NEAR EAST UNIVERSITY

INSTITUTE OF GRADUATE STUDIES

DEPARTMENT OF CLINICAL PHARMACY

ANALYSIS OF CLINICAL AND ECONOMIC IMPACT REGARDING ANALGESICS AND SEDATIVES DRUGS USE ON CRITICALLY ILL PATIENT

M.Sc.THESIS

Mohammed Abu Arab

NICOSIA

June, 2024

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Advisor

Ph.D Ugochukwu Chukwunyere

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Approval

We certify that we have read the thesis submitted by Mohammed Abu Arab titled "**Analysis of Clinical and Economic Impact Regarding Analgesic and Sedative Drugs Use on Critically ill Patient**" and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of M.Sc in Clinical Pharmacy.

Examining Committee	Name-Surname	Signature
Head of the Committee:	Yard. Doç. Dr. Nevzat Birand	
Committee Member:	Yard. Doç. Dr. Meryem Deniz Aydin	
Supervisor:	Yard. Doç. Dr. Ugochukwu Chukwunyere	

Approved by the Head of the Department

24/02/2025

.....

Yard. Doç. Dr. Ugochukwu Chukwunyere

Head of the Department

Approved by the Institute of Graduate Studies

.../.../2025

.....

Prof. Dr. Kemal Hüsnü Can Başer

Head of the Institute of Graduate Studies

Declaration

Hereby, I declare that all the information, documents, analysis, and results included in this thesis are written based on academic rules and ethical guidelines suggested by the Institute of Graduate Studies, Near East University. I hereby also declare that, where required, according to these rules and conduct, I have fully cited and referenced information and data that are not original to this study.

Mohammed Abu Arab

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Mohammed Abu Arab

Abstract

ANALYSIS OF CLINICAL AND ECONOMIC IMPACT REGARDING ANALGESICS AND SEDATIVES DRUGS USE ON CRITICALLY ILL PATIENT

Mohammed Abu Arab

Advisor: Ph.D Ugochukwu Chukwunyere

MA, Department of Clinical Pharmacy June 2024

Background: The intensive care unit (ICU) consumes many resources and has therefore been identified as a target for efforts to reduce the escalating costs of healthcare. The use of analgesics and sedatives plays an important role in improving patient outcomes in the intensive care unit (ICU). Different medications exist, each with associated differences in patient outcomes. Pain management in critically ill patients in the ICU is challenging for intensivists due to inconsistencies in pain assessment, which may lead to variations in the number of analgesic medications or dosages. This study investigates the current use of analgesics and sedatives in the ICU of the Near East Hospital in Lefkosa, Cyprus. In addition, we compared the use of analgesics and sedatives in the ICU based on the latest guidelines. We conducted a retrospective study using data available in the archives of the Near East Hospital.

Methodology: This retrospective observational study analysed data from 98 patients aged ≥ 18 years and only patients admitted to ICU more than 24 hour between 1st of November 2023 and 30th of April 2024. The study utilized hospital databases to gather demographic data and details of administered medications. The average purchasing price of each drug was elicited from RMS

orders and tenders in 2023 and 2024. The total cost of each drug was calculated by multiplying the average purchasing price with the total consumed quantities of that drug. The sum of all drugs' total cost in each group represents the total cost of that group.

Results: The study found that out of the total number of patients who entered the ICU, 177 patients received analgesics in the ICU. Paracetamol IV emerged as the most administered medication, being used in almost all patients, with 87 out of the 98 total patients. The other category comprises opioid analgesics, represented by tramadol, which was used in 32 of the 98 patients. NSAIDs were represented by five different drugs and were used in 21 patients, making up only 21% of the 98 patients. In the analgesic adjuncts category, there were four other drugs, with dexmedetomidine being the most used, administered to 15 patients to manage their pain and provide sedation as well. The total cost for analgesic therapy in the ICU between November 1, 2023, and April 30, 2024, was $10,919. IV Paracetamol accounted for the largest share of the analgesic cost, taking 55.6% of the total analgesic ICU cost, amounting to $6,075 for 2,333 flacons of Paracetamol 10 mg/ml, 100 ml. Following dexmedetomidine, which cost $4,560, making up 41.8%. In contrast, Tramadol IV/IM was used in 32 patients, accounting for 1.5% of the total analgesic ICU cost, amounting to $190 for 249 ampoules of Tramadol 100 mg/2 ml. The remaining analgesics made up less than 2.5% of the total analgesic cost in the ICU. Lastly, the data collected during this study period show the use of three drugs as sedation agents; midazolam was the preferred drug, with 417 ampoules administered to 18 patients. Propofol was given in 577 ampoules to 12 patients. Finally, dexmedetomidine was used in 245 flacons for 15 patients. The findings regarding analgesic drug use align with global trends emphasizing safety and rapid action in intensive care unit pain management. Regarding sedation drugs, there remains frequent use of midazolam in the ICU, while international trends suggest a

decrease in the use of benzodiazepines and an increased use of other sedatives is desirable and associated with better outcomes.

Conclusions. Critical care and intensive care associations provide guidelines on medication use based on sufficient evidence and suggest appropriate medication use in ICUs. Near East University ICU strategies demonstrate adherence to global trends by reducing the use of opioids and NSAIDs due to their associated risks and use Propofol and Dexmedetomidine over Midazolam in sedation. These strategies illustrate ICU commitments to patient safety and effective pain management and present a model worthy of consideration and potential adoption in similar healthcare settings. From an economic perspective, providing alternative medication options or other approaches may enhance cost efficiency and even reduce opioid use, leading to better clinical and economic outcomes.

Keywords: pain management, Intensive Care Unit, analgesics, pain assessment.

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CHAPTER III

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List of Abbreviations

ICU: Intensive Care Unite

NSAID: Non-steroidal Anti-inflammatory Disease

IV: Intravenous

VAS: Visual Analogue Scale

NRS: Numeric Rate Scale

IASP: International Association for the study of pain

SCCM: Society of Critical Care Medicine

CHAPTER I

Introduction

Most critically ill patients experience pain in intensive care units, either at rest or during routine care by ICU doctors and nurses, and these patients have the right to receive appropriate pain management when needed (Tsuruta R & Fujita M, 2018). The origin of pain may arise from cancer, burns, surgery, or trauma. Pain is a common condition in ICU patients, occurring in up to 50% of cases. (Chanques G et al., 2014).

Defining the concept of pain is challenging due to the absence of a precise definition that mainly resides in the traits intrinsic to the phenomenon. However, the Association of Pediatrics has defined pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Kappesser et al., 2006). At times, pain severity is underestimated by healthcare providers (Kappesser et al., 2006; Sheiner et al., 2000). Neglecting this element may result in insufficient pain management, potentially negatively affecting patients' outcomes, quality of life, and satisfaction (Larue et al., 1997).

The severe pain that patients may experience can be the primary factor that leads to many physiological changes. Severe pain activates the stress response, leading to tachycardia, increased myocardial oxygen demand, elevated blood pressure, and possibly myocardial ischemia in at-risk individuals. Furthermore, inadequate pain management from abdominal incisions impairs diaphragmatic function and may lead to hyperventilation and pulmonary collapse, negatively impacting patients in an apparently transient state (C. Middleton, 2003).

Pain, especially in patients undergoing anesthesia in the intensive care unit, can present as agitation and delirium; if not managed effectively, it can lead to psychological consequences such as post-traumatic stress disorder, depression, and anxiety, or it can develop into chronic pain. Systemic adverse effects of pain include systemic inflammatory response syndrome, hyperglycemia, decreased immunity, impaired wound healing, increased coagulability, and increased catabolism. All of these adverse outcomes can lead to longer ICU stays, longer hospital stays, and higher ICU mortality rates (Johnson & Johnson., 2005).

Acute pain itself is quite distressing, and if untreated, it can lead to complicated or serious consequences, as there is a risk of developing chronic pain in the long term. Alleviating acute pain requires timely intervention. Thus, ensuring effective and timely treatment becomes an absolute necessity (Simpson et al., 2013; PlattsMills et al., 2012).

Adult patients in the ICU commonly endure pain, whether at rest or during standard care activities like wound treatment or procedures. Unmanaged pain can result in several complications, such as delirium and an increased risk of mortality; therefore, quick evaluation, treatment, and management of pain in the intensive care unit are essential (Yamashita A et al., 2017). The PADIS guidelines suggest routine pain monitoring for all adult ICU patients. The most important criterion for assessing pain in patients is self-report. Vital signs alone should not be used to assess pain in patients who are unable to communicate (Gelinas et al., 2006).

In the United States, more than 5 million patients are admitted to intensive care units (ICUs) each year, with an average length of stay in the ICU of 3.8 days (SCCM, 2021). Unfortunately, many of these patients will experience moderate to severe pain at rest, likely associated with their hospitalization, and 80% of them

will experience pain during procedures performed by nurses and doctors (Chanques G et al., 2007; Damico V et al., 2020; Merskey HAFD et al., 1979). In Jordan, the incidence of painful conditions among cancer patients has been estimated to be as high as 73.3% (Qadire et al., 2013). In a different recent study conducted in Jordan, it was found that 72.0% of patients studied experienced moderate to severe pain at rest in the ICU after surgery (Massad et al., 2013).

Upon transferring to the intensive care unit, healthcare providers focus on monitoring vital signs, including ventilator settings, respiratory mechanics, hemodynamics, and accessory organ systems. Pain is viewed as a non-critical vital sign, often given a lower priority, which leads to it being easily overlooked. Reliance on hypertension and tachycardia as indicators of pain is not reliable because different factors influence them (Gélinas C, Puntillo KA, Joffe AM, Barr J, 2013; Chen HJ, Chen YM, 2015).

At the time of medical admission, the patient typically shows signs of inflammatory or ischemic pain associated with their underlying condition. Neuropathic pain may also involve elements linked to different disease processes, along with postoperative and traumatic pain in patients undergoing surgery or experiencing trauma. All these factors add to discomfort when at rest. Moreover, the methods trigger distinct episodes of pain. Recent research indicates that patients consider ICU-related procedures such as drain removal, arterial line insertion, and chest tube placement to be the most painful experiences for ICU survivors (Puntillo KA et al., 2014; Puntillo KA et al., 2014).

Evaluating pain in critically ill patients is a difficult endeavor. During their stay in the intensive care unit (ICU), patients might feel pain during different procedures. Non-ventilated patients can self-report pain, but it is challenging for those who are ventilated (Payen JF et al., 2001).

Several scales are used by ICU health providers to assess patient's pains. In patients capable of self-reporting their pain, the behavioral pain scale (BPS), visual analog scale (VAS), or numeric rating scale (NRS) can be utilized. In contrast, for patients who cannot self-report, the critical care pain observation tool (CPOT) or behavioral pain scale (BPS) can be employed (Gélinas C, Puntillo KA, Joffe AM, Barr J, 2013; Azevedo-Santos IF, DeSantana JM, 2018).

Effective pain management is a fundamental aspect of care in the (ICU). Close pain monitor is associated with better patient outcomes in the ICU (e.g., decreased sedative drugs use and shorter length of stay). Therefore, it is crucial for physicians to detect and monitor pain to adjust analgesic doses and minimize their overuse and serious side effects (Chanques G et al., 2006; Payen JF et al., 2009).

The benefits of critical care pharmacists in the ICU have been demonstrated in various areas according to numerous studies. Clinical pharmacists have been shown to reduce the incidence of medication errors and preventable adverse events (AEs) resulting from patient medication (Wang T et al., 2015); (Lipp LL, 1999). Critical care pharmacist activities have been associated with shorter treatment durations and more appropriate dosing regimens, leading to increased cost savings and better patient satisfaction with healthcare (Jiang SP et al., 2014); (Ibrahim KH, 2001).

Intensive care treatments account for a large proportion of rising health care costs (Halpern NA & Pastores SM & Greenstein RJ., 2004) To comprehensively evaluate the economic feasibility of different interventions, cost-effectiveness analysis is a valuable tool to study both the health and costs outcomes associated with these interventions (Wilcox ME et al,.2019).

1.1 Problem Statement of the Study

Intensive care is costly and represents a significant share of hospital expenses. For instance, in the United States, intensive care units comprise approximately 5% to 10% of all hospital beds, yet they consume 20% to 34% of a healthcare facility's overall care resources. (Henning RJ et al., 1987; Berenson RA, 1984).

A retrospective study was conducted in the USA to analyze the benefits of clinical pharmacists within a multidisciplinary neurosurgical environment, comparing the two years prior to and the two years following the introduction of specialized surgical pharmacy services. Throughout that period, the clinical pharmacist documented 11,250 actions. Consequently, the costs of pharmacy and IV therapy per patient dropped from $4,833 in the pre-implementation group to $3,239 in the post-implementation group, leading to an overall savings of $1,718,260 throughout the study duration. The typical duration of hospital stays dropped from 8.56 to 7.24 days. The initial hospital mortality rate declined from 3.34% to 1.95% (Kyle A, 2009).

Sedation of critically ill patients is an expensive endeavor. The costs of sedatives commonly used in the ICU range from pennies to more than $500 per day. Prolonged mechanical ventilation and length of stay are frequent complications resulting from the suboptimal use of these medications. Opioids can cause gastrointestinal dysfunction, leading to malnutrition and possibly bacterial transmission and sepsis. Although these drugs contribute to this expense, complications associated with their use in the ICU generate even greater costs (Kress JP, Hall JB , 2001).

1.2 Purpose of the Study

The aim of this study is to analyze and explore the strategies for the use of analgesic and sedative drugs in the Intensive Care Unit (ICU) at Near East University Hospital. It also compares the use of analgesics and sedatives in the ICU based on the latest guidelines. This study will have a greater impact on the community by providing better healthcare plans to reduce hospitalization time and decrease the number of medications used on individuals by identifying areas with potential improvements, whether clinically or economically. This study, therefore, seeks to contribute to the optimization of strategies for analgesic and sedative use in the ICU and to enhance the quality of care and experiences of patients in similar healthcare environments through the analysis of these patterns.

1.3 Research Questions

- What is the predominant analgesics category used in the ICU?
- How do the sedatives and analgesics in the ICU correlate with patient outcomes?
- How can the analgesics and sedatives used strategies be improved to increase healthcare quality in the ICU?
- How are non-opioid analgesics administered to patients in the ICU, and what factors influence the choice of administration route?

1.4 Significance of the Study

The findings of this study are changing the overall cost by professional drugs selection depending on new tested findings considering the pathophysiological overview, promoting greater collaboration among pharmacists and other healthcare professionals to achieve targeted results. Such an observation is likely to attract very critical considerations from healthcare teams, such as physicians and clinical pharmacists regarding rendering evidence-

based strategies in successful pain management that reduce the ICU cost and increase cost efficiency and health care quality.

The findings from this study will be very applicable for knowledge gaps around using analgesics and sedatives among ICUs, and the findings will provide a means by which the competence of health practitioners concerning the selection and use of analgesics and sedatives can be improved through comparing it with the administration of analgesics and sedatives in the ICU according to the most recent guideline. This actively turns out to play a part in a broad objective of the optimization of care patients' outcomes, minimization of risks associated with analgesics and sedatives, and elevation of patient satisfaction within the settings of emergency care.

1.5 Limitations of the Study

It is crucial to remember that the research will not offer a broad view for all patients; it will be specific to those who use any category of analgesic medication only, due to the intensive care unit 's use of it for almost all patients. Additionally, the study is limited in resources because we do not have a range of different medications; it is more dependent on the available medications in the hospital pharmacy to conduct sufficient research on the issue and we were not provided with some drug prices like sedative drugs. Furthermore, the studies require more research on the subject to obtain more accurate data to work with and ensure the best results. Additionally, concentrating solely on Near East University Hospital (NEUH) implies that the results cannot be applied to the larger population, and drawing conclusions about the prevalence of pain management in ICUs more generally may be infeasible.

1.6 Definition of Terms:

Non-opioid Analgesics: Medications used to relieve pain without acting on opioid receptor in the brain. These include drugs such as Paracetamol (Acetaminophen) and Non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen and naproxen. They are often preferred for treating mild to moderate pain and reducing fever without the risk of addiction associated with opioid analgesics.

Opioid Analgesics: A class of drug that includes both natural and synthetic substances derived from the opium poppy or chemical related to it. Opioids are prescribed for moderate to severe pain but carry risks such as addiction, tolerance and overdose.

Analgesic adjuncts: A medication that has weak or nonexistent analgesic effect when administered alone but can improve analgesic actions when co-administered with other known analgesic drug. Adjuvant analgesics have analgesic properties in some painful conditions like neuropathic pain.

Intensive care units: A distinct unit within a hospital or healthcare center that delivers critical care. Patients are moved directly from an emergency department or the ward in cases of severe or life-threatening conditions and injuries that necessitate ongoing care and careful monitoring of life support systems and medications to maintain normal and stable bodily functions. It employs highly skilled doctors and nurses who focus on providing care for

critically ill patients. Intensive care units are set apart from other hospital departments by their elevated staff-to-patient ratio and availability of sophisticated medical equipment and resources that are not commonly found in other areas.

Pain Management: The process of providing medical care that reduces the severity of pain. Pain management can involve pharmacological treatments, including the administration of analgesics, as well as non-pharmacological approaches such as physiotherapy and mental health assistance.

Chapter Two

Literature Review

2.1 Theoretical framework

Managing pain in critically ill patients is becoming a crucial standard of care in the intensive care unit (ICU) due to its influence on patient outcomes. Managing pain in critically ill patients in the ICU poses several challenges for intensivists. Inconsistencies in evaluating pain, which can arise from various factors, prescriptions for analgesics, and differences in the monitoring of anesthesia and analgesics, result in inadequate pain management. Insufficient pain management can negatively impact various organ systems in severely ill patients. Complications related to the use of these drugs in the ICU elevate expenses (Eric E, 2016).

Critical care professionals are increasingly facing pressure to tackle cost issues. The ICU utilizes a large portion of the hospital's resources and is often recognized as a focus for initiatives aimed at lowering rising healthcare expenses. (Andrew F, 2002).

The intensive care unit is a prospective area for drug-related problems. Since many of the patients treated are complex cases prescribed medications that require close monitoring, clinical pharmacist intervention can identify problems in drug therapy and resolve them (Pichala, 2013).

As fundamental members of multidisciplinary teams, clinical pharmacists play a vital role in the care of patients in the intensive care unit. Their specialized experience and knowledge provide patients with access to specialized intensive

care teams and improve the number of recommendations implemented, leading to enhanced critical care drug therapy and improved quality of care (Lee, 2019).

Pharmacist actions involve rectifying and clarifying prescriptions, offering medication details, recommending alternative therapies, detecting drug interactions, and overseeing therapeutic medications. The participation of clinical pharmacists in enhancing clinical outcomes for critically ill patients is linked to notable decreases in the incidence of adverse drug events and medication administration mistakes. Additionally, economic assessments of clinical pharmacy services in the ICU frequently demonstrate the possibility of significant cost reductions (Dasta, 1996).

It can be deriving that clinical pharmacist requires various professional tasks and abilities towards the patient which can be improved by promoting greater collaboration among pharmacists and other healthcare personnel to achieve the intended outcomes (Buch, 2010).

2.2 Pain assessment

Patients in intensive care suffer distress from various factors, with a significant portion attributed to pain. Nearly all patients experience moderate to severe pain at some stage during their stay in the intensive care unit. Pain can be triggered or intensified by various pre-existing conditions, such as surgical factors or standard elements of intensive care (Schelling G et al., 1998).

Less than 50% of professionals in the intensive care assess pain, and even when they assess pain, they do it infrequently. A common reason for inadequate pain management is the insufficient training in pain assessment (Payen JF et al., 2007)

The fundamental principles of evaluating pain in critically ill patients are:

- ❖ Recognize and comprehend the reasons for distress, primarily, though not exclusively linked to pain.
- ❖ Evaluate pain and delirium employing authorized scales, consistently and precisely, integrating all available information.
- ❖ Understand that vital signs should not be solely relied upon for pain assessment, but may serve as an indicator to prompt additional evaluation (Barr J et al., 2013).

2.3 Pain scales

Self-reporting of pain is regarded as the optimal standard, and whenever feasible, healthcare professionals should attempt to assess patients' self-reported pain with validated scales. Pain scales may be either discrete or continuous, and they can be unidimensional or multidimensional. Pain scales typically utilized in the ICU are one-dimensional and are quite effective in evaluating pain and monitoring treatment responses (Sessler CN et al., 2008).

Pain scales for patients able to communicate.

- ❖ **Visual Analogue scale (VAS):** Patients indicate their pain level on a 100 mm line, with verbal descriptors at each end (0: no pain; 100: very severe pain). The outcome is achieved by gauging the distance in millimeters from the left edge of the line.
- ❖ **Numerical rating scale (NRS):** Patients assess their pain using an 11-point scale (0: no pain; 10: extreme pain).
- ❖ **Verbal Rating Scale (VRS):** 4-point scale, in which the pain can be classified as 1: absent, 2: mild, 3: moderate, and 4: severe.

Pain scales for patients unable to communicate.

- **Behavioral Pain Scale (BPS):** This scale employs clinical assessments of facial expressions, upper limb movements, and coordination with mechanical ventilation. BPS varies from 3 to 12, and those scoring above 6 necessitate pain management.
- **Critical Care Pain Observation Tool (CPOT):** The scale employs clinical observation that includes four elements: facial expressions, muscle tone, body movements, and ventilator compliance for intubated individuals or vocalization for extubated individuals. Every element is assigned a score between 0 and 2, resulting in a total score that varies from 0 to 8. A score exceeding 2 demonstrates high sensitivity and specificity for forecasting considerable pain in ICU patients (Barr J et al., 2013); (Sessler CN et al., 2008).

2.4 Principles of pain management in the ICU

The pain management principles in the ICU are very similar to the pain management of perioperative setting:

- Adopt a holistic strategy for managing pain through a blend of pharmacological and non-pharmacological methods (systemic analgesics and regional topical approaches).
- Implement a multimodal strategy for pain management to enhance analgesia quality and minimize side effects.
- Consider patient's distress after pain has been adequately managed due of anxiety and delirium.

- ❖ Titrate analgesia to specific individual goals with reassessment and avoid prolonged continuous infusion.
- ❖ Recognizing that analgesic medications can lead to organ dysfunction, and that such dysfunction can affect drug selection and dosing, it is essential to have a personalized analgesic regimen (Fraser GL et al,. (2002); (Pontello K et al., 2013).

2.5 Analgesics

Analgesics are medications that relieve pain. Unlike anaesthesia medications that used during surgery, analgesics do not block nerves, alter the ability to sense the surrounding environment, or alter consciousness. They are sometimes called pain relievers or painkillers. The range of medications available for pain management illustrates the diverse and intricate characteristics of pain experienced by critically ill patients.

The analgesic medications can be classified into:

- ❖ Opioid analgesics.
- ❖ Non-opioid analgesics.
- ❖ Analgesic adjuncts: neuropathic drugs.

Opiate analgesics

Opioids are the cornerstone of treating acute pain in patients who are critically ill. Opioid drugs work by activating μ-, κ-, and δ-opioid receptors, which are extensively located in the central nervous system and across peripheral tissues. All opioid medications are regarded as having comparable analgesic effectiveness when adjusted to the same pain intensity targets, showing no

variations in clinical results. Prolonged use of opioids has been linked to an increased occurrence of side effects. Negative consequences of opioids encompass hypotension, ileus, nausea/vomiting, bradycardia, urinary retention, constipation, delirium, and hallucinations (Jacobi et al., 2015).

Non-opioid analgesics

Known analgesic such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are effective in treating mild pain. Paracetamol reduces the use of opioid medications and, therefore, unless contraindicated, it should be considered a first-line medication in the treatment of mild to moderate pain. It should be included in a multimodal regimen for the treatment of severe pain (Abbott FV et al., 2000).

Non-steroidal anti-inflammatory drugs

NSAIDs have anti-inflammatory, analgesic and antipyretic properties. However, they are rarely used because the analgesic properties of NSAIDs have not been well studied in critically ill patients. In a retrospective study of patients admitted to the intensive care unit after rib fractures, the use of ketorolac was associated with a reduction in pneumonia, an increase in the duration of mechanical ventilation and a reduction in the length of stay in the intensive care unit (Yang Y et al., 2014). Aside from postoperative stable patients, NSAIDs have limited use in the ICU and are generally avoided due to their contraindications. However, NSAIDs have a role in critical care because of their inhibition of prostaglandin synthesis (Chaiamnuay et al., 2006).

Analgesic adjuncts

Opioids poorly treat the neuropathic pain, and it is most effectively managed with analgesic adjuncts such as the antiepileptic or antidepressant or both.

Clonidine and dexmedetomidine also provide both analgesia and sedation (Moulin DE et al., 1997).

Dexmedetomidine

Dexmedetomidine provides both analgesia and sedation. However, there is limited evidence supporting its routine use for sparing opioid use in intensive care. In contrast to clonidine, which has taken its place as an adjuvant analgesic in the perioperative period, dexmedetomidine is more commonly used as an analgesic and sedative in intensive care units (Riker RR et al., 2009).

Antiepileptic and Antidepressant

The widespread occurrence of chronic pain among the elderly prompts an ongoing quest for effective and safe management techniques for this patient demographic. Antiepileptic and antidepressant drugs might offer an analgesic effect for different kinds of chronic pain (primarily neuropathic pain). Different antiepileptics utilized as pain relievers show inconsistent safety and effectiveness in older adults.

Some forms of cancer-related pain can be difficult to manage with conventional treatments, occasionally leading to persistent pain and distress for the patient. Relying solely on opioids for pain relief may result in inadequate pain management and a range of side effects. Nonopioid pain relievers, including antidepressants and antiepileptic medications, frequently enhance pain management and lower the incidence of side effects. Levetiracetam effectively and safely improves pain relief in patients with neoplastic plexopathies that were resistant to conventional analgesic treatments.

CHAPTER III

Methodology

The Methodology Chapter includes the design of the research study, the processes for data collection and analysis, the participants or sample involved, and the manner in which the findings or results are examined.

3.1 Research Design

This observational retrospective research aimed to assess pain management practices and the utilization of analgesic and sedative medications in the Intensive Care Unit (ICU) at Near East University Hospital in Nicosia – Northern Cyprus. Retrospective observational research involves a comprehensive review and thorough evaluation of documented assessments and databases to study the events that occurred from November 1, 2023, to April 30, 2024. The research was conducted in English and included demographic data and medications given.

3.2 Participants/ Population and Sample

Individuals aged 18 and older, who were hospitalized in the intensive care unit for over 24 hours and were administered analgesics from November 1, 2023, to April 30, 2024. Patients with incomplete information and those who did not finish their treatments at the Near East University Hospital (NEUH) were excluded.

3.3 Sample Size

All patients admitted to ICU during the study period and met the inclusion criteria. Using 95% confidence level, a 5% margin of error, a minimal sample size of 80 patients should be included if a total of 170 patients were admitted to ICU during the 6 months study period. Hence, In this research, a total of 98 patients satisfied the inclusion criteria during the study period (01.11.2023 - 30.05.2024) and were examined in the study.

3.4 Data collection Tools/Materials

Data were collected from the hospital database. The collected data covers the demographics of the patients, name of drugs administered, dose and pharmaceutical dosage forms, and prices of drugs administered.

3.5 Data Analysis Procedure

The collected data were entered into Microsoft Excel and Jamovi. We used both descriptive and inferential statistical analysis.

3.6 Ethical Considerations

Ethical permission for this research project was secured on 20.04.2024 from the Institutional Review Board (IRB) at Near East University Hospital (Project No: NEU/2024/120-1810).

CHAPTER IV

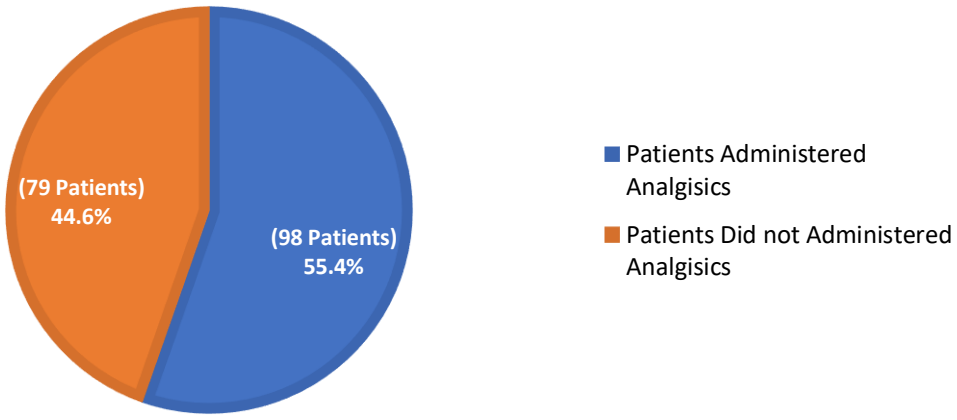
Results And Findings

4.1 Demographic Data

A total of 177 patients were admitted to an ICU between 1st November 2023 and 30th April 2024 at Near East University Hospital. The frequency of analgesic and its adjuvant usage is shown in Table 2.

Out of the total patients that entered the ICU (177 patients), 98, about 55.4% of total patients, were identified as patients administered analgesic, and 79, about 44.6% of total patients, did not receive any analgesic therapy in the intensive care unit during the study period, as shown in (Chart 1). The mean age of patients that administered analgesic therapy in the ICU was 63.99 years old.

CHART 1: NUMPER OF PATIENTS ADMINISTERED ANALGESIC IN THE ICU FROM 1ST OF NOVEMBER 2023 TO 30TH OF APRIL 2024



Out of 98 patients who received analgesic therapy, 53 were females and 45 were males. Regarding age categories, the count and ratio of patients entering the ICU rose with age. Adults aged 18 to 64 years comprised 39 patients, constituting

39.8% of the 98-patient population. Patients of geriatric age (65 years or older) constituted the largest portion of this patient population, with 59 individuals making up 69.8% of the total 98 patients, as shown in Table 1. Among all age groups, paracetamol was the most used analgesic in the ICU. All 98 patients had used one or more types of analgesic in the ICU between November 1, 2023, and April 30, 2024.

Gender	18 To 64 Years Old	65 To 100 Years Old	Total Patients
Male	14	31	45
Female	25	28	53
TABLE 1: Demography Data			98

4.2 Administered Analgesics

The collected data from the Near East Hospital archive regarding the administration of analgesic drugs in the Intensive Care Unit shows that there are two main categories of analgesics used in the ICU; one of them is the non-opioid analgesics, which are represented by Paracetamol with its different trade names, which is used by almost all patients, with 88 out of the 98 total patients. The other category is the opioid analgesics that are represented by Tramadol and used in 32 of the 98 patients. Nonsteroidal anti-inflammatory drugs were represented by 5 different drugs; Dexketoprofen was the most used in that category. NSAIDs were used in 21 patients, making up only 21% of 98 patients. In the analgesic adjuncts category, there were four other drugs; dexmedetomidine was the most used of them, where it was used in 15 patients to manage their pain and to provide sedation too, as shown in (Tablet 2). These analgesics used during that period provided good pain control, according to the doctors and nurses in the ICU at Near East University.

Drug Category		Drug Name	Quantity	Number of patients / recipients	Unite Price	Total Drug Cost ($)
Opioid Analgesics		Tramadol 100 MG/2 ML Ampul	249 Ampuls	32	0.763	190
Non-Opioid Analgesics	**Paracetamol**	Paracetamol 10 MG/ML 100 ML Flacon	2333 Flacons	84	2.603	6 075
		Paracetamol 500 MG Tablet	197 Tablets	7	0.101	20
	NSAID	Dexketoprofen 25 MG Tablet	12 Tablets	3	0.166	2
		Dexketoprofen 50 MG/2 ML Ampul	60 Ampuls	12	0.666	40
		Ibuprofen 400 MG Tablet	42 Tablets	1	0.19	8
		Diclofenac Sodium 75 MG/3 ML Ampul	7 Ampuls	3	0.428	3
		Flurbiprofen 100 MG Tablet	6 Tablets	3	0.333	2
		Tenoxicam 20 MG/2 ML Flacon	3 Flacons	2	2.333	7
Analgesic Adjuvant	**Gabapentinoids**	Pregabalin 75 MG Capsule	10 Capsules	2	0.4	4
	Central alpha-2 Agonist	Dexmedetomidine 200 MCG/2 ML Flacon	245 Flacons	15	18.612	4560
	Tricyclic Antidepressants	Amitriptyline 25 MG Tablet	26 Tablets	4	0.153	4
		Mirtazapine 30 MG Tablet	14 Tablets	2	0.285	4

Table 2: Administered Analgesics From 1st Of November 2023 to 30th Of April in 2024

4.3 Compare Between Age Groups And Drug Use

Drug Name		Adults Patients		Geriatric Patients		Total Patients
		Male	Female	Male	Female	
Analgesics	Tramadol	5	11	8	8	32
	Paracetamol	13	23	26	26	88
	NSAID	2	6	9	4	21
	Pregabalin	0	0	0	2	2
	Tricyclic Antidepressants	1	1	2	2	6
Sedatives	Dexmedetomidine	1	3	7	4	15
	Midazolam	3	3	8	7	21
	Propofol	5	2	2	3	12

TABLE 3: Drug Use In Adults And Geriatric Patients

According to Table 3, comparing adults with geriatric patients in ICU in using analgesics shows age and gender don't effects the use of tramadol and paracetamol except in NSAIDs that show decrease in use by (56%), while there is increase by (120%) of patients for tramadol use in female adult patients compared to male in same age group, and these increase was also observed in Paracetamol (77%) and in NSAIDs (300%). In sedation medications Midazolam had higher use (150%) in geriatric patients compare to the adult patients. On contrary, in Propofol had more use in adult patients by (40%).

The preformed independent Samples T-Test to compare the means of age on patients used and didn't use analgesic medications. There was no statistically significant difference between the age means in the two groups [t(df) = 175, P = 0.874]. Which means the patient's age has no role in whether the patient receives pain management therapy or not.

4.4 Analgesic Administered Routs and cost

The total cost for analgesic therapy in the ICU from November 1, 2023, to April 30, 2024, was $10,919. According to the administered analgesics, the most used drug was paracetamol via the IV route, characterized by strong analgesic and antipyretic activity. It accounted for 55.6% of the total analgesics ICU cost at $6,075 for 2,333 flacons of paracetamol 10 mg/ml 100, while paracetamol tablets were used in only 7 patients. Following behind was dexmedetomidine, totalling $4,560, which made up 41.8%, reflecting its role in pain management and sedation. Tramadol IV/IM, an opioid used in 32 patients, comprised 1.5% of the total analgesics ICU cost, amounting to $190 for 249 ampules of tramadol 100 mg/2 ml. The remaining analgesics accounted for less than 2.5% of the total analgesic cost in the ICU.

CHART 2: Incidence Of In-Hospital Delirium In Patients Administered Tramadol

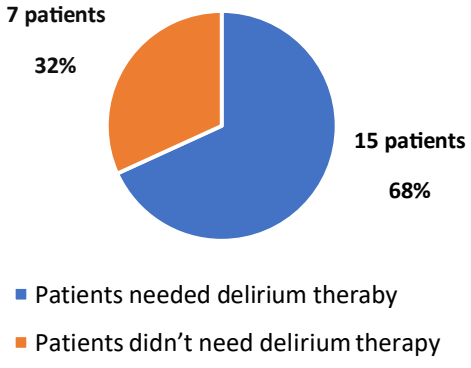


CHART 3: Incidence Of In-Hospital Delirium In Patients Administered Tamadol and Midazolam

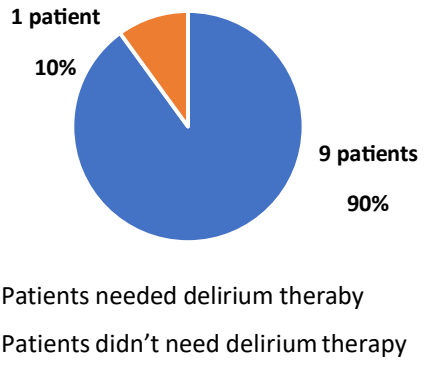
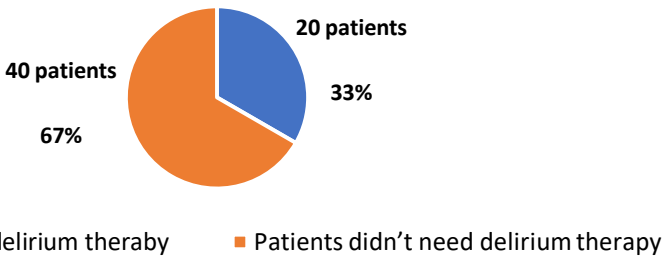


CHART 4: Incidence Of In-Hospital Delirium In Patients Administered any analgesic drug except Tramadol and Midazolam



4.5 Tramadol and Midazolam role in delirium incidents in the ICU

Regarding the collected data on delirium treatment drugs (Quetiapine and Haloperidol), Charts 1, 2 and 3 compare patients who experienced delirium during their ICU stay after receiving Tramadol alone or as part of a multimodal analgesic regimen with patients who received Tramadol with Midazolam or neither of them. Chart 2 indicates that Tramadol, a commonly used analgesic in ICU settings, has the potential to lead to delirium, causing it in 15 of 22 patients, resulting in a 68% chance of delirium incidence. On the other hand, Chart 3 shows that the use of Midazolam with Tramadol increased the possibility of delirium incidence, as 10 patients received both Tramadol and Midazolam, and 9 of them required delirium therapy. On contrary, patients that didn't administered Tramadol or Midazolam had 33% of patients only needed delirium therapy and 67% didn't need it.

4.6 Analgesic therapy cost with and without delirium therapy in ICU

	Patients with delirium therapy	Patients without delirium therapy
Number of patients	50	48
Analgesic therapy cost	$9025	$1894
Average analgesic therapy cost per patient	$180.5	$39.4

TABLE 4: Analgesic therapy cost with and without delirium therapy in ICU

The application of analgesics may pose risks for delirium, as both untreated pain and pain relief drugs can be contributing factors. Delirium is linked to increased health care expenses for medications in the Intensive Care Unit.. Table 3 shows that for patients without delirium therapy, the cost of pain management per patient is $39.4, while for patients with delirium therapy, it costs $180.5.

4.7 Delirium therapy cost and age link

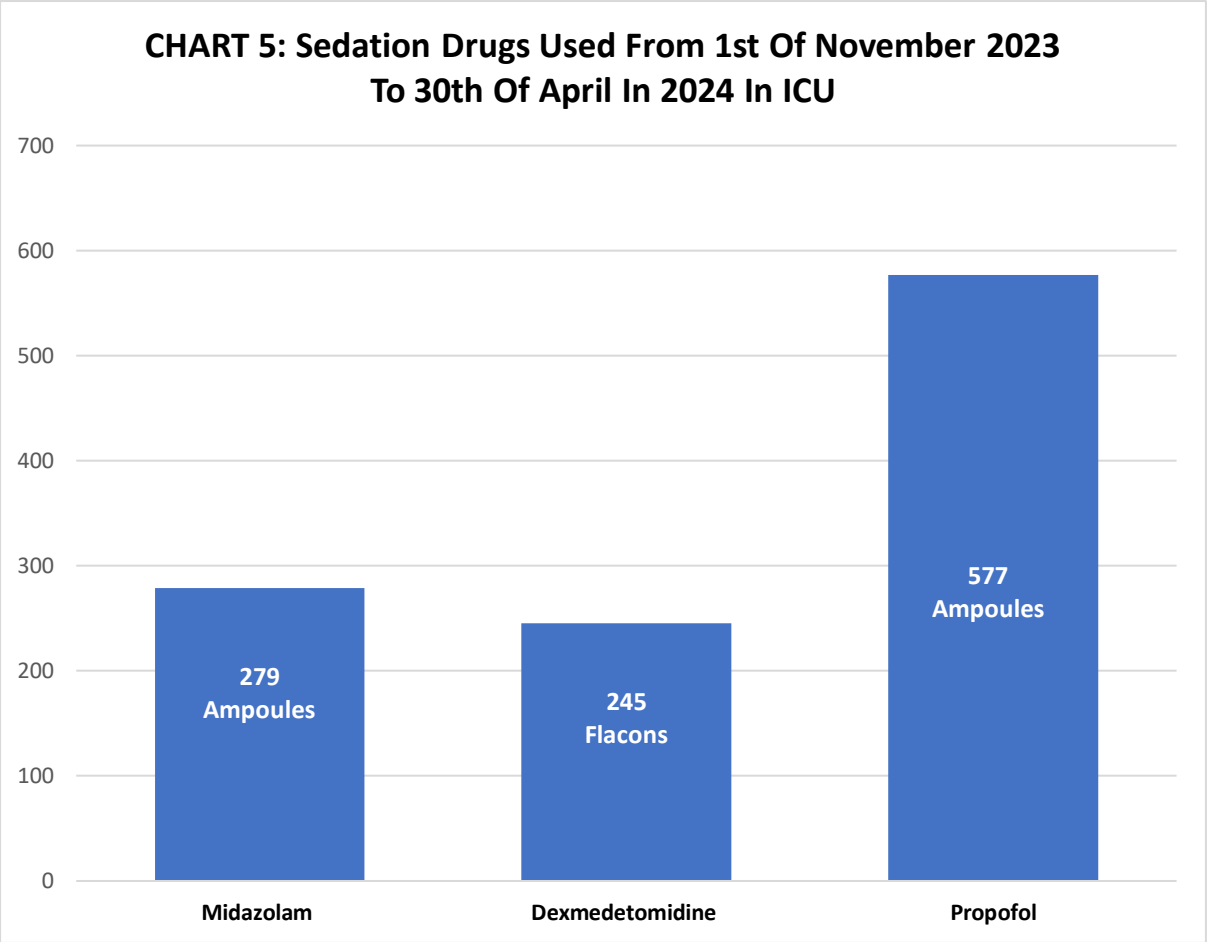
Drug Name	Adults Patients		Geriatric Patients	
	Number of patients / recipients	Treatment Cost ($)	Number of patients / recipients	Treatment Cost ($)
Haloperidol 5 mg/1 ml Ampul	1	3.5	3	22
Haloperidol 5 mg Tablet	0	0	1	0.5
Haloperidol 2 mg/ml 20 ml Oral drops	1	2	1	2
Quetiapine 25 mg Tablet	15	130.5	34	278.5
Quetiapine 100 mg Tablet	1	5.5	8	45
Quetiapine 200 mg XR Tablet	2	17.5	1	3
Total	15	159	35	351

TABLE 5: Delirium Treatment Cost In Adult And Geriatric Patients

Table 5 show two drugs for delirium treatment. Quetiapine was preferred in both adult and geriatric patients, while it had double patient administered it with double delirium therapy cost in the geriatric patients. Overall, 50 patients (51%) needed delirium therapy in ICU with their pain management treatment during this study period. Our result indicates a link between delirium incidence and patients age by (70%) of patents need delirium therapy were 65 years old or more. The average delirium treatment cost in adult patents were 10.5$ and 10 $ in geriatric patients.

The preformed independent Samples T-Test to compare the means of age on patients used and didn't use delirium medications. There was a statistically significant difference between the age means in the two groups [t(df) = 96, P = 0.002]. Which means the geriatric patients had more delirium incidents compared in adults.

4.8 Used sedation drugs in ICU



Moreover, the collected data during this study period shows the use three drugs as sedation agents. Where was Midazolam 50 MG/10 ML the preferred by using 279 ampoules in 21 patients. Then Propofol 200 MG/ 20 ML by 577 ampoules in 12 patients. Lastly Dexmedetomidine 200 MCG/2 ML by 245 Flacons used in 15 patients (n, %).

CHAPTER V

Discussion

In this regard, this study in the ICU of the Near East University Hospital aimed to examine the practices of managing pain, including patient demographics, analgesic medication costs, drug administration patterns, and encouraging greater cooperation between pharmacists and other healthcare staff to achieve desired outcomes. In our study, most patients were of geriatric age, between 65 and 100 years old (60.2%). The most common form of analgesic drug administration for pain management was Paracetamol IV, which was administered to 87 patients, approximately 88.7% of all patients who received analgesic therapy in our study.

This can be explained by the intravenous form of Paracetamol, which passes easily through the blood-brain barrier and starts its central analgesic effects within about 15 to 20 minutes, then begins to decline after 4 hours of administration. A prospective study conducted in an Iranian hospital ICU investigates the side effects and efficacy of Paracetamol IV compared to fentanyl IV in postoperative patients experiencing mild to moderate pain in the ICU. The study did not indicate any statistically significant difference between the Paracetamol IV and fentanyl IV patient groups regarding pain scores, physiological parameters, side effect profiles (both laboratory and clinical), or neurological and liver function at 24 or 48 hours (Mehran Kouchek et al., 2013).

In another study, giving 1 g of intravenous Paracetamol before hysterectomy was shown to improve postoperative pain control and lead to a reduction in Morphine use (Arici S et al., 2009).

A research involving patients who had lower-segment caesarean sections revealed that intravenous Paracetamol, used alongside Morphine, provided better pain management than oral ibuprofen as an analgesic supplement (Alhashemi JA et al., 2006).

According to another study of 40 patients in a randomized, double-blind clinical trial examining pain management after lumbar laminectomy, one group received 1 gram of intravenous Paracetamol every six hours in addition to Morphine administration, while the remaining group was given an intravenous placebo. The quantity of intravenous Morphine administered revealed no notable difference between the two groups. The Paracetamol group exhibited superior pain management results compared to the placebo group (Cakan T et al., 2008).

This further emphasizes the similar preference observed for Paracetamol regarding its safety profile and minimal drug interactions with other medications. The preference for IV administration in our study reflects the quick onset of action assured by the parenteral routes, which is especially relevant in emergency settings where rapid intervention is required. The ICU physician's preference for Paracetamol may stem from its well-documented safety, minimal effects on other drugs, and applicability to a wide range of individuals due to its few contraindications. It can also be administered in various forms, such as orally (tablet, liquid suspension) and parenterally (intravenous or intramuscular) (Bannwarth & Pehourcq, 2003; Day et al., 2000).

So, we can conclude that Paracetamol alone is not inferior to Paracetamol/Tramadol. Currently used postoperative analgesics include strong opioids, weak opioids, NSAIDs, and Paracetamol (Subedi M et al., 2019).

It is worth noting that patients with contraindications to NSAIDs tend to be prescribed weak opioids, such as Tramadol. Tramadol often causes side effects like nausea, delirium, seizures, vomiting, and constipation, which can lead to discomfort for the patient. Moreover, there is significant concern regarding the overprescribing of opioids (Nakhaee S et al., 2021).

In our study, the use of NSAIDs was so limited that they were only utilized by 21 out of 98 patients. This may explain why the analgesic properties of these category have not been well studied in critically ill patients, rendering it uncertain if the possible advantages (e.g., shorter ileus duration or lesser mechanical ventilation period) surpass the possible hazards (e.g., kidney impairment, gastrointestinal bleeding). In a retrospective cohort study involving patients admitted to the ICU with rib fractures, the use of ketorolac was linked to a rise in ventilator-free and ICU-free days, as well as a lower occurrence of pneumonia. The incidence of acute kidney injury, gastrointestinal bleeding, and non-union of fractures showed no significant differences. It is advisable to avoid NSAIDs in patients at risk for renal dysfunction (inotropic-dependent shock, hypovolemia), gastrointestinal bleeding (alcoholic liver disease, mechanical ventilation, burns), and those with coagulopathy or platelet abnormalities. Concomitant use of angiotensin-converting enzyme inhibitors and congestion are also concerns, as well as cirrhosis, heart failure, or aspirin-sensitive asthma. For these reasons, in the intensive care unit at NEU hospital, NSAIDs were not commonly used. Nevertheless, NSAIDs do have a role in critical care due to their inhibition of prostaglandin synthesis (e.g., closure of the ductus arteriosus in premature neonates, hypothermic sepsis) (Yang Y et al., 2014).

Patients in the intensive care unit (ICU) who experience moderate to severe acute pain require opioid treatment; nevertheless, it is essential to

achieve a balance that keeps patients comfortable during their ICU stay while also avoiding increased long-term opioid dependency after leaving the ICU (Todsaporn S., 2023).

The use of opioids was significantly less frequent, with Tramadol, which can be administered intravenously or intramuscularly, being given to 32 patients, representing approximately 32.6% of cases. This cautious approach to opioids aligns with global trends aimed at reducing the risk of addiction and side effects.

Opioids are the mainstay of pain management in critically ill patients. Among the 32 patients who needed to receive a Tramadol dose to manage their pain, 5 of them received a high opioid Tramadol dose regimen therapy (400 mg daily), and these high doses increase the chances of developing opioid adverse effects. Due to these adverse effects, the ICU has resulted in the adoption of approaches designed to minimize these side effects. Among these strategies are multimodal analgesia protocols, which emphasize pain control and use a mix of various analgesics to prevent overdoses of opioids and sedatives in continuous infusion (Chanques G., 2007). The application of these protocols in the ICU was observed in 27 of the 32 patients who received a multimodal analgesic regimen, primarily involving Tramadol and Paracetamol.

Prospective, observational, multicentre, one-day point prevalence research carried out in ICUs across Australia and New Zealand. Observational data were collected for every adult patient admitted to an ICU. Out of the 499 patients accepted from 45 intensive care units. In total, 286 patients (57%) were administered an opioid on the day of the study with the predominant opioid oxycodone and infusion being fentanyl. Paracetamol was administered to 227 patients (45%), while 2% of all patients (11/499) received a non-steroidal anti-inflammatory drug. Ketamine infusions were used in 15 patients (3%).

Antineuropathic agents (predominantly gabapentinoids) were used in 53 patients (11%) (Benjamin L., 2022).

The International Clinical Practice Guidelines for Sedatives and Analgesics in Critically Ill Adults offer direction for healthcare providers to create cohesive, evidence-supported, patient-focused protocols aimed at preventing and managing pain, agitation, and delirium in severely ill patients.

These guidelines recommend that intravenous (IV) opioids should be viewed as the primary medication class to address non-neuropathic pain in critically ill patients. Proposing that nonopioid pain relievers be taken into account to reduce the quantity of opioids used (or to entirely avoid the necessity for IV opioids) and to lessen opioid-related adverse effects (Barr., 2013). Based on that, NEUH ICU results indicate the following these recommendations by dependence on non-opioid analgesic (Paracetamol) in pain management and using it in about 88.7% compared to 32.6% use of opioid (Tramadol) of total population that needed pain management in ICU.

Additionally, the recommendations suggest not routinely use of NSAIDs as an adjunct to opioid therapy for pain management in critically ill adults due their adverse effects like AKI, GI bleeds and cardiovascular events (Barr., 2013). This recommendation is consistent with the results of the study by the limited use in the ICU by (21%) only of total study patients.

Furthermore ,regarding the selection of sedatives, guidelines indicate that strategies employing non-benzodiazepine sedatives (such as propofol or dexmedetomidine) could be favoured compared to sedation with benzodiazepines (like midazolam or lorazepam) to enhance clinical outcomes in adult ICU patients on ventilation. (Barr, 2013). However, there is still frequent use of midazolam in the ICU (21 patients) and this use can lead to poor patient

outcomes as we have shown in Figure 3. It may increase the risk of delirium, which is also suggested by the guidelines on delirium risk factors by indicating that benzodiazepine use may be a risk factor for the development of delirium in adult ICU patients. Regardless to prolonged ICU stay and increased duration of mechanical ventilation.

A prospective study aimed to investigate the effect of benzodiazepine or opioid consumption on the length of ICU delirium in an elderly group at a fourteen-bed medical intensive care unit in an urban teaching hospital. Delirium was observed in 239 out of 304 patients (79%). The acquisition of a benzodiazepine or opioid was linked to a longer duration of delirium (Margaret A., 2009).

Another study to assess the relationship between opioid exposure in the ICU and the incidence of delirium. A total of 4,075 adults experienced 26,250 days in the ICU; opioids were given to 57.0% (14,975). In awake patients without delirium, the administration of any opioid was linked to a heightened risk for developing delirium the following day. Every daily 10-mg intravenous dose of morphine equivalent was linked to a 2.4% heightened risk for delirium the following day (Matthew S., 2020). These two studies consistent with or results and findings.

A prospective cohort investigation conducted in the medical and surgical intensive care units of a major academic medical centre examined critically ill patients (n = 479) experiencing respiratory failure and/or shock. Results: The total patient-level cost of ICU delirium over 30 days due to higher resource usage amounted to $17,838. The largest share of the additional costs linked to ICU delirium came from a mix of professional, dialysis, and bed expenses. The total 30-day additional expenses of ICU delirium prevented because of delirium-

related early deaths were $4,654 (Edward E, 2018). Our results are consistent with our findings that delirium causes a significant increase in ICU healthcare costs

A multicentre, retrospective, cohort study compares use propofol to midazolam in ICU adult patients. The data obtained from the multicentre ICU database (2003–2009) shows 2,250 propofol-midazolam matched patients. ICU The data indicated that patients treated with propofol had a statistically greater likelihood of being discharged from the ICU (78.9% vs. 69.5%) and a quicker extubation (84.4% vs. 75.1%) in comparison to those receiving midazolam (Lonardo., 2013).

A systematic review and meta-analysis encompass 41 studies (N=3948). Dexmedetomidine was found to have no significant effect on ICU length of stay relative to propofol, but it notably decreased the duration of mechanical ventilation and the likelihood of delirium in patients undergoing cardiac surgery. It also notably heightened the risk of bradycardia among various ICU patient groups (Kiyan Heybati., 2022).

CHAPTER VI

Recommendation And Conclusion

6.1 Recommendation

Based on the findings of the ICU pain management assessment, we believe that the ICU physicians have optimal use of the available analgesic drugs in the Near East University Hospital pharmacy. However, there is still room for improving the quality and the cost efficiency of analgesic use in the ICU. We recommend targeted interventions to further refine pain management practices in the ICU.

When we compare effervescent tablets to IV Paracetamol, it takes about 15 minutes to reach maximal plasma concentration with Paracetamol intravenously, while Paracetamol effervescent tablets take approximately 27 minutes. However, in terms of cost, a single Paracetamol 10 mg/ml 100 ml flacon costs around $ 1.45, compared to two effervescent tablets of 500 mg Paracetamol that cost about $ 0. 90, which is roughly 60% of the cost of the single Paracetamol flacon. Thus, in eligible patients who have a swallowing reflex or can drink without nausea, providing Paracetamol effervescent tablets will reduce the cost of analgesic therapy in these patients, leading to a decrease in the cost of the most used analgesic drugs in the ICU.

Patients who have moderate to severe pain that cannot be managed by Paracetamol find that physicians in the ICU have dexmedetomidine, Tramadol, ketamine, and Midazolam as alternative choices. Unfortunately, the rare and limited availability of ketamine and dexmedetomidine often leaves Midazolam and Tramadol as the only available options. Due to the short- and long-term side

effects of Midazolam and Tramadol, providing other non-opioid analgesics or a consistent supply of the other options can help reduce opioid and Midazolam use, thereby improving healthcare quality outcomes in the ICU at Near East University Hospital.

In a study examining the pain-relieving effectiveness and blood flow impacts of nefopam in severely ill individuals, it was demonstrated that a single slow infusion of the medication over 30 minutes is beneficial for patients experiencing moderate-to-severe pain. The research indicated that nefopam's onset time and peak effect seem to occur at a minimum of 30 and 60 minutes, respectively, lasting between 4 to 6 hours after the infusion starts. Nefopam infusion may elevate heart rate and cardiac output while reducing arterial pressure; thus, it should be administered carefully to ICU patients with a background of coronary artery disease, hemodynamic instability, or both. No effects of nefopam on respiratory function or vigilance status were noted. Nefopam is linked to reduced opioid needs in postoperative patients, and studies have shown that nefopam provides at least an additive pain-relieving effect when combined with acetaminophen. It acts as a strong substitute for opioids for these patients because it does not have respiratory and neurological side effects. Therefore, it can be given to suitable patients who have no contraindications. Nonetheless, ICU doctors must stay alert to the hemodynamic impacts of nefopam (Muaddi, H et al., 2021; G Chanques et al., 2011).

Strengthening educational curricula in the professional training of analgesic use and pain protocols for other health providers, such as physicians and nurses practicing in the ICU, would greatly enhance informed decision-making, patient care, and drug cost efficiency. Furthermore, comprehensive workshops on the rational use of analgesics, including the latest strategies for

pain management, are likely to significantly optimize treatment approaches. It is also essential that such educational interventions be expanded to pharmacy students and other health professionals involved in pain management, with a focus on the broader effects of analgesics.

Both untreated pain and opioid use for pain management are separate triggering factors for delirium. The precise way in which Tramadol induces delirium is unclear, but it is believed that elevated plasma levels of the metabolite O-desmethyl Tramadol may be the likely cause (Gleason PP et al., 1997). The outcome shown in chart 3, which suggests that Tramadol may elevate the occurrence of delirium in the ICU, aligns with a retrospective study assessing the connections between pain intensity, its treatment using opioids, and the development of delirium in older patients admitted to the surgical intensive care unit (SICU), where a review was conducted on patients aged 65 and above admitted to the SICU during a 5-month timeframe. Upon evaluation, opioids, rather than pain, were notable in forecasting the delirium status for the next day. After accounting for pain, patients given opioids were 2.5 times more prone to developing delirium compared to those who were not exposed. Additionally, data indicate that opioid use was a predictor of the occurrence of delirium the following day (Kara J et al., 2020).

Global trends indicate a shift from deep sedation based on hypnotics to light sedation based on analgesics (Barr et al., 2013). However, there is still frequent use of Midazolam in the ICU of Near East University Hospital, where it has been administered to 18 patients, particularly those on mechanical ventilation. Excessive use of benzodiazepines may lead to poor patient outcomes, such as a longer length of stay in the ICU and an extended duration of mechanical ventilation. Thus, reducing the use of benzodiazepines (Midazolam) and

increasing the use of other sedatives, such as dexmedetomidine, which can provide analgesic properties, or propofol, is desirable and is associated with better outcomes (Hyuk-Hoon Kim et al., 2018).

6.2 Conclusion

The study aimed to evaluate pain management assessment and to determine the effect of having a other analgesic drugs on the cost of the pain management therapy in the Intensive Care Unit (ICU) of the Near East University Hospital in Nicosia. The results showed a significant preference for all analgesic categories in analgesia, with Paracetamol IV being the first line in the spectrum of applied drugs, and Paracetamol IV is the most used to manage mild to moderate pain. This preference underscores an operational priority for the swift and effective management of pain, in line with the essential objectives of the Intensive Care Unit. Greater emphasis on the parenteral route, primarily IV and IM, reflects the concern of healthcare professionals regarding ensuring quick relief for patients in severe pain. The results further reveal that the ICU has made a judicious selection of analgesics to mitigate the risks associated with opioid use, enhancing patient care outcomes. Finally, in addition to increasing the types of analgesics in the hospital pharmacy, implementing clinical pharmacy practices in the ICU may have the potential to reduce drug therapy costs and improve healthcare quality, benefiting both patients and the hospital's health cost burden.

REFERENCES

Abbadie C, Besson JM. C-fos expression in rat lumbar spinal cord during the development of adjuvant-induced arthritis. *Neuroscience* 1992;48:985–993.

Abbadie C, Besson JM. Chronic treatments with aspirin or acetaminophen reduce both the development of polyarthritis and Fos-like immunoreactivity in rat lumbar spinal cord. *Pain* 1994;57:45–54.

Aghamir SK, Mojtahedzadeh M, Alizadeh F, Alizadeh F, Khalili H, Sadeghi M, Najafi A, Rezaie K, Rafizadeh F, Shabani F. Propacetamol vs. Tramadol for post- operative pain management after urologic surgery. *Int. J. Pharmacol*. 2006;4:1–8.

Airaksinen O, Brox JI, Cedraschi C. European guidelines for the management of chronic non-specific low back pain. *Eur Spine J* 2006;15(Suppl 2):S192–S300.

Akça, S., Eray, O., Ersoy, F., Karsli, B., Oktay, C., Çete, Y., & Çete, N. (2002). Intravenous single-dose Tramadol versus meperidine for pain relief in renal colic. *European Journal of Anaesthesiology*, *19*(5), 368–370. https://doi.org/DOI: 10.1017/S0265021502000595

Albert KS, Sedman AJ, Wagner JG. Pharmacokinetics of orally administered acetaminophen in man. J *Pharmacokinet Biopharm* 1974;2:381–393.

Alhashemi JA, Alotaibi QA, Mashaat MS, Kaid TM, Mujallid RH, Kaki AM. Intravenous acetaminophen vs oral ibuprofen in combination with Morphine PCIA after Cesarean delivery. *Can. J. Anaesth*. 2006;53:1200–6. doi: 10.1007/BF03021581.

Alhashemi JA, Doghistaui MF. Effect of intraoperative IV acetaminophen vs. IM meperidineon post-tonsillectomy pain in children. *Br. J. Anaesth*. 2006;96:790–95. doi: 10.1093/bja/ael084.

Ambuel, B., Hamlett, K. W., Marx, C. M., & Blumer, J. L. (1992). Assessing Distress in Pediatric Intensive Care Environments: The COMFORT Scale1. *Journal of Pediatric Psychology*, *17*(1), 95–109. https://doi.org/10.1093/jpepsy/17.1.95

Anderson BJ, Holford NHG, Woollard GA, Chan PLS. Paracetamol plasma and cerebrospinal fluid pharmacokinetics in children. *Br J Clin Pharmacol* 1998;46:237–243.

Anderson BJ, Holford NHG, Woollard GA, et al. Perioperative pharmacodynamics of acetaminophen analgesia in children. Anaesthesiology 1999;90:411–421.

Anderson BJ, Woollard GA, Holford NHG. Pharmacokinetics of rectal Paracetamol after major surgery in children. *Paediatric Anaesth* 1995;5:237–242.

Anwar, K. (2016). Pathophysiology of pain. *Disease-a-Month*, *62*(9), 324–329.2016.05.015

Anwar-ul-Huda, Hamid, M., Baqir, M., Almas, A., & Ahmed, S. (2012). Pain assessment and management in different wards of a tertiary care hospital. *JPMA. The Journal of the Pakistan Medical Association*, *62*(10), 1065–1069.

Arendts, G., & Fry, M. (2006). Factors Associated With Delay to Opiate Analgesia in Emergency Departments. *The Journal of Pain*, *7*(9), 682–686. https://doi.org/https://doi.org/10.1016/j.jpain.2006.03.003

Arici S, Gurbet A, Turker G, Yavascaoglu B, Sahin S. *Preemptive analgesic effects of intravenous Paracetamol in total abdominal hysterectomy.* Agri. 2009;21:54–61.

Arthur, A. O., & Holder, P. (2012). *A Review of Transbuccal Fentanyl Use in the Emergency Department*. *2012*, 3–6. https://doi.org/10.1155/2012/768796

Arthur, A. O., Whiteside, S., Brown, L., Minor, C., & Thomas, S. H. (2012). Patient use of tablet computers to facilitate emergency department pain assessment and documentation. *International Scholarly Research Notices*, *2012*.

Asadi, P., Ghafouri, H.-B., Yasinzadeh, M., Kasnavieh, S. M. H., & Modirian, E. (2013). Ketamine and atropine for pediatric sedation: a prospective double-blind randomized controlled trial. *Pediatric Emergency Care*, *29*(2), 136–139.

Attard, A. R., Corlett, M. J., Kidner, N. J., Leslie, A. P., & Fraser, I. A. (1992). Safety of early pain relief for acute abdominal pain. *BMJ: British Medical Journal*, *305*(6853), 554.

Babl, F. E., Oakley, E., Puspitadewi, A., & Sharwood, L. N. (2008). *Limited analgesic efficacy of nitrous oxide for painful procedures in children*. 717–721. https://doi.org/10.1136/emj.2007.053751

Babl, F. E., Oakley, E., Seaman, C., Barnett, P., & Sharwood, L. N. (2008). High-concentration nitrous oxide for procedural sedation in children: adverse events and depth of sedation. *Pediatrics*, *121*(3), e528–e532.

Bae YC, Oh JM, Hwang SJ, et al. Expression of vanilloid receptor TRPV1 in the rat trigeminal sensory

Bailey, B., Bergeron, S., Gravel, J., & Daoust, R. (2007). Comparison of Four Pain Scales in Children With Acute Abdominal Pain in a Pediatric Emergency Department. *Annals of Emergency Medicine*,

50(4), 379-383.e2. https://doi.org/https://doi.org/10.1016/j.annemergmed.2007.04.021

Ballas, S. K., Viscusi, E. R., & Epstein, K. R. (2004). *Management of Acute Chest Wall Sickle Cell Pain with Nebulized Morphine*. *191*, 190–191. https://doi.org/10.1002/ajh.20064

Bannwarth B, Netter P, Lapicque F, et al. Plasma and cerebrospinal fluid concentrations of Paracetamol after a single intravenous dose of Paracetamol. Br J Clin Pharmacol 1992;34:79–81.

Bannwarth B, Netter P, Lapicque F, Gillet P, Pere P, Boccard E, Royer RJ, Gaucher A. *Plasma and cerebrospinal fluid concentrations of Paracetamol after a single intravenous dose of propacetamol. Br. J. Clin. Pharmacol*. 1992;34:79–81. doi: 10.1111/j.1365-2125.1992.tb04112.x.

Bannwarth B, Pehourco F, Lagrange F, et al. Single and multiple dose pharmacokinetics of acetaminophen (Paracetamol) in polymedicated very old patients with rheumatic pain. J Rheumatol 2001;28:182–184.

Barden J, Edwards J, Moore A, et al. Single dose oral Paracetamol (acetaminophen) for postoperative pain (Cochrane Review). *Cochrane Lib* 2004;1:1–54.

Bar-Joseph, G., Guilburd, Y., Tamir, A., & Guilburd, J. N. (2009). Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension. *Journal of Neurosurgery: Pediatrics*, *4*(1), 40–46.

Barker JD Jr, de Carle DJ, Anuras S. Chronic excessive acetaminophen use and liver damage. *Ann Intern*

Barkin RL. Topical Nonsteroidal Anti-Inflammatory Drugs: The Importance of Drug, Delivery, and Therapeutic Outcome. *Am J*

Ther. 2015 Sep-Oct;22(5):388-407.

Barr J, Fraser GL, Puntillo K, Ely EW et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013; 41: 263–306

Barr R, Wentowski C, Curhan G, et al. Prospective study of acetaminophen use and newly diagnosed asthma among women. Am J Respir Crit Care Med 2004;169:836–841.

Bartolucci, P., & Galactéros, F. (2012). Clinical management of adult sickle-cell disease. *Current Opinion in Hematology*, *19*(3), 149–155.

Beck DH, Schenk MR, Hagemann K, et al. The pharmacokinetics and analgesic efficacy of larger dose rectal acetaminophen (40 mgkg) in adults: A double-blinded, randomized study. Anesth Analg 2000;90:431–436.

Beckwith, M. C., Fox, E. R., & Chandramouli, J. (2002). Removing meperidine from the health-system formulary—frequently asked questions. *Journal of Pain & Palliative Care Pharmacotherapy*, *16*(3), 45–59.

Behav Brain Res 2000;112:177–186.

Bell, R. F., Dahl, J. B., Moore, R. A., & Kalso, E. A. (2006). Perioperative ketamine for acute postoperative pain. *Cochrane Database of Systematic Reviews*, *1*.

Beltramo M, Stella N, Calignano A, Lin SY, et al. Functional role of high-affinity anandamide transport, as revealed by selective inhibition. Science 1997;277:1094–1097.

Bennett WM, Aronoff GR, Golper TA, et al. Drug Prescribing in Renal Failure, 3rd Edition. Philadelphia: American College of Physicians, 1994. Bentley E, Mackie IC. Trends in prescriptions of Paracetamol

for children. Br Med J 1995;311:362.

Bennett, M. (2001). *The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. Pain*, *92*(1), 147–157. https://doi.org/https://doi.org/10.1016/S0304-3959(00)00482-6

Bennett, M. I., Smith, B. H., Torrance, N., & Lee, A. J. (2006). *Can pain can be more or less neuropathic? Comparison of symptom assessment tools with ratings of certainty by clinicians. Pain, 122*(3), 289–294. https://doi.org/https://doi.org/10.1016/j.pain.2006.02.002

Bentley KC, Head TW. The additive analgesic efficacy of acetaminophen, 1000 mg, and codeine, 60 mg, in dental pain. Clin Pharmacol Ther 1987;42:634–640.

Berkes EA. Anaphylactic and anaphylactoid reactions to aspirin and other NSAIDs. *Clin Rev Allergy Immunol.* 2003 Apr;24(2):137-48.

Bertolini A, Ottani A, Sandrini M. Selective COX-2 inhibitors and dual acting anti-inflammatory drugs: Critical remarks. Curr Med Chem 2002;9:1033–1043.

Birmingham P, Tobin M, Henhorn T, et al. Twenty-four-hour pharmacokinetics of rectal acetaminophen in children. Anestesiology 1997;87:244–252.

Bisogno T, Melck D, Bobrov M, et al. N-acyl-dopamines: Novel synthetic CB1 cannabinoid-receptor ligands and inhibitors of anandamide inactivation with cannabimimetic activity in vitro and in vivo. Biochem J 2002;315:817–824.

Bizovi KE, Smilkstein MJ. Acetaminophen. In: Golfrank LR, Howland MA, Flomenbaum NE, Hoffman RS, Lewin NA, Nelson RS, Eds. Goldfrank's Toxicologic Emergencies, 7th Edition. New York: McGrawHill, 2002;480–501.

Bjorkman R, Hallman KM, Hedner T, Henning M. Acetaminophen blocks spinal hyperalgesia induced by NMDA and substance P. Pain 1994;57:259–264.

Blume H, Ali SL, Elze M, et al. Relative bioavailability of Paracetamol in suppository preparation in comparison to tablets. Arzneimittelforschung 1994;44(12):1333–1338.

Boeijinga JJ, Boerstra EE, Ris P, et al. Interaction between Paracetamol and coumarin anticoagulants. Lancet1982;1:506.

Borin MT, Ayres JW. Single dose availability of acetaminophen following oral absorption. Int J Pharm 1989;54:199–209.

Botting R, Ayoub SS. COX-3 and the mechanism of action of Paracetamolacetaminophen. Prostaglandins Leukot Essent Fatty Acids 2005;72:85–87.

Boutaud O, Aronoff DM, Richardson JH, et al. Determinants of the cellular specificity of acetaminophen as an inhibitor of prostaglandin H2 synthases. Proc Natl Acad Sci USA 2002;99:7130–7135.

Bowman WC, Rand MJ. Textbook of Pharmacology. Oxford: Blackwell Scientific Publications, 1980.

Breen K, Wandscheer JC, Peignoux M, Pessayre D. In situ formation of the acetaminophen metabolite covalently bound in kidneys and lung. Supportive evidence provided by total hepatectomy. Biochem Pharmacol

Breivik H, Högström H, Niemi G, Stalder B, Hofer S, Fjellstad B, Haugtomt H, Thomson D. 2 *Safe and effective post-operative pain relief: introduction and continuous quality-improvement of comprehensive post-operative pain management progmes.*

Baillière's Clin. Anaesthesiol. 1995;9:423–60.

Brent JA. New ways of looking at an old molecule. *J Toxicol Clin Toxicol* 1996;34:149–153.

Brodie BB, Axelrod J. The fate of acetanilide in man. *J Pharmacol Exp Ther* 1948;94:29–38.

Bromm B, Forth W, Richter E, Scharein E. Effects of acetaminophen and antipyrine on non-inflammatory pain and EEG activity. Pain 1992;50:213–221.

Brooks PM, Day RO. Nonsteroidal antiinflammatory drugs–differences and similarities. *N Engl J Med*

Bruton L, Lazo J, Parker K. Goodman & Gilman's the Pharmacological Basis of Therapeutics, 11th Edition. New York: *McGraw-Hill,* 2006.

Buckpitt AR, Rollins DE, Mitchell JR. Varying effects of sulfhydryl nucleophiles on acetaminophen oxidation and sulfhydryl adduct formation. *Biochem Pharmacol* 1979;28:2941–2946.

Bujalska M. Effect of nitric oxide synthase inhibition on antinociceptive action of different doses of acetaminophen. *Pol J Pharmacol* 2004;56:605–610.

Burger DM, Meenhorst PL, Koks CH, et al. Pharmacokinetics of zidovudine and acetaminophen in a patient on chronic acetaminophen therapy. Ann Pharmacother 1994;28:327–330.

Cakan T, Inan N, Culhaoglu S, Bakkal K, Basar H. *Intravenous Paracetamol improves the quality of postoperative analgesia but does not decrease narcotic requirements*. J. Neurosurg. Anesthesiol. 2008;20:169–73. doi: 10.1097/ANA.0b013e3181705cfb.

Calvert LJ, Linder CW. Acetaminophen poisoning. *J Fam Pract* 1978;7:953–956.

Campbell NR, Baylis B. Renal impairment associated with an acute Paracetamol overdose in the absence of hepatotoxicity. *Postgrad Med J* 1992;68:116–118.

Carlsson J. Central analgesic effect of Paracetamol manifested by depression of nociceptive activity in thalamic neurones of the rat. *Neurosci Lett* 1987;77:339–343.

Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001;345:1809–1817.

Chaiamnuay S, Allison JJ, Curtis JR. Risks versus benefits of cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs. *Am J Health Syst Pharm.* 2006 Oct 01;63(19):1837-51.

Chan A, Hepp P. Das Antifebrin, ein neues Fiebermittel. Centralbl Klein Med 1886;7:561–564.

Chandrasekharan NV, Dai H, Roos KL, et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesicantipyretic drugs: Cloning, structure, and expression. *Proc Natl Acad Sci* USA 2002;99:13926–13931.

Chanques G, Sebbane M, Barbotte E, Viel E, Eledjam JJ, Jaber S. Anesthesiology. *A prospective study of pain at rest: incidence and characteristics of an unrecognized symptom in surgical and trauma versus medical intensive care unit patients.*. 2007;107:858–860. doi: 10.1097/01.anes.0000287211.98642.51.

Chao TC. Adverse drug reactions: Tales of a forensic pathologist. *Ann Acad Med Singapore* 1993;22:86–89.

Chem Res Toxicol 1998;11:295–301.

Chen W, Koenigs LL, Thompson SJ, et al. Oxidation of acetaminophen to

its toxic quinone imine and nontoxic catechol metabolites by baculovirus-expressed and purified human cytochromes P450 2E1 and 2A6.

Cichewicz DL. Synergistic interactions between cannabinoid and opioid analgesics. *Life Sci 2004*;74:1317–1324.

Clark JH, Russell GJ, Fitzgerald JF. Fatal acetaminophen toxicity in a 2-year-old. *J Indiana State Med Assoc* 1983;76:832–835.

Clements JA, Heading RC, Nimmo WS, et al. Kinetics of acetaminophen absorption and gastric emptying in man. *Clin Pharmacol Ther* 1978;24:420–431.

Clissold SP. Paracetamol and phenacetin. *Drugs* 1986;32(Suppl 4):46–59.

Dawood MY. Primary dysmenorrhea: advances in pathogenesis and management. *Obstet Gynecol.* 2006 Aug;108(2):428-41.

Depre M, van Hecken A, Verbesselt R, Tjandra-Maga TB, Gerin M, de Schepper PJ. *Tolerance and pharmacokinetics of propacetamol, a Paracetamol formulation for intravenous use. Fundam. Clin. Pharmacol. 1*992;6:259–62. doi: 10.1111/j.1472-8206.1992.tb00119.x

G Chanques 1, M Sebbane 1, J.M. Constantin 2, N Ramillon 1, B Jung 1, M Cissé 1, J.Y. Lefrant 3, S Jaber 1. *Analgesic efficacy and haemodynamic effects of nefopam in critically ill patients. British Journal of Anaesthesia* 106 (3): 336–43 (2011)

Guillou N, Tanguy M, Seguin P et al. *The effects of small-dose ketamine on Morphine consumption in surgical intensive care unit patients after major abdominal surgery*. *AnesthAnalg* 2003; 97: 843–7

Harirforoosh S, Asghar W, Jamali F. Adverse effects of nonsteroidal antiinflammatory drugs: an update of gastrointestinal,

cardiovascular and renal complications. *J Pharm Pharm Sci*. 2013;16(5):821-47.

Hernandez-Palazon J, Tortosa JA, Martinez-Lage JF, Perez-Flores D. *Intravenous administration of propacetamol reduces Morphine consumption after spinal fusion surgery.* Anesth. Analg. 2001;92:1473–76. doi: 10.1097/00000539-200106000-00024.

https://doi.org/10.1016/j.heliyon.2022.e11462

Hunter LJ, Wood DM, Dargan PI. The patterns of toxicity and management of acute nonsteroidal anti-inflammatory drug (NSAID) overdose. Open Access Emerg Med. 2011;3:39-48.

Jacobi J, Fraser GL, Coursin DB, Riker R et al. *Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult*. *Crit Care Med* 2002; 30: 119–41

Kara J. Pavone, Juliane Jablonski, Pamela Z. Cacchione, Rosemary C., Peggy Compton, PhD, RN, FAAN. *Evaluating Pain, Opioids, and Delirium in Critically Ill Older Adults.* Clinical Nursing Pages: 455 – 463 (2020)

Katz R, Kelly HW, Hsi A. *Prospective study on the occurrence of withdrawal in critically ill children who receive fentanyl by continuous infusion*. *Crit Care Med* 1994; 22: 763–7

Kress J P, Hall J B. *Cost considerations in sedation, analgesia, and neuromuscular blockade in the intensive care unit.* 2001;22(2):199-210. (2001)

May JJ, Lovell G, Hopkins WG. Effectiveness of 1% diclofenac gel in the treatment of wrist extensor tenosynovitis in long distance kayakers. *J Sci Med Sport*. 2007 Feb;10(1):59-65.

Med 1977;87:299–301.

Mehta S, McIntyre A, Dijkers M et al. *Gabapentinoids are effective in*

decreasing neuropathic pain and other secondary outcomes after spinal cord injury: a meta-analysis. *ArchPhys Med Rehabil* 2014; 95: 2180–6

Moller PL, Juhl GI, Payen-Champenois C, Skoglund LA. *Intravenous acetaminophen (Paracetamol): comparable analgesic efficacy, but better local safety than its prodrug, propacetamol, for postoperative pain after third molar surgery.* Anesth. Analg. 2005;101:90–96. doi: 10.1213/01.ANE.0000155297.47955.D6.

Moulin DE, Hagen N, Feasby TE, Amireh R, Hahn A. *Pain in Guillain-Barré syndrome. Neurology* 1997; 48: 328–31

Muaddi, H.; Hafid, M.E.; Choi, W.J.; Lillie, E.; de Mestral, C.; Nathens, A.; Stukel, T.A.; Karanicolas, P.J. *Clinical Outcomes of Robotic Surgery Compared to Conventional Surgical Approaches (Laparoscopic or Open): A Systematic Overview of Reviews*. Ann. Surg. 2021, 273, 467–473.

Nakhaee S, Hoyte C, Dart RC, et al. *A review on Tramadol toxicity: mechanism of action, clinical presentation, and treatment. Forensic Toxicol* 2021; 39: 293–310.

nuclei. J Comp Neurol 2004;478:62–71.

Oyler DR, Parli SE, Bernard AC, Chang PK, Procter LD, Harned ME. Nonopioid management of acute pain associated with trauma: Focus on pharmacologic options. *J Trauma Acute Care Surg*. 2015 Sep;79(3):475-83.

Paediatr Anaesth 1998;8:324.

Payen J, Bru O, Bosson J et al. Assessing pain in critically ill sedated patients by using a behavioural pain scale. *Crit Care Med* 2001; 29: 2258–63

Payen JF, Chanques G, Mantz J et al. Current practices in sedation and

analgesia for mechanically ventilated critically ill patients: a prospective multicenter patient-based study. *Anesthesiology* 2007; 106: 687–95

Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. *Anesthesiology.* 2000;93:1123–33. doi: 10.1097/00000542-200010000-00038.

Petterson PH, Jakobsson J, Owall A. *Intravenous acetaminophen reduced the use of opioid compared with oral administration after coronary artery bypass grafting.* J. Cardiothorac. Vasc. Anesth. 2005;19:306–309. doi: 10.1053/j.jvca.2005.03.006.

Phillips WJ, Currier BL. Analgesic pharmacology: II. Specific analgesics. J *Am Acad Orthop Surg.* 2004 Jul-Aug;12(4):221-33.

Piletta P, Porchet HC, Dayer P. *Central analgesia effect of acetaminophen but not of aspirin. Clin. Pharmacol*. Ther. 1991;49:350–54. doi: 10.1038/clpt.1991.40. http://www.medsafe.govt.nz/profs/Datasheet/f/FentanylcitrateinjUSP.htm.

Prescott LF. Paracetamol (Acetaminophen): *a Critical Bibliographic Review. Washington DC: Taylor and Francis*; 1996.

Puntillo KA. Pain experiences of intensive care unit patients. *Heart Lung* 1990; 19: 526–33

Rawal N, Berggren L. *Organization of acute pain services: a low-cost model. Pain.* 1994;57:117–23. doi: 10.1016/0304-3959(94)90115-5.

Rieck B, Schwemmlek *Systemic pain therapy, evaluation from surgeon's point of view.* Reg. Cancer Treat. 1990;3:122–25.

Riker RR, Shehabi Y, Bokesch PM et al. *Dexmedetomidine vs Midazolam for sedation of critically ill patients: a randomized trial*. *JAMA* 2009;

301: 489–99

Rod B, Monrigal JP, Lepoittevin L, Granry JC, Cavellat M. *Treatment of postoperative pain in children in the recovery room. Use of Morphine and propacetamol by the intravenous route*. Cah.Anesthesiol. 1989;37:525–30.

Rothenberg RJ, Holcomb JP. Guidelines for Monitoring of NSAIDS: Who Listened? *J Clin Rheumatol.* 2000 Oct;6(5):258-65.

Sabetkasaei M, Rezai Gharai L. *Effect of Spinal and Systemic Clonidine Administration on the Postoperative Analgesia in Morphine-dependent and Naïve Rats. Iranian J.Pharm*. Res. 2006;2:117–121.

Schafer AI. Effects of nonsteroidal anti-inflammatory therapy on platelets. *Am J Med.* 1999 May 31;106(5B):25S-36S.

Schelling G, Stoll C, Haller M et al. Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. *Crit Care Med* 1998; 26: 651–9

Schmittner MD, Vajkoczy SL, Horn P et al. *Effects of fentanyl and S(+)-ketamine on cerebral hemodynamic, gastrointestinal motility, and need of vasopressors in patients with intracranial pathologies*: a pilot study. *J Neurosurg Anesthesiol* 2007; 19: 257–62

Schug SA, Sidebotham DA, McGuinnety M, Thomas J, Fox L. *Acetaminophen as an adjunct to Morphine by patient-controlled analgesia in the management of acute postoperative pain. Anesth. Analg*. 1998;87:368–72. doi: 10.1097/00000539-199808000-00024.

Scott LJ. Intravenous ibuprofen: in adults for pain and fever. Drugs. 2012 May 28;72(8):1099-109.

Sessler CN, Grap MJ, Ramsay MA. Evaluating and monitoring analgesia and sedation in the intensive care unit. *Crit Care* 2008; 12(Suppl.

3): S2

Shekelle PG, Newberry SJ, FitzGerald JD, Motala A, O'Hanlon CE, Tariq A, Okunogbe A, Han D, Shanman R. Management of Gout: A Systematic Review in Support of an American College of Physicians Clinical Practice Guideline. *Ann Intern Med*. 2017 Jan 03;166(1):37-51.

Sinatra RS, Jahr JS, Reynolds LW, Viscusi ER, Groudine SB, Payen-Champenois C. *Efficacy and safety of single and repeated administration of 1 g intravenous acetaminophen injection (Paracetamol) for pain management after major orthopedic surgery.* Anesthesiology. 2005;102:822–31. doi: 10.1097/00000542-200504000-00019.

Sostres C, Gargallo CJ, Arroyo MT, Lanas A. Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs, aspirin and coxibs) on upper gastrointestinal tract. Best Pract Res Clin Gastroenterol. 2010 Apr;24(2):121-32.

Sriuttha P, Sirichanchuen B, Permsuwan U. Hepatotoxicity of Nonsteroidal Anti-Inflammatory Drugs: A Systematic Review of Randomized Controlled Trials. *Int J Hepatol.* 2018;2018:5253623.

Subedi M, Bajaj S, Kumar MS, et al. *An overview of Tramadol and its usage in pain management and future perspective. Biomed Pharmacother* 2019

Szczeklik A. Adverse reactions to aspirin and nonsteroidal anti-inflammatory drugs. Ann Allergy. 1987 Nov;59(5 Pt 2):113-8.

Thomas, 1976;213.

UK, N. C. C. for C. (2012). *Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults*.

van den Bekerom MPJ, Sjer A, Somford MP, Bulstra GH, Struijs PAA,

Kerkhoffs GMMJ. Non-steroidal anti-inflammatory drugs (NSAIDs) for treating acute ankle sprains in adults: benefits outweigh adverse events. *Knee Surg Sports Traumatol Arthrosc.* 2015 Aug;23(8):2390-2399.

Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat New Biol.* 1971 Jun 23;231(25):232-5.

Wang HE, Muntner P, Chertow GM et al. Acute kidney injury and mortality in hospitalized patients. *Am J Nephrol* 2012; 35: 349–55

Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. *Am J Med*. 1999 May 31;106(5B):13S-24S.

Yang Y, Young JB, Schermer CR, Utter GH. *Use of ketorolac is associated with decreased pneumonia following rib fractures*. *Am J Surg* 2014; 207: 566 72

Zacher J, Altman R, Bellamy N, Brühlmann P, Da Silva J, Huskisson E, Taylor RS. Topical diclofenac and its role in pain and inflammation: an evidence-based review. *Curr Med Res Opin*. 2008 Apr;24(4):925-50.

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