 minutes) and has a duration of up to 60 minutes when administered at intermittent doses.<sup>16</sup> Intermittent doses of fentanyl in children, namely 1-2 mcg/kg intranasal and 0.5-3 mcg/

kg intravenously, and 0.5-2 mcg/kg/hour intravenously. With continuous and prolonged administration, fentanyl can accumulate in peripheral compartments, increasing half-life and prolonging sedation. In contrast to fentanyl and morphine, fentanyl has an inactive metabolite, norfentanyl, and does not cause the release of histamine. Fentanyl can suppress the heart rate response, this has a negative effect on children who physiologically rely on heart rate and increased heart rate to increase cardiac output. In contrast, fentanyl has advantages, especially for reducing the heart rate response when intubation is performed using a laryngoscope. Although rare, the use of fentanyl has a risk of chest wall stiffness. This usually occurs at large doses administered rapidly (>5 mcg/kg) so it is not uncommon to trigger respiratory failure.<sup>25</sup>

#### c. Remifentanyl

Remifentanyl is a new synthetic opioid equivalent to fentanyl and has a very short half-life of about 3-4 minutes. Remifentanyl is metabolized by plasma esterase, does not accumulate and shows a small volume distribution (Vd).<sup>17</sup> Remifentanyl may be optimally administered in patients with renal or hepatic dysfunction. The strategy to avoid the risk of accumulation of active metabolites is to extend the half-life as well as the duration of work. The rapid onset and offset of remifentanyl, making it widely used in pediatric intensive care rooms. Remifentanyl has the same effects as other opioids namely respiratory depression and myocardial depression, therefore it must be anticipated and managed appropriately. Remifentanyl causes opioid hyperalgesia (Opioid-Induced Hyperalgesia/OIH) side effects, prolonged postoperative recovery, increased length of treatment and significant discomfort.<sup>26</sup>

#### d. Hydromorphones

Hydromorphones are semi-synthetic opioids (hydrogenated ketones from morphine) that selectively bind to  $\mu$  receptors ( $\mu$ ).<sup>27</sup> Hydromorphones are hydrophilic and have 7-10 times greater potential compared to

**FIGURE 1. COMFORT Behavior Scale and Scoring Form**

Date \_\_\_\_\_ Time \_\_\_\_\_

Observer \_\_\_\_\_

Patient Sticker

<b>Alertness</b>	• Deeply asleep (eyes closed, no response to changes in the environment)	<input type="checkbox"/> 1
	• Lightly asleep (eyes mostly closed, occasional responses)	<input type="checkbox"/> 2
	• Drowsy (child closes his or her eyes frequently, less responsive to the environment)	<input type="checkbox"/> 3
	• Awake and alert (child responsive to the environment)	<input type="checkbox"/> 4
	• Awake and hyperalert (exaggerated responses to environmental stimuli)	<input type="checkbox"/> 5
<b>Calmness-Agitation</b>	• Calm (child appears serene and tranquil)	<input type="checkbox"/> 1
	• Slightly anxious (child shows slight anxiety)	<input type="checkbox"/> 2
	• Anxious (child appears agitated but remains in control)	<input type="checkbox"/> 3
	• Very anxious (child appears very agitated, just able to control)	<input type="checkbox"/> 4
	• Panicky (child appears severely distressed, with loss of control)	<input type="checkbox"/> 5
<b>Respiratory response</b> (score only in mechanically ventilated children)	• No spontaneous respiration	<input type="checkbox"/> 1
	• Spontaneous and ventilator respiration	<input type="checkbox"/> 2
	• Restlessness or resistance to ventilator	<input type="checkbox"/> 3
	• Active breathing against ventilator or regular coughing	<input type="checkbox"/> 4
	• Fighting against ventilator	<input type="checkbox"/> 5
<b>Crying</b> (score only in children breathing spontaneously)	• Quiet breathing, no crying sounds	<input type="checkbox"/> 1
	• Occasional sobbing or moaning	<input type="checkbox"/> 2
	• Whining (monotone)	<input type="checkbox"/> 3
	• Crying	<input type="checkbox"/> 4
	• Screaming or shrieking	<input type="checkbox"/> 5
<b>Physical movement</b>	• No movement	<input type="checkbox"/> 1
	• Occasional (3 or fewer) slight movements	<input type="checkbox"/> 2
	• Frequent (more than 3) slight movements	<input type="checkbox"/> 3
	• Vigorous movements limited to extremities	<input type="checkbox"/> 4
	• Vigorous movements including torso and head	<input type="checkbox"/> 5
<b>Muscle tone</b>	• Muscles totally relaxed, no muscle tone	<input type="checkbox"/> 1
	• Reduced muscle tone, less resistance than normal	<input type="checkbox"/> 2
	• Normal muscle tone	<input type="checkbox"/> 3
	• Increased muscle tone and flexion of fingers and toes	<input type="checkbox"/> 4
	• Extreme muscle rigidity and flexion of fingers and toes	<input type="checkbox"/> 5
<b>Facial tension</b>	• Facial muscles totally relaxed	<input type="checkbox"/> 1
	• Normal facial tone	<input type="checkbox"/> 2
	• Tension evident in some facial muscles (not sustained)	<input type="checkbox"/> 3
	• Tension evident throughout facial muscles (sustained)	<input type="checkbox"/> 4
	• Facial muscles contorted and grimacing	<input type="checkbox"/> 5
<b>Total Score</b>		
<b>VAS (Visual Analogue Scale)</b>		
Put a mark on the line below to indicate how much pain you think the child has <b>at this very moment</b> .		
no pain  -----  worst pain		<b>VAS Score</b>
Treatment details		
Details of child's condition		
Assessments made (before or after medication or standard assessment)		

**Figure 1.** COMFORT Behavior Scale and Scoring Form.

morphine. Hydromorphones have an onset of 5-10 minutes and a working length of 3-4 hours. Hydromorphones are metabolized by liver glucuronidation into hydromorphon-3-glucuronides and excreted in the urine. Hydromorphones have fewer unfavorable effects, such as nausea, and pruritus than morphine.<sup>24</sup> Continuous Intravenous Infusion has been shown to be effective for prolonged sedation (>24 hours) in pediatric intensive care rooms. The initial dose of hydromorphone averaged 0.024 mg/kg/hour and the maximum mean dose was 0.05 mg/kg/hour.

e. Methadone

Methadone is a synthetic opioid  $\mu$  receptor agonist ( $\mu$ ) that has a rapid

onset (5-10 minutes in iv and 30-60 minutes orally). Methadone has the longest duration of action of all opioids (4-24 hours). Methadone is used to prevent opioid withdrawal in pediatric patients receiving morphine or fentanyl continuously for >5 days, due to the lack of active metabolites, high oral bioavailability, as well as a long duration of action. Enteral methadone administration has been shown to accelerate opioid cessation and reduce the risk of withdrawal in critically ill children who have a very high risk for opioid abstinence syndrome.<sup>28</sup>

Methadone doses equivalent to 2.5 times the daily dose of fentanyl have demonstrated therapeutic success.<sup>29</sup> with standard guidelines for the conversion

of adult doses to children equivalent to 23.7 mg of oral morphine to 1 mg of oral methadone.<sup>30</sup>

Non-Opioid Analgesics

a. Acetaminophen

Acetaminophen is a synthetic non opioid that works centrally as an analgesic and antipyretic derived from p-aminophenol. Acetaminophen is widely used for single or combination treatment with other types of analgesia in pediatric intensive care rooms to relieve symptoms of mild to severe pain and fever, because acetaminophen has a broad therapeutic index and efficacy to safety ratio. Acetaminophen does not affect platelet function or kidney function and has no gastrointestinal and respiratory effects. Acetaminophen iv achieves an analgesic effect within 5 minutes after administration and reaches a higher maximum concentration (Cmax) at an earlier time (Tmax) than the equivalent dose administered by oral or rectal route. Acetaminophen is metabolized by the liver through glucuronidation, oxidation, and sulfation.<sup>31</sup> The limitations of the use of acetaminophen iv are often due to its high cost. Acetaminophen iv tops the list of the most expensive drugs used in pediatric intensive care rooms, along with dexmedetomidine, eculizumab, and immunoglobulin botulism.<sup>32</sup>

b. Nonsteroidal anti-inflammatory drug (NSAID)

NSAIDs work by blocking the production of prostaglandins to reduce pain and inflammation. There are two types of NSAIDs: Non-Selective NSAIDs (ibuprofen, naproxen, ketorolac, and acetylsalicylic acid) work to block two enzymes involved in the inflammatory process, namely the enzymes cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), and selective COX-2 (celecoxib). These non-selective NSAIDs are most widely used in pediatric intensive care rooms. The COX enzyme catalyzes the conversion of arachidonic acid to prostaglandins and regulates the cellular processes of platelet aggregation, vasodilation of afferent arterioles in the kidneys,

and protection of the gastric mucosa. COX-2 enzyme is an enzyme that can be induced and increased during the inflammatory process, the COX-2 enzyme is present in the brain, kidneys, bones, and reproductive tract. NSAIDs are widely used due to their analgesic, anti-inflammatory and antipyretic properties. Ibuprofen being the NSAIDs of choice for enteral administration, preferred for its efficacy profile and tolerability without the risk of Reye's syndrome.<sup>33,34</sup>

Intravenous ketorolac is not commonly used for pediatric patients, but is a frequent option for postoperative analgesics in pediatric intensive care rooms. NSAIDs are preferred over opioids, due to the lack of side effects such as nausea, vomiting, pruritus, respiratory depression, sedation, and urinary retention that can occur in opioids. NSAIDs are metabolized in the liver into inactive metabolites through oxidation and conjugation processes. The administration of NSAIDs should be carried out carefully in patients at risk of acute renal failure, post-surgical bleeding, or gastrointestinal toxicity. In pediatric populations, NSAIDs have not been shown to increase the risk of kidney complications and bleeding for post-cardiac and non-cardiac care.<sup>34</sup>

## DISCUSSION

The assessment of pain in a child is very complex and involves physiological, psychological, behavioral, social and developmental factors. In the pediatric intensive care room, we must consider the severity of the disease and the child's ability to participate in the assessment of pain.<sup>35-38</sup> Verbal reports of pain can be considered the most effective way to communicate the subjective emotional and sensory experiences of the individual. In infants and children with cognitive and communication abilities that are not yet optimal in their development, pain observations can be based on observations of physiology and behavior in children. Pain can be caused by many factors, namely, complex child conditions, the administration of pharmacological agents, such as the use of sedatives and neuromuscular inhibitory agents that affect the ability to react to the disease as

well as the use of mechanical ventilation necessary to maintain vital functions.<sup>35,38-40</sup>

There are two validated pain assessment scales most commonly used in pediatric intensive care rooms, namely the COMFORT and FLACC (Face, Legs, Activity, Cry, and Consolability) scales for use in young children and children who cannot self-report their pain.<sup>35,38,41,42</sup> The COMFORT-B score is a customized version of the COMFORT score, based on observation items such as alertness, calmness, respiratory response in ventilated or crying patients in unventilated patients, muscle tone, physical movement, and facial tension. This scale has been introduced and validated for pain assessment as well as for sedation management in pediatric intensive care rooms. A COMFORT-B score of 12-18 is assumed to be the optimal range of analgesics and sedatives.<sup>43-45</sup>

The FLACC scale has been used in a variety of populations and ages including, children who cannot speak yet, children with cognitive impairment and also as a postoperative pain assessment.<sup>8</sup> Analgesics are given taking into account the assessment of the degree of pain. Most children in intensive care rooms experience moderate to severe pain as a result of different sources of pain, namely underlying disease, surgery, trauma, and invasive procedures. Opioid analgesics are used to score pain with moderate to severe categories.<sup>35,46</sup> Morphine and fentanyl are the most widely used opioid analgesics in terms of dosage effectiveness, method of administration, and side effects. This widespread use of opioids is in line with the recommendations of the World Health Organization (WHO), which recommends administering opioid analgesics to children with moderate to severe pain levels.

Non-opioid analgesics such as ketorolac are effective for treating moderate to severe pain, but some children who receive ketorolac experience side effects in the form of nausea and vomiting. Acetaminophen has been shown to reduce pain in pediatric intensive care rooms after surgery with mild to moderate pain and unventilated children. Intravenous administration is more effective than oral or rectally. Existing recommendations do

not support the use of acetaminophen as a single drug for the therapy of moderate or severe pain in children.<sup>17</sup>

From several studies conducted to assess the effectiveness of analgesics on the pain scale in children, a significant decrease in the pain scale was found after administration of analgesic agents, in a study conducted by Neunhoeffler F et al with the Randomized Controlled Trial method on 337 children aged 1-24 months with analgesic post-sedation pain, it was found that the average COMFORT-B score was 14.72. COMFORT-B scores showed optimal analgesics & sedation at 70% of all observations (CF-B 12-18) with a morphine infusion dose of 10 mcg/kg/hour and fentanyl infusion of 0.5 mcg/kg/hour, oversedation at 12% (CF-B <12) and undersedation at 18% (CF-B >18).<sup>19</sup>

The study with the same method as postoperative pain obtained an average COMFORT-B score per patient was 8 (range 6-19) during the pre-implementation period and 9.5 (range 6-15.5) during the post-implementation period. The difference between these two periods is significant ( $p=0.002$ ). The average number of adequate sedation and analgesic levels (scores 11-17) was significantly greater after implementation (22.2 vs 31.7%), while the average number of excessive sedation and analgesic levels (score <11) decreased significantly from 73.3% in pre-implementation to 60.7% in the post-implementation period by sufentanil 0.1 g/kg/h.<sup>21</sup>

Research conducted by Welzing L et al in 2012 with the Randomized Controlled Trial method comparing the effectiveness of analgesics and sedation of remifentanyl/midazolam and fentanyl/midazolam obtained results that the need for mechanical ventilation was longer in the remifentanyl group at a dose of 6-30 mcg/kg/hour compared to the phenytanyl group dose 2-10 mcg/kg/hour (average difference of 25 hours).<sup>47</sup> Furthermore in 2013 a study from Ceeli et al in 71 infants under the age of 1 year who undergoing major thoracic surgery (non-cardiac) or abdominal showed that the average duration of mechanical ventilator use was 34 days in the paracetamol group of 30 mg/kg/day in 4 doses and decreased to 23 days in the morphine group with a dose

age of  $\leq 10$  days 2.5 mcg/kg/hour; Patients aged 11 days to 1 year 5 mcg/kg/hour ( $p=0.43$ ).<sup>18</sup>

Research conducted by Neunhoeffler F et al using standard pre- and post-implementation therapy consisting of continuous iv infusion of opioids (morphine [5-100 mcg/kg/hour, initial dose 30 mcg/kg/hour]  $\leq 2$  years and fentanyl [0.1-6.0 mcg/kg/hour; initial dose 0.5 mcg/kg/hour]  $> 2$  years) stated that the average length of mechanical ventilator use in the preimplementation group was 2.02 days and 1.71 days post-implementation.<sup>19</sup> The same results were also shown by the study from Dreyfus et al in with sufentanil opioid therapy started at 0.2-0.3 mcg/kg/h concluded that the duration of mechanical ventilator use in the preimplementation group was significantly longer when compared to the post-implantation group of 5.6 days and 4.8 days.<sup>21</sup> Another study by Magner C et al in 2020 with a retrospective study concluded, the amount of morphine administered during the first 72 hours after surgery between the pre- and post-implementation groups found that the median length of mechanical ventilator use became shorter post-implementation from 30.5 hours to 25.7 hours.<sup>48</sup>

A study conducted by Hanser A et al in 2020 with a retrospective study method. The results were obtained that, after the implementation of the analgesic and sedation protocol, the average duration of mechanical ventilator use was shorter than 72 hours to 49 hours with a value of  $p=0.407$  but this value was not significant in both groups.<sup>20</sup> Although from all the above studies, the two groups had insignificant differences, the preimplantation group required a longer ventilator use time compared to the post-implant group.

Research conducted by Khalili et al in 2012 with the Cross Sectional Retrospective method concluded that no significant changes were shown in the length of hospitalization in PACU for the use of 0.2 mg/kg of dexamethasone intravenously for 54.71 minutes and 20 mg/kg of oral codeine-acetaminophen syrup for 55.14 minutes with a value of  $p=0.33$ .<sup>49</sup> Neunhoeffler F et al in 2015 with the Randomized Controlled Trial method using pre- and post-implementation

standard therapy consisting of Infusion IV continuous opioids (morphine [5-100 mcg/kg/h, initial dose 30 mcg/kg/h]  $\leq 2$  years and fentanyl [0.1-6.0 mcg/kg/h; initial dose 0.5 mcg/kg/h]  $> 2$  years) stated that the average length of hospitalization was 5.8 days in the preimplementation group and 5.0 days post-implementation.<sup>19</sup> Then, a study from Magner C et al in 2020 with a retrospective study stated that, the amount of morphine administered during the first 72 hours after surgery between the pre- and post-implementation groups median length of hospitalization decreased from 3.5 days in pre-implementation and to 2.8 days post-implementation with a value.<sup>48</sup>

A retrospective study by Barnes et al of 140 postoperative cardiac patients using morphine dose range of 0-5 mg/kg/day also showed that the length of stay at the PICU was from 6 days to 5 days.<sup>22</sup> With the same method, Hanser A et al in 2020 were treated using morphine continuous iv-infusion opioid analgesics: 5-100 mcg/kg/h, initial dose: 30 mcg/kg/h proved that the length of treatment at the PICU was significantly reduced in the preimplementation group compared to the post-implementation group from 7 days to 5 days with a  $p$  value = 0.017.<sup>20</sup>

Different results were shown from a study conducted by Dreyfus et al in 2017 with the Randomized Controlled Trial method concluded that the median length of hospitalization of the pre-implementation group of 9 days and 9.8 days post-implementation with a value of  $p=0.767$  however, was not significantly meaningful.<sup>21</sup> The longer the treatment period will increase the costs incurred and decrease the quality of life of the patient.

Sedation and analgesia also affect the patient's extubation time. Extubation is the act of removing the endotracheal pipe. Extubation is carried out at the right time for the patient to avoid the occurrence of reintubation and other complications. A study conducted by Khalili et al in 2012 with the Cross Sectional Retrospective method concluded that there was no significant difference in the time of extubation.<sup>49</sup> Research conducted by Welzing L et al in 2012 stated that the median extubation time in the remifentanyl group at a dose of 6-30 mcg / kg / hour was 80.0 minutes and

the fentanyl group dose was 2-10 mcg/kg/hour which was 782.5 minutes ( $p = 0.005$ ) so that there was a significant difference.<sup>47</sup> In the same year Honarmand et al with post-tonsillectomy pain obtained results that there was a significant difference in extubation time, namely the ketamine iv group 0.5 mg/kg 10.7 $\pm$ 24 minutes and the ketamine iv group 0.5 mg / kg + tramadol peritonsil 2 mg / kg which was 13.8 $\pm$ 21.5 min.<sup>23</sup> Another study conducted by Dreyfus et al using opioid sufentanil dose range 0.2-0.3 mcg/kg/ hour obtained results that there was no significant change between pre and post implementation.<sup>21</sup>

Another study conducted by Neunhoeffler F et al in 2015 using pre- and post-implementation standard therapy consisting of continuous iv infusion of opioids at the age of  $\leq 2$  years and fentanyl at the age of  $> 2$  years showed that there was no significant difference in the unplanned extubation rate, which was 0.54 in preimplementation and 0.71 post-implementation per 100 days of ventilator.<sup>19</sup> Then, a study from Barnes et al in 2020 with retrospective studies using morphine dose range of 0-5 mg/kg/day concluded that the extubation time was consistent in the 2017 group and the 2018 group with the median time of extubation in each group was 1 day.<sup>22</sup>

Limitations of this study included factors such as most included studies had concerns related to risk of bias. We were unable to thoroughly explore the influence of potential effect modifiers such as treatment duration and route of administration because of the limited data and poor network structure. Further research is needed, particularly high-quality trials comparing analgesics to placebo. In future trials, we encourage investigators to report the number of participants who had any adverse event, as well as type and severity of those adverse events.

## CONCLUSION

Critically ill pediatric patients should be assessed for pain and comfort. Many scores have been validated to assess the pain and comfort of critically ill patients in the PICU. Adequate administration of sedation and analgesics will shorten hospital stay, shorten ventilator use, and

shorten patient extubation time. When deciding whether to give analgesics or sedation, it should be based on the patient's clinical condition and can use pain scores to determine pain and discomfort in critically ill pediatric patients.

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## CONFLICT OF INTEREST

The authors have no competing interests to declare

## AUTHOR CONTRIBUTION

All authors have contributed to all processes in this research, including preparation, data gathering, analysis, drafting, and approval for publication of this manuscript.

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