GHANA COLLEGE OF PHYSICIANS AND SURGEONS

Faculty of Surgery

POSTOPERATIVE PAIN MANAGEMENT IN EMERGENCY ABDOMINAL SURGERY: BIMODAL VERSUS UNIMODAL ANALGESIA

Submitted to the Faculty of Surgery, in Partial Fulfilment of the Requirements for the Conferment of a Fellow of the Ghana College of Surgeons (FGCS)

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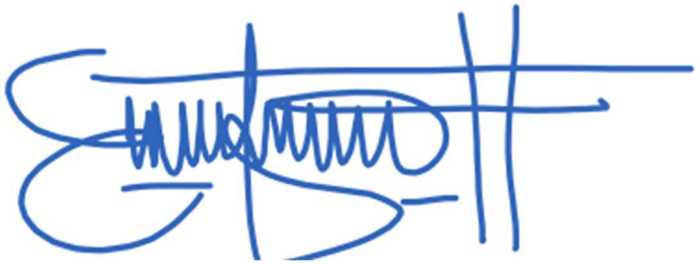
DECLARATION

I, Frank Enoch Gyamfi, hereby declare that the work presented here is the result of my composition except for other people's work which has been appropriately acknowledged in the reference section. I affirm that neither the whole nor part of this dissertation has been presented to any institution. I am solely responsible for the content of this dissertation.



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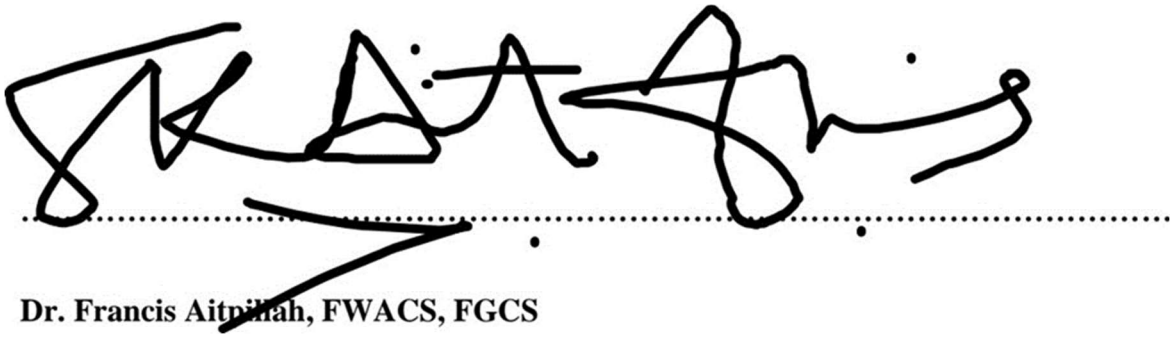

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ABSTRACT

Introduction

Emergency abdominal surgery may be the right intervention for patients who have traumatic abdominal injuries or surgically correctible abdominal disease processes. The pain after surgery can be distressful to patients if not optimally managed. Postoperative pain management in developing countries like Ghana is considered to be suboptimal. In Ghana, there is a paucity of data comparing the efficacy of parenteral opioids as unimodal analgesia with a combination of paracetamol and opioids in postoperative pain management.

Aim

This study compared the efficacy of intramuscular (i.m.) morphine as unimodal analgesic with bimodal administration of i.v paracetamol and i.m. morphine in managing postoperative pain in emergency abdominal surgery.

Methods/Design

This study was conducted at the Surgery Directorate of Komfo Anokye Teaching Hospital, Kumasi, Ghana. It was a single-blinded randomised controlled trial (RCT). Participants were randomised into two arms: those receiving i.m. morphine only and those receiving a combination of i.v. paracetamol and i.m. morphine. Inclusion criteria were patients between 18 and 80 years undergoing emergency abdominal surgery. Elective surgery, contraindications to morphine or paracetamol were exclusion criteria. Pain intensity was measured at intervals of one, three, six, twelve and twenty-four hours after a patient received the first dose of analgesia at the recovery ward, using the Numeric Rating Scale for pain. Data were collected with a structured questionnaire, using an electronic data capturing system and extracted onto STATA 13 for analysis. Chi-Square test and multivariate logistic regression analysis were carried out, putting into consideration odd ratios where statistical significance was derived with $p<0.05$.

Results

A total of 110 participants were recruited and data from 108 were analysed of which 75% were males and 25% were females. Mean pain scores were lower at six hours, twelve hours and twenty-four hours after the administration of the first dose of analgesia with statistical significance (P-value 0.02, 0.002 and 0.001 respectively) for those who received only Morphine as opposed to morphine with paracetamol.

There was no statistically significant difference between the length of stay and whether a participant received morphine or morphine with paracetamol (P-value 0.33). Those who received only morphine had their first bowel movement earlier than those who received a combination of morphine and paracetamol (P-value 0.03). Nausea and/or vomiting was likely to occur if a participant received only morphine as opposed to receiving morphine with paracetamol (P-value 0.02).

Conclusion

Receiving morphine alone or morphine with paracetamol provided adequate pain relief after emergency abdominal surgery even though those who received morphine alone had a lower mean pain score. Whether a patient received morphine alone or morphine with paracetamol did not have any statistical difference in the length of stay. Nausea and vomiting were common in those who received morphine only.

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CHAPTER ONE

INTRODUCTION

1.0 Background Information

Emergency abdominal surgery may be the right intervention for patients who have traumatic abdominal injuries, surgically correctible abdominal disease or surgical complications.[1] Emergency surgical intervention forms an integral element of acute care that necessitates timely evaluation due to the short duration of most of the disease processes.[2] Proper perioperative and anaesthesia care may avert morbidity and mortality that may be associated with emergency surgery.[3] This highlights the point that there is the need to step up the health care system to meet the surgical demands with the attendant requirement for optimum care.[4] Moreover, there is another challenge in the post-operative management of these patients.

It is estimated that 3.5% of the 234 million surgical procedures worldwide annually, occur in Low and Middle Income Countries (LIMCs).[4,5] The pain after surgery can be distressing to the patient if not optimally managed. Managing postoperative pain after emergency abdominal surgery can be critical and plays a significant role in the recovery process. Pain may be an insult to the body and the ripples of its effects may be devastating if not properly and timely managed. The International Association for the Study of Pain (IASP) defines pain as an 'aversive sensory and emotional experience typically caused by or resembling that caused by, actual or potential tissue injury'.[6] For some patients, the thought of postoperative pain alone can be the only demotivating factor to avoid surgery.

During surgery, the trauma caused by incision results in the release of inflammatory mediators.[7] This causes hyperalgesia leading to a range of discomfort to the patient. Apart from the discomfort associated with uncontrolled pain, there are other unwanted consequences such as complications leading to prolonged length of hospital stay.[6] For this study, effective pain control is defined as the appropriate assessment of pain and the provision of physical, psychological, and/or pharmacological support to control pain to an acceptable level.

Postoperative pain in emergency abdominal surgery is severe in the first six (6) hours after the surgical procedure.[8] Adequate pain management after emergency abdominal surgery can enhance recovery through attenuation of responses to the stress of surgery. The stress of surgery may cause a neurohormonal response. This cascade of stress action starts preoperatively due to the disease process even before emergency abdominal surgery. The consequent adverse effects of this neurohormonal response may be fatigue and gastrointestinal dysfunction. Post-surgery fatigue discourages ambulation and promotes the tendency for patients to stay in bed. The prolonged stay in bed may predispose patients to pneumonia, deep vein thrombosis and subsequent pulmonary embolism. Gastrointestinal dysfunction, on the other hand, may cause postoperative ileus and delayed bowel function.[9]

The use of opioids has become the main stay for the management of severe pain especially after surgery. Commonly, patients are given opioids by surgeons after surgery with the intent of controlling postoperative pain. While the use of opioids after surgery is seen to be a trigger of abuse of opioids in several patients, this may be so because of their efficacy in the management of moderate to severe pain and thus remains the cornerstone in alleviating severe pain after surgery.[10] Some patients may attain so much relief in the use of opioids and may want more which could trigger the said abuse.[10] This opioid abuse or dependence may be averted by the minimal use of opioids by combining them with non-opioid analgesics thus reducing the overall dosage of opioids that may be required by the patients in managing their pain. In the elderly, the sedative effects of opioids may be pronounced. As a result, dose modification or its avoidance in this cohort may be warranted. Several of the studies in the literature comparing unimodal and bimodal analgesia focused mostly on the use of opioids versus opioids combined with NSAIDs. Most of these studies were carried out in the advanced countries and reported mostly the superiority of the combined mode against the unimodal group. The main focus of these studies had been on the efficacy in the relief of pain.

Postoperative pain management in developing countries has been described as suboptimal.[6] This has largely been influenced by several factors which include tenuous concerns about

the patient getting addicted to opioids, perennial unavailability of certain analgesics and patients' inability to afford these drugs. In choosing analgesics for a patient, factors such as the age of the patient, surgical procedure, as well as availability and affordability are considered. In Ghana, less than 40% of the population are enrolled on the National Health Insurance Scheme (NHIS), therefore, affordability of some parenteral analgesics may be challenging for some of the non-insured patients.[11] The inability to purchase these medicines may affect they getting regular supply of their prescribed analgesia. This may lead to poor postoperative pain management. This may guide some surgeons in prescribing unimodal analgesia using opioids even though there is a recommendation for multimodal mode.

Strict protocols or clinical guidelines in managing pain after surgery are not available for health institutions in Ghana.[12] Even when present, the lack of adequate knowledge of the healthcare professional on the analgesic may have a profound impact on postoperative pain management.[13,14] From observation, i.v. paracetamol is now commonly used in the management of postoperative pain in some hospitals in Ghana. Whilst this new trend seems to be growing rapidly especially in the teaching hospitals, a greater number of doctors still prescribe opioids such as morphine in the management of postoperative pain. This is mostly used in combination with non-opioids to manage postoperative pain. There is no known indigenous study on the effect of managing postoperative pain using morphine alone or combining it with i.v. paracetamol. The perception of pain can be affected by several factors such as ethnicity and cultural background.[15] Therefore, using protocols that were drawn out of research from other race or cultural background to fit into local institutions may be inappropriate without considering local studies.

1.1 Problem Statement

Acute postoperative pain remains a major surgical treatment problem that leads to numerous undesirable surgical outcomes when not adequately managed. More than 80% of patients experience pain after surgery and this may result in untoward consequences if not properly managed.[16] The poor postoperative pain management may be ascribed to several factors. These include the lack of knowledge on optimal pain management, age-

related issues, cultural beliefs, and subjective patient self-report of pain that often might be exaggerated or underestimated. Furthermore, the fear of addiction or opioid dependence, non-availability of analgesics at the facility, fear of inadequate pain control from unimodal analgesic or overdosing with multimodal analgesia may also contribute to poor postoperative pain management. There have been modern advancements in the objective assessment of postoperative pain without patient direct participation. This makes use of analgesia nociception index, pupillometry, skin conductance and photoplethysmography-derived parameters. Despite these advancements, preventive analgesia is increasingly common based on the theoretical model of precluding central sensitisation.[16] The prescription for opioids to control postoperative pain is becoming routine worldwide, especially with the implementation of multimodal analgesia technique.[17] Notwithstanding the recommendation of the use of non-opioid or nonsteroidal anti-inflammatory drugs (NSAIDs) in postoperative pain management by the Enhanced Recovery After Surgery (ERAS) protocol, many surgeons are reluctant to change the practice of using opioids.[18,19] It has been observed that, with the availability of i.v paracetamol on the market in the country some surgeons prescribe it for postoperative pain management, being combined with other classes of analgesia. While some surgeons combine opioids with paracetamol in managing post operative pain after emergency abdominal surgery, others give opioids alone. In Ghana, there is a paucity of published data on the comparison between the efficacy of opioids as unimodal analgesia or a combination of i.v. paracetamol and opioids to manage postoperative pain. The efficacy of bimodal approach such as the combination of i.m morphine and i.v paracetamol compared with unimodal approach like i.m morphine only in managing postoperative pain has not been explored extensively locally. This research, therefore, aims to compare the efficacy of unimodal i.m. morphine with bimodal administration of i.v. paracetamol and i.m. morphine in managing postoperative pain after emergency abdominal surgery.

1.2 Significance of the Study

The study findings will establish the efficacy of bimodal approach such as opioid plus non-opioid analgesics or unimodal approach such as opioid analgesic only in the management

of postoperative pain. The findings of the study will inform policymakers and stakeholders about the need to develop standard written protocols for post-emergency abdominal surgery pain management. This will serve as a guide in the prescription of analgesics for surgical care in Ghana. The findings of the study will also be a reference point and serve as pointers for further research work in areas of improving the quality of pain management in emergency abdominal surgery.

1.3 Objectives of the Study

1.3.1 Main Objective

To compare the efficacy of unimodal i.m. morphine with bimodal administration of i.v. paracetamol and i.m. morphine in managing postoperative pain after emergency abdominal surgery.

1.3.2 Specific Objectives

i. To assess the response of patients to i.m. morphine in pain management after emergency abdominal surgery.

ii. To assess the response of patients to a combination of i.v. paracetamol and i.m. morphine in managing pain after emergency abdominal surgery.

iii. To determine the association between the administered analgesic and length of hospital stay.

iv. To determine the association between administered analgesic and postoperative complications.

1.4 Hypothesis

1.4.1 Null Hypothesis

There is no difference in the outcome of unimodal i.m. morphine and bimodal administration of i.v. paracetamol and i.m. morphine in managing pain after emergency abdominal surgery**.**

1.4.2 Alternate Hypothesis

There is a difference in the outcome of the response to unimodal i.m. morphine and bimodal administration of i.v. paracetamol and i.m. morphine in managing pain after emergency abdominal surgery.

1.5 Justification of the Study

In spite of the evidence-based practice employed by many surgeons to control postoperative pain, data on the efficacy of the combination of an opioid and a non-opioid analgesic compared with an opioid analgesic for managing postoperative pain in Ghana is not available. Hence, this study will compare the efficacy of unimodal i.m. morphine with bimodal administration of i.v. paracetamol and i.m. morphine in managing postoperative pain after emergency abdominal surgery.

1.6 Operational Definition of Terms

Abdominal surgery: A broad classification of surgical procedures performed in the abdominal region to diagnose or treat a disease condition.

Analgesic: A drug used to control pain.

Emergency: A serious, unexpected, and often dangerous situation requiring immediate action.

Multimodal analgesia: Using two or more analgesics to control pain.

Bimodal analgesia: Using two analgesics to control pain.

Postoperative pain: Unpleasant sensation experienced by patients after surgery.

Unimodal analgesia: Using one analgesic only to control pain.

Efficacy: The ability of a drug to treat a condition for which it is indicated.

CHAPTER TWO

REVIEW OF LITERATURE

2.0 Introduction

This review incorporated the exploration of research works on pain management in emergency abdominal surgery. It involved the review of books, articles, reports, and clinical audits of patients who had emergency abdominal surgery. The search then focused on the interrelated studies comparing a combination of parenteral paracetamol and morphine with morphine alone in managing pain after emergency abdominal surgery.

2.1 Empirical Review

2.1.1 Postoperative Pain

According to the Lancet Commission of Global Surgery report, Global Surgery 2030, surgically treatable conditions account for nearly 30% of the global disease burden.[3] The principal aim of surgical treatment is a better and early recovery for improved quality of life in the absence of complications and sequelae.[16] Over 80% of patients experience pain after surgery, which is mostly undertreated resulting in varying degrees of negative consequences and remains a major global problem.[16,20,21] Persistent postsurgical pain (PPP) occurs in up to 50% of cases due to suboptimal pain management, significantly decreasing the quality of life of patients.[21]

Adequate analgesia in the early postoperative phase in the recovery ward is critical to preventing PPP.[16] About 20-40% of patients who undergo major surgery experience severe postoperative pain.[22] The attempt to achieve optimal postoperative pain control is essential for ERAS. Poor postoperative pain management after abdominal surgery, may lead to chronic pain from the early visceral pain.[23] Chronic pain occurs in up to 56% of patients whose postoperative pain persists due to suboptimal management.[24] Effective postoperative pain management strategy for surgical patients is thus essential to prevent chronic pain after surgery.

In many parts of the world, emergency abdominal surgery constitutes a significant portion of the general surgeon's workload.[25] In Cape Coast, Ghana, it constitutes 81.5% of the emergencies handled by the general surgery team.[25] This indicates the enormous task of the general surgeon in achieving patient satisfaction following appropriate postoperative pain management. Pain relief has been recognised by the World Health Organisation (WHO) and the International Association for the Study of Pain (IASP) as a human right.[26] Adequate pain relief has substantial physiological benefits to the patient after surgery apart from abating the unpleasant discomfort that pain brings.[27] Further, complications after surgery are minimal with proper perioperative pain management. When postoperative pain is unbearable, the quality of life of the patient can be greatly affected. The degree of postoperative pain has not been much influenced by the education given to patients' family alongside educating the patient on what to expect after surgery.[27]

There is always patient gratification following adequate postoperative pain management.[27] After a major surgery, the effect of pain on activities such as ambulation is severe in the first 48-72 hours.[28] This is mostly because activities during the first 3 days after surgery increase the intensity of pain as opposed to pain at rest which mostly may be moderate.[28] There is therefore a reduction in functional capability during this period especially if pain management is not optimal.[28] Whilst postoperative pain at rest may abate after a week, pain on activity may be severe and can linger on for days to even weeks. The reduction in the functional capability may be limited and is influenced by the pain that lingers on for weeks.[28,29] Proper pain management improves patient recovery after surgery, minimises complications and shortens the length of hospital stay.[27]

In some advanced countries, patient-controlled analgesia (PCA) has been introduced in hospitals but this may not be available in many LMICs. When attending nurses do not administer prescribed medications to patients at the right dose or frequency, it may contribute to the ineffective management of postoperative pain.[30] This has become a significant barrier to adequate pain relief. Pain may not be recognised as a subjective feeling by some nurses and may approach the management of same with some form of prejucdice.[30] As a result, they may rely on their expectation of how a patient may feel

instead of approaching pain management based on the patient's degree of expression. However, since the nurse relatively gets more contact with the patient during hospitalisation, adequate assessment of the patient's degree of pain is essential in adequate management.[30]

Similarly, some doctors are often hesitant to prescribe strong opioids to patients for the fear of addiction, although this is unlikely to occur when given for periods such as up to 48 hours.[30,31] The knowledge of the doctor on this is essential on whether patients will receive adequate doses of required opioids not affected by the fear of addiction.

2.1.2 Pathophysiology of postoperative pain

There is a distinction between the pathophysiology of surgery-induced pain and other forms of clinical pain.[32] This distinction reflects peripheral and central sensitisation contributing to pain at rest and on activity.[33] Peripheral afferent fibres to pain are known as nociceptors. The identification of nociceptors to mechanical stimulation sensitisation has been difficult leading to theories by some scientists that they may not have a role to play in postoperative pain.[32] However, it has been established that inputs from nociceptors can heighten responses by pain transmission neurons in the central nervous system. This is referred to as central sensitisation.

Nociceptors abound in humans. They are found in most tissues in the human body but are principally prevalent in superficial layers of the skin, arterial walls, and periosteum of bones. Various nociceptors respond to various stimuli. Mechano, thermos and polymodal nociceptors respond to mechanical, heat or cold and a mixture of these with chemical stimuli respectively. Incision of tissue during surgery causes activation and subsequent sensitisation of nociceptors. Multiple signaling pathways promote enhanced nociceptive sensitivity distal to the site of nerve injury, a process known as peripheral sensitisation.[16] Consequently, there is a pronounced response to stimuli at the site, known as hyperalgesia and allodynia due to peripheral sensitisation.[16,34] This pronouncement to injury is to both mechanical and thermal stimuli. Some electrophysiological studies have however not demonstrated changes in mechanical stimuli threshold response in mechanosensitive

receptors experiments. Furthermore, some studies have suggested the existence of a group of receptors that may contribute to hyperalgesia in the setting of inflammation. These fibres, known as mechano-insensitive afferents (MIA), can respond to mechano-stimuli but their actual impact on hyperalgesia due to an incision is unclear.[34]

Additionally, non-neuronal cells play a major part in pain signal processing by the nervous system. Of significance to this are keratinocytes, fibroblasts as well as immune cells.[35] Their contribution to signal processing is noted throughout the perioperative period. There is substantial evidence from several studies that pro-inflammatory and anti-inflammatory cytokines and neurotrophins such as brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), neurotrophin (NT)-3 play vital roles in processing pain.[33,35] During the perioperative period, inflammatory mediators like interleukins and prostaglandins significantly increase the sensitisation of nociceptors.[35] Nociceptive neurons centrally respond to noxious input at surgery. This increases the intensity of postoperative pain.[28] Central sensitisation for acute pain can be affected in magnitude by the site as well as the length of the incision.[33] Conversely, Nicholls-Dampsey and Abenhaim (2019) found that the length of incision did not have any impact on the level of postoperative pain in the first 48 hours after surgery.[36]

Many surface receptors on nociceptors, including those for γ-aminobutyric acid (GABA), opioids, capsaicin, bradykinin, and mechanosensitive ion channels, regulate neuronal reactivity to stimulus. Stimuli such as touch and pressure are detected by these mechanosensitive ion channels.[31] An action potential is generated resulting from an influx on Na^{+}/Ca^{2+} when the ion channels are activated. The conduction of pain is by rapidly conducting Aδ fibre axons and slowly conducting C fibre axons. These axons connect to ascending routes after entering the spinal cord's dorsal and ventral horns. The afferent impulse travels through the spinal cord via synapses and ascending route projections to the thalamus, where it is routed to the reticular formation and cortex.[31]

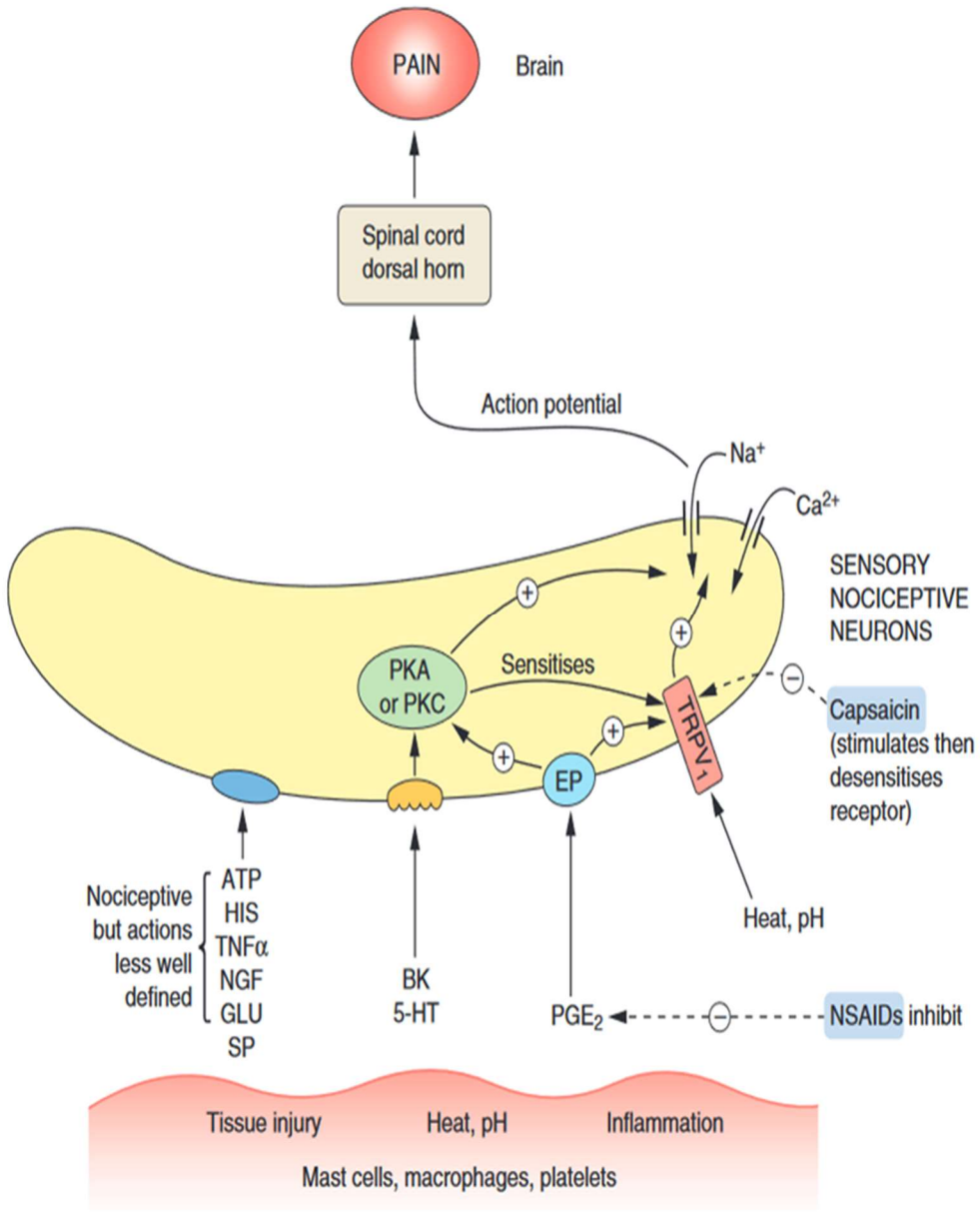

Figure 2.1 Mediation and pain modulation. Source: Waller DG, Sampson AP. Opioid analgesics and the management of pain. In: Medical Pharmacology and Therapeutics. Elsevier; 2018.

A prolonged painful stimulation permits the dorsal horn to act on the central sensitisation sites. This triggers repetitive nociception, which in addition to chemical changes, stimulate the brainstem and causes a reduced descending inhibitory modulation.[37]

Postoperative pain hypersensitivity occurs due to both peripheral and central sensitisation. The sensitisation lowers the pain threshold in the peripheral nociceptors and increasing spinal neuron excitability that eventually result in PPP if acute postoperative pain is not adequately controlled in a timely manner.[38]

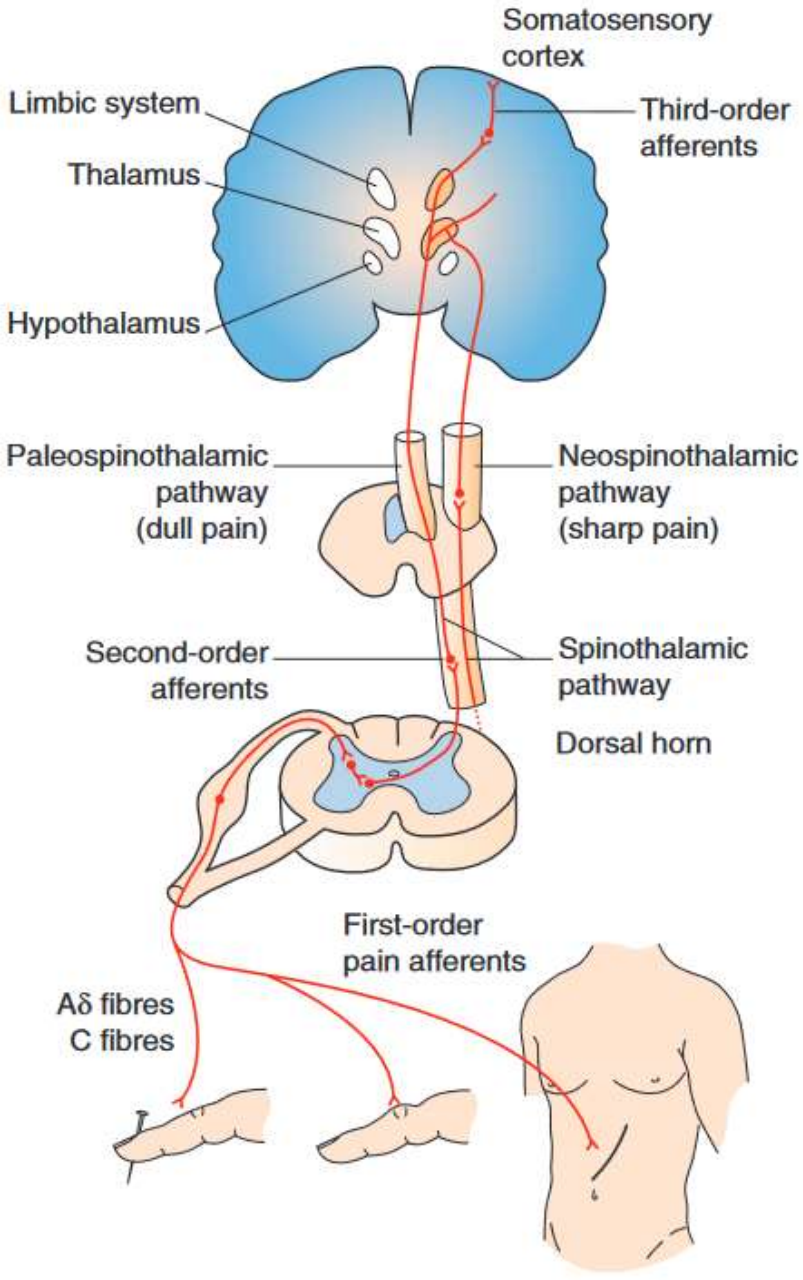

Figure 2.2 Pathways of pain perception. Source: Waller DG, Sampson AP. Opioid analgesics and the management of pain. In: Medical Pharmacology and Therapeutics. Elsevier; 2018.

2.1.3 Effects of culture and race on postoperative pain

The mechanism of nociception and reaction affecting people are influenced by various biological, psychological and cultural factors. In the last decade, the biopsychosocial model has been the core of the formation of multidisciplinary pain management teams in treating pain, especially chronic pain.[39] The components of this model have been noted to influence the degree to which an individual perceives pain and not just the stimulation of the nociceptors. According to the biopsychosocial model, pain and disability are caused by a complex and dynamic interaction of physiological, psychological, and social elements that continue to promote and even exacerbate one another, leading to chronic and complicated pain syndromes.[39] Consequently, with even the same degree of nociceptive stimuli, the extent of pain perceived and expressed is varied among people. The expression of pain may differ from individuals of different races and ethnicity.[40]

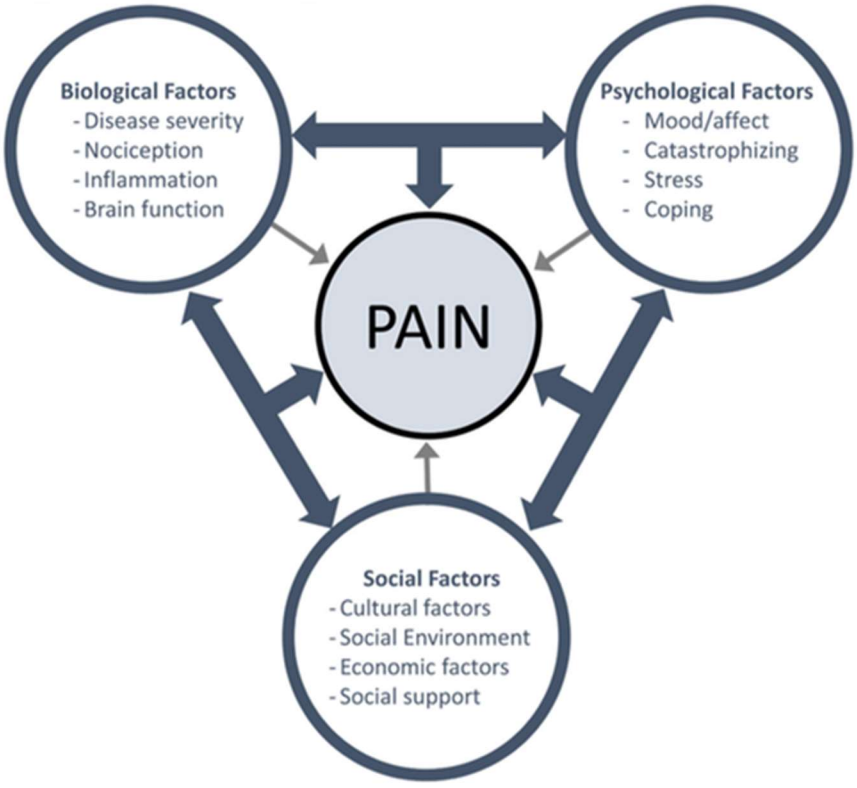

Figure 2.3 Biospychosocial pain model. Source: Fillingim, RB. Individual differences in pain. PAIN. 2017;158: S11–S18

Cultural and environmental influences impact significantly on the way a person expresses pain. The experiences that people get from the complex interactions with their environment passed on over generations to their community affect how they perceive these and their impact on their emotional expressions. The way a group of people live, their beliefs and experiences can have a profound effect on the expression of pain.[36,40,41] The conceptualisation of pain can therefore vary among various tribes and ethnicities. It is therefore essential that healthcare providers can recognise this and implement it in the management of the postoperative patient. The intricacy of the association between culture, ethnicity, experience and the perception of pain, allows different individuals to express the quality and tolerance of pain in diverse situations.

The biopsychosocial model of pain is so complex with mosaic interactions such that even pain expression can be so varied among individuals from the same ethnicity.

In the management of postoperative pain, a greater concern should be attached to the cultural and ethnic background of the patient as a significant aspect of the pain experience.[40] This part of cultural influence is sometimes overlooked, which leads to misunderstandings about how a person may respond to pain. This can be a barrier to properly assessing a person's level of discomfort and providing them with the necessary intervention. In the management of pain how an individual is treated in response to the pain is very crucial and this can be appropriate when the person is understood. This form of understanding should be from a socio-cultural perspective as these may vary from place to place and from person to person.

A study conducted in the United Kingdom reported that individuals of African-Caribbean and South Asian origin reported extensive pain more commonly than the general population, the South Asians having the least probability to develop personal strategies to deal with their pain but instead rely on other family members.[40] A wide-scale population study in the United States consolidated findings from earlier works that found a strong association between the prevalence of pain and ethnicity. The study further went on to indicate the prevalence and burden of pain variability among various ethnic groups with age as a factor.[42] Similarly, people of African-American origin tend to express more pain

than whites. The factors underlying ethnic group disparities in pain experience are inherently heterogeneous and include socioeconomic status and access to shelter, food and appropriate health care. The severity of pain usually is higher in ethnic groups who have some chronic pain and may influence clinical pain expressed by individuals from this group.[43]

In Ghana pain tolerance variability among the various ethnic groups has been noted to affect the way people may express pain.[41] The cultural influence on pain threshold and expression is believed to significantly affect how an individual expresses pain. This may also affect how the person's pain is responded to by healthcare providers. Among the Akans of Ghana, a man is not expected to openly express pain, and people of Mole-Dagbani descent are thought to be hardy and able to tolerate pain better.[41]

Adaptation to a community's beliefs and customs, even if the individual is not originally from that ethnicity, can influence the perception of pain. A person from a different culture living in another community or culture may express pain similar to that of the indigenes.[40,44] This adaptation occurs when that individual has lived in the new community for several years and has become well accustomed to their practices. Hence, a person of Mole-Dagbani descent living in the Akan community after a while may express pain akin to the people in the community.

2.1.4 Effect of Ageing on Postoperative Analgesia

The elderly population is expanding rapidly and constitutes a larger proportion of those who may require surgical intervention.[45] A lot of these surgical operations are performed as a result of malignancies or complications of metabolic illnesses that may be related to aging. A thorough grasp of the effects of aging and how it affects pain management may influence postoperative pain management in this group. Inadequate postoperative pain management may affect the already fragile physiological state and worsen the outcome.

Chronological age should not be the only means for assessing pain. Physiological age and the cognitive state of the patient should be considered as well.[45] Whilst the physiological age can affect the functional state of vital organs like the liver and kidneys that may be

involved in the excretion of metabolites of administered analgesic, significant cognitive function directly influences the perception of pain.

The challenges of achieving effective postoperative pain control is established by several studies but a few of them relate to postoperative management of the elderly.[45] Postoperative pain management in the elderly is generally complicated by several factors that are age-related or disease-related causing changes in their physiology as well as disease-drug and drug-drug interactions.[45] The elderly may be on medications for age-related health conditions. These may also affect the choice of analgesic because of drug-drug interaction. Therefore, in the assessment of pain in older patients it is essential to consider the pathologic profile and prescribed medications.[45]

Postoperative pain management in the elderly may affect cardiovascular and respiratory functions and lead to complications such as tachycardia, hyperventilation, decreased alveolar ventilation and transition from acute to chronic pain. This may eventually lead to agitations, sleeplessness, and poor wound healing.[45,46,47] Postoperative pain treatment in the elderly can be unimodal or multimodal in the acute phase. Due to variations in pharmacokinetics and pharmacodynamics associated with old age, medications may need to be started with low dose and gradually increased.[45] Cognitive function, cardiovascular, respiratory, hepatic, endocrine and renal systems may alter the pharmacokinetics and pharmacodynamics of administered drugs. This is likely to have a significant effect on the benefits-to-risks ratios.[46]

In the elderly, special consideration is required for planning perioperative opioid therapy to overcome possible tolerance.[45, 46] The pharmacology of perioperative pain management in older patients requires low doses but this does not justify unjustifiable undertreatment of pain.[49] A close monitoring of the potential overmedication and adverse effects should be in place to decrease the risk for prolonged opioid therapy following discharge.[46,48] However, elderly patients may receive inadequate pain medication because of the undue fear of what this medication may have on them.[50] This inadequate analgesic administration that stems from the fear of their effects on the elderly eventually leads to poor postoperative pain management in the older population.

There may be underreporting of postoperative pain in the elderly by some health professionals. There is the erroneous impression that all elderly patients have diminished pain perception or have cognitive dysfunction.[46] This leads to an improper assessment of the pain, the patient therefore not receiving adequate analgesia leading to ineffective postoperative pain management. Misconceptions and gaps in training among some healthcare personnel about pain in the elderly can hinder their ability to recognise and assess the intensity of pain in the elderly.[46] Making educated judgments about postoperative pain management requires a full understanding of the specific challenges that physiological and pathological changes linked with aging bring for pain management.

There is ample evidence to imply that sensory perception declines with age due to a reduction in the number of specialized peripheral receptors as well as degradation of supporting tissues for taste, touch, hearing, vision, and smell. This waning of sensory acuity has been documented alongside the general changes in the anatomical structure associated with aging.[51] As a person ages, the number and quality of sensory neurons also decline. There is notable demyelination of peripheral sensory neurons that are associated with aging. Age-related reduction in receptors such as opiate receptors and impairment of sensory transmission pathways have been associated with changes in pain sensitivity.[51] However, pain sensitivity is increased with aging as a result of repetitive peripheral nociceptors sensitisation that is associated with chronic inflammation.

2.2 Assessment of postoperative pain

Pain is a subjective feeling and it is the sufferer that can best express the extent of the obnoxious feeling from the stimuli.[52] A proper assessment of pain is key if the pain is to be managed well. In the effective management of postoperative pain, correct and timely assessment is therefore necessary. This, however, poses a challenge when the patient is in the post-anaesthesia care unit (PACU).[16] Moderate to severe pain have been reported in up to 41% of patients in the PACU, which if not well assessed and properly managed can contribute to persistent post-surgical pain.[16] Accurate and timely assessment of postoperative pain is essential for intervention. Generally, a detailed description of the

character needs to be assessed all the time but practically, the intensity and time to analgesic are what are usually documented for managing immediate postoperative pain at the PACU.[16] In this respect, it is practically important to assess the intensity of pain, noting the time of administering the first analgesic, the dose that is administered, its effects and the strategies of modulating analgesics ladder according to the patient's response and satisfaction. In assessing pain, the mental status of the patient ought to be put into consideration. It is also essential to identify any existing anxiety and depression for the fact that such psychological factors have a profound influence on pain perception.[18] Some studies have recognised the inefficiencies in the assessment of postoperative pain.[13,53] This may be because pain assessment may not be done using the appropriate tool. Studies have found that 12% of healthcare personnel have never used any pain assessment tool whilst 57% of nurses have a deficiency in knowledge on the use of pain assessment tools.[13] The pain assessment scales validated in Ghana have not been formalised and widely introduced in clinical practice in the country.[52] Pain scales used in Ghana are mostly ones that are adopted for use after their development in some jurisdictions.[52]

Postoperative pain can have a deleterious effect on the outcome of the surgery if not properly assessed and managed. Poorly managed postoperative pain can trigger the release of stress hormones, which may affect the physiological stability of the patient. The subjectivity of pain makes it such that the patient's perception is of utmost importance. It is by this that the intensity can be accurately described.[52] To assess the intensity of postoperative pain fairly, a standardised pain assessment tool is recommended. Pain assessment tools are in two forms: multidimensional and unidimensional tools. Multidimensional tools are complex and seldom used in clinical practice as opposed to unidimensional tools that are commonly used in clinical practice. Patients can sometimes underestimate or overestimate the pain that they have.[54] As a result, it is essential for the person administering the pain assessment tool to make sure that the patient appreciates the scale being used so that the incidence of overestimation and underestimation of pain intensity will be minimal.

The Visual Analogue Scale (VAS) is the commonest scale used by researchers in pain assessment research. It consists of points that measure the pain felt by the subject in a

continuum from no pain to extreme pain. This scale may be difficult for young children and elderly patients with cognitive impairment to conceptualise.[55]

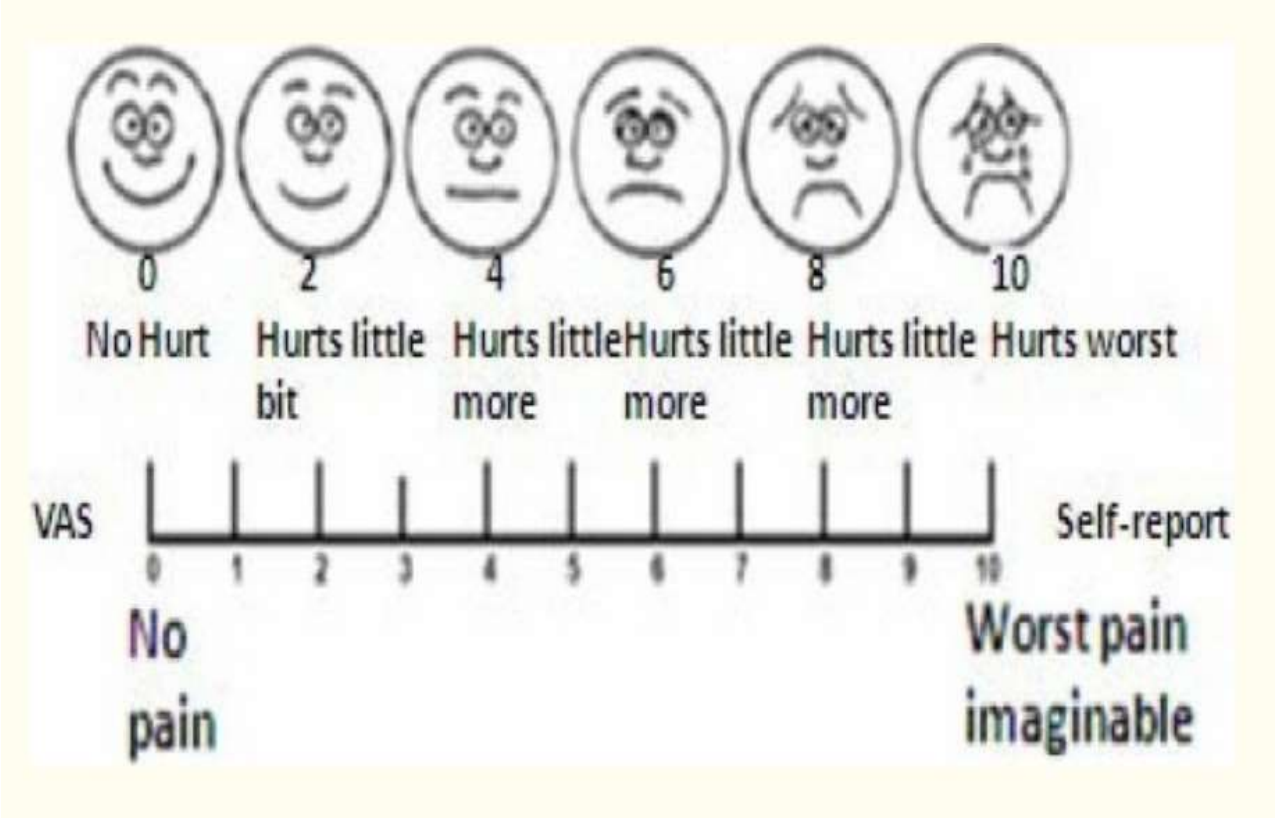

Figure 2.4 Visual Analogue Scale. Source: Gupta A, Kaur K, Sharma S, Goyal S, Arora S, Murthy RSR. Clinical aspects of acute post-operative pain management & its assessment. J Adv Pharm Technol Res. 2010;1(2):97–108

The Numerical Rating Scale (NRS) is an 11-point tool with which patients are asked to indicate which number on the scale equates to their pain.

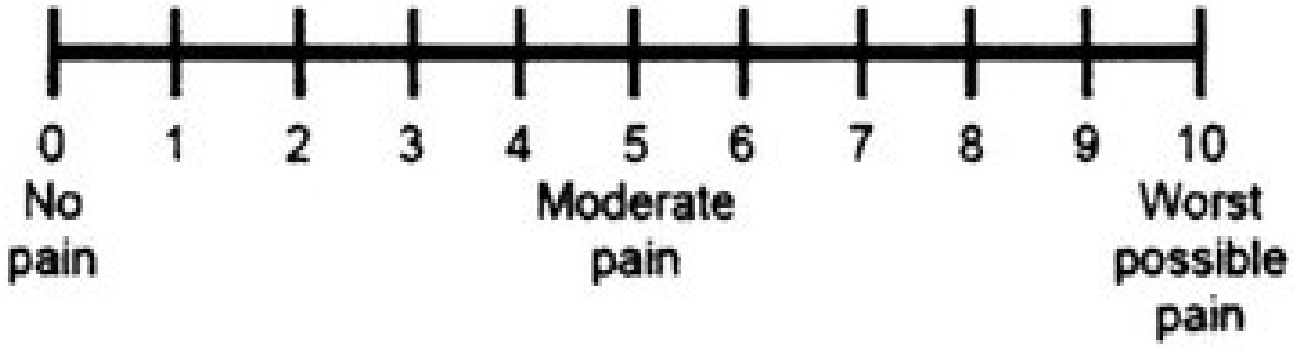

Figure 2.5 Numeric Rating Scale. Source: Aziato L, Dedey F, Marfo K, Asamani JA, Clegg-Lamptey JNA. Validation of three pain scales among adult postoperative patients in Ghana. BMC Nurs. 2015 Aug 11;14.

The Brief Pain Inventory is a multidimensional pain scale that begins pain assessment with the most severe pain at the point of assessment. It then considers the percentage of pain alleviation subsequently. This pain scale is cumbersome and may be inappropriate for use in persons with impaired cognitive function.[55] The McGill Pain Questionnaire is the commonest multimodal scale that looks at the intensity and character of pain by assessing both sensory and affective dimensions.[55] Like all other multimodal pain scales this is complex and difficult to use in the clinical setting.

The Colour Circle Pain Scale (CCPS) consists of six circles with increasing size and filled up with different colours that tend to reflect how a person feels and describes the intensity of pain. To ensure an accurate assessment of postoperative pain, culturally appropriate assessment tools should be administered. Most pain assessment tools used globally are validated among various groups.[52,56] In clinical research the use of appropriately validated

pain scales is important. Where two or more scales are used, then the inter-rater reliability of these scales has to be considered.

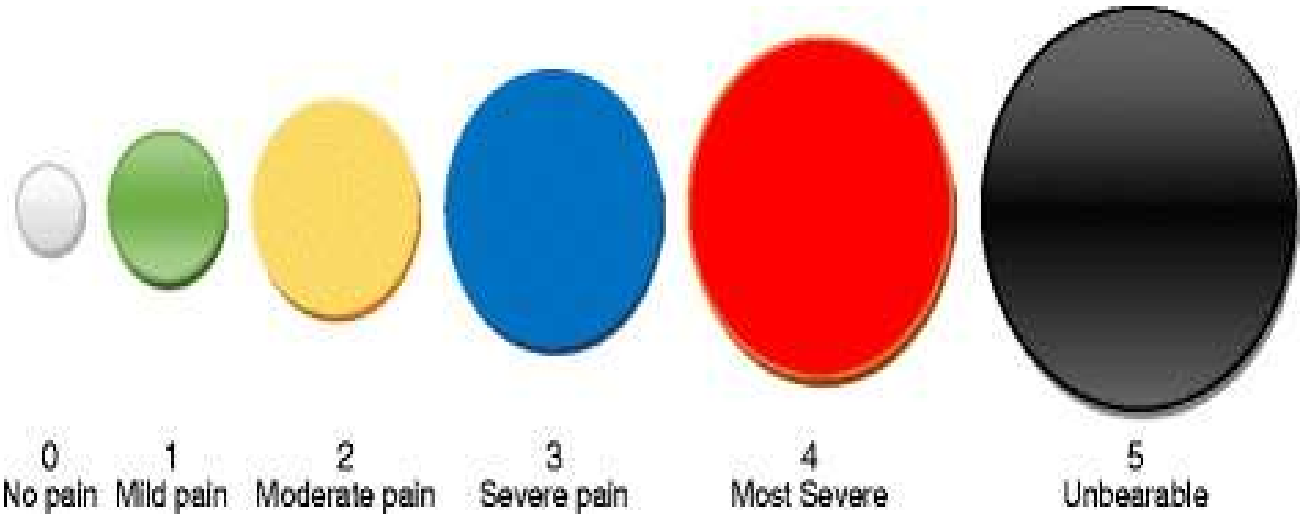

Figure 2.4 Colour-Circle Pain Scale. Source: from Aziato L, Dedey F, Marfo K, Asamani JA, Clegg-Lamptey JNA. Validation of three pain scales among adult postoperative patients in Ghana. BMC Nurs. 2015 Aug 11;14.

The NRS and the CCPS have been validated for use among adults in Ghana.[52] These pain scales have high inter-rater reliability and are sensitive to pain changes before and after administering analgesics.[52]

The observer-based pain assessment tool such as Behavioural Pain Scale (BPS) is one objective option for effective postoperative pain treatment.[16] In recent times, more advanced methods of objective assessment are being employed independently of patients' direct participation such as photoplethysmography (PPG)-derived parameters, analgesia nociception index (ANI) and skin conductance (SC) and pupillometry.[16] These methods

fundamentally are based on the assessment of autonomic response to noxious stimulation to indicate nociception balance.[57]

PPG is a sensitive indicator to reflect blood volume changes and correlated with vascular resistance to detect hemodynamic variables that indicate the autonomic nervous system response to pain promptly.[16] This parameter uses surgical pleth index (SPI), which objectively assesses nociception-anti-nociception balance, that SPI value has been predictive postoperative pain only if obtained prior to arousal from general anaesthesia.[42,58,59] An SPI value of 30 could be a useful predictor of moderate-to-severe postoperative pain.[60]

The variability of the heart rate is used to calculate the ANI. The value is positively correlated with parasympathetic predominance within the autonomic cardiac control for assessing immediate postoperative pain.[175] Measurement of ANI has proven to be effective and indicates a significant association with intensity of pain on arrival to the post-anaesthesia care unit immediately before extubation.[174] The flaw of the ANI is its reported inability to undoubtedly differentiate between minor and severe pain.[176]

The number of fluctuations within the mean of SC per second (NFSC), which reflects the bursts of skin sympathetic nerve gives sensitivity and specificity to moderate-to-severe postoperative pain.[16] However, the NFSC has failed to delineate postoperative pain from other stressors postoperatively. The inconsistencies require further studies for standardizing its application for postoperative pain assessment and treatment.[61]

Autonomic pain responses can be used to assess the sensitivity and specificity of acute pain. These responses include heart rate, blood pressure, pupillary diameter and pupillary light reflex amplitude. Pupillometry is superior in the assessment over the other autonomic responses to pain.[62]

However, the residual effects of intraoperative opioids do not permit a significant association with acute postoperative pain assessment with the application of pupillometry, unless all confounding factors are well controlled.[63]

2.3 Non-pharmacological Management of Postoperative Pain

After a proper assessment of pain, the ideal pain management should be a multidisciplinary approach that will individualise the postoperative pain management plan for the patient. This postoperative treatment plan should be realistic and involve both pharmacological and non-pharmacological modalities in the setting of the patient's condition and response to treatment.[46] Despite the availability of a large range of non-pharmacological methods of relieving postoperative pain, there is a paucity of its clinical application.[64]

The methods in the non-pharmacological management of postoperative pain may be either by distraction, physical activities, psycho-spiritual approach or applications to the skin. Distraction methods such as watching television or listening to music are the commonly used methods on the various wards and can reduce pain intensity on a ten (10) point scale by 0.5 in postoperative pain.[64] Despite controversies on the actual effect on reducing pain, topical cold and heat pack applications are relatively uncommon on the wards. There is documentation of the reduction of pain in patients who have hernia repair done after application of ice to the site but this benefit did not extend to patients who had undergone exploratory laparotomy.[64] Transcutaneous electrical stimulation (TENS) can reduce pain intensity up to 50%.[64] Though physical activities such as walking and deep breathing exercises have been employed in an attempt to reduce postoperative pain, there is no existing literature on the benefit of these on the management of postoperative pain.[64] With the variability in its effect on postoperative pain management, non-pharmacological pain management should not replace the standard analgesic management.[64]

2.4 Pharmacological Management of Postoperative Pain

Conventionally, a multimodal approach to postoperative pain management is recommended and has been a fundamental component of effective postoperative pain rehabilitation pathways such as enhanced early recovery after surgery (ERAS).[16] However, different surgeries produce varying degrees of severity of postoperative pain and the need for analgesia. A particular approach has diverse effects on patients undergoing different surgeries and for that matter, procedure-specific and individual postoperative pain management approaches are of the essence.[65] Preventive analgesia is considerably

beneficial to curtail the incidence and severity of both acute postoperative pain and PPP by targeting central sensitisation.[38] However, some studies have demonstrated no benefit of the use of preemptive analgesia for certain groups of drugs such as non-steroidal anti-inflammatory drugs (NSAIDs).[66]

There are several pharmacological approaches to the management of pain. These include the use of well-known traditional approaches to administering analgesics for postoperative pain management. In modern times, new modalities such as transdermal patches, intranasal instillation and oral sprays have been developed. Whilst some of these modalities may be quite easy to use by the patient and may not require a skilled person for administration, they may also not be appropriate for use in the postoperative setting. Whichever modality may be selected must therefore be appropriate for the patients assessed or expected intensity of pain and availability of the chosen root of administration. Transdermal opioid patch, for instance, may be used in pain management but because it takes 12-32 hours for therapeutic concentration it may not be appropriate for immediate postoperative pain management.[66] The use of transmucosal formulations can increase substantially bioavailability as the drug eludes first-pass metabolism. Such drug formulations, such as fentanyl lozenges, can be used for patients on long-term medication such as in osteoarthritis and patients with malignancies that develop break-through pain.[66] This may also be used in rescue analgesia.

NSAIDs have been well accepted and used as analgesics and anti-inflammatory drugs. This property of NSAIDs and their potent effect in pain management has led to the recommendation of their use in multimodal analgesia. There is a 30-50% opioid-sparing effect when NSAIDs are used in the multi-modal approach with morphine in PCA.[66] However, the associated gastrointestinal complications with the use of NSAIDs make it less desirable for use after certain postoperative procedures.[66]

The concerns raised due to these gastrointestinal complications motivated the development of the coxibs, that selectively inhibit COX-2, for postoperative use in non-cardiac patients. The coxibs, despite their relatively better effect on the gastrointestinal system, have other serious complications. Notable among these is the effect on the cardiovascular system which can lead to myocardial infarction.[117] Prostaglandins are necessary to maintain renal

blood. The inhibition of prostaglandins synthesis by NSAIDs may compromise renal blood flow and may lead to acute renal failure in susceptible patients.[64]

2.4.1 Opioid Analgesics

The use of opioids across the globe has doubled over the last two decades such that its misuse is reaching epidemic proportions. In 2013, there was twice the number of opioids prescribed as compared to 2001 across the world with most of these prescriptions in the advanced countries.[67] This can partly be attributed to the abuse of opioids for managing chronic pain and frequent prescription for managing postoperative pain. Patients sometimes are given opioids for managing their postoperative pain though it may not be warranted.[67] Inappropriate and unnecessary prescription of opioids for managing postoperative pain can have effects on the patient. This may range from dealing with the common side effects like nausea and vomiting to serious adverse effects like respiratory depression. There may also be opioid tolerance and dependence especially for those that use it for managing chronic pain.

Because of the associated side effects, there is the need for close monitoring of patients on opioids. In the postoperative setting, opioids are usually given through the parenteral route within the first 48 hours after surgery. Patients without any cognitive impairment may receive opioids via PCA.[46] This has been noted to provide adequate pain relief at the will of the patient. Morphine, pethidine, tramadol, fentanyl and codeine are the commonly used postoperative opioid medications.

Opioid analgesics continue to be the substratum of analgesic options to control postoperative pain, especially in the multimodal approach. Notwithstanding the pain relief opioids provide to patients, the analgesic efficacy is much repressed by the development of tolerance and opioid-related side effects.[68] The goal of opioid treatment is to achieve the greatest pain relief while minimizing potentially harmful side effects. The majority of opioid-related side effects are dose-related.[68] In managing postoperative analgesic failure, it has been established that if patients do not respond to multiple doses of morphine, no other opioid would be effective for postoperative pain treatment. It thus becomes imperative to consider the early administration of non-opioid analgesics for such patients.[69]

The administration of opioids is largely meant to achieve maximum analgesia with no intolerable adverse effects. In any case, much more attention needs to be given to postoperative opioid-related adverse effects such as dependence, nausea and vomiting, respiratory depression and excessive sedation. It is therefore vital for proper monitoring and timely intervention for opioid-related adverse effects.[16] It has been found that supervised continuous positive airway pressure management in gastric surgery improves sleep-disordered breathing in postoperative patients and reduces respiratory-depressant effects of opioids without undue hemodynamic changes.[70] Extended-release epidural morphine (EREM) is single-dose morphine that provides effective analgesia for 48 hours post-surgery.[71] This has led to the usage of EREM as a conventional pain management approach and plays a major role in facilitating ERAS.[72]

Opioid analgesia works best for nociceptive pain, but it can also relieve neuropathic pain.[31] Opioids, in addition to their antinociceptive activity, alter the perception of pain, making it less unpleasant. Some opioids have a milder supraspinal effect, probably targeting the limbic system. Opioid analgesics lack anti-inflammatory effects. Morphine can cause peripheral vasodilation and hypotension by causing the release of inflammatory mediators such as histamine.[31]

Mechanism of action

Three distinct opioid receptors have been identified that are involved in the mechanism of pain mediation by this class of drugs. The receptors are μ (mu) receptor (MOP receptor), κ (kappa) receptor and δ (delta) receptor.[31] In the body, endogenous opioid peptides are produced by the brain. These act as neurotransmitters and are produced by breaking down larger molecules. In the central nervous system, presynaptic and postsynaptic membranes of neurons contain opioid receptors. Upon their activation, the presynaptic receptors cause neurotransmitter release inhibition whilst that of the postsynaptic cause inhibition of neuronal depolarisation.[31]

The specific distribution of the various opioid receptors in the limbic system and spinal cord is responsible for the different physiological effects. The activity of opioid drugs is not the same based on their action at the receptor level. This selective activity may be because they produce agonist and a mixture of agonist-antagonistic activity. They are thus

full agonist, mixed agonist-antagonistic, or mixed partial agonist-antagonist. Morphine, fentanyl, codeine, diamorphine and pethidine are full agonists that principally act on μ receptors.[31,45] On the κ receptor, pentazocine, has an agonist effect whilst it exhibits weak antagonism on the μ-receptor. Buprenorphine is a mixed partial agonist-antagonist opioid with by way of its partial agonist effect at the μ-receptor. It also has some antagonist effects on κ-receptors. It is worth mentioning that there are some other cellular or non-opioid receptor activity that opioids may exhibit. These may include muscarinic agonist activity as well as inhibition of neuronal noradrenaline uptake as may be seen with meptazinor and tramadol respectively.[31]

Analgesic effect of opioids

The most desirable clinical need of the effect of opioids on the CNS is its analgesic effect. There is a central perception of pain by opioids in addition to its antinociceptive effect leading to the relief of pain. The most potent opioids that produce optimal analgesic effects are the full agonist opioids such as morphine.[31] This potency of opioids in managing pain has made them desirable analgesia in managing postoperative pain. In the event when the affinity for the μ-receptor is low, then the analgesic effect of the drug is limited as can be seen in codeine.[31,45]

Euphoria from opioids

The activation of the μ-receptor may be associated with the elevated feeling of well-being. This euphoric state is common especially with opioids that have a strong affinity for the μ-receptor. Morphine is therefore noted to be associated with the euphoric state in patients for whom the drug is administered in even in the management of postoperative pain.[31]

Endocrine effect

Opioids such as morphine may have a significant effect on the endocrine system. When a person is given opioids to manage pain, the drug can have a direct effect on the hypothalamic-pituitary-adrenal axis.[31] Significant and progressive reduction of the levels of plasma cortisol may occur as a result of the inhibition of the HPT axis by the administration of opioids.[31] In males, a documented effect is a deficiency in testosterone level. This is due to the increase in the release of serum prolactin and a decrease in

leutinising hormone. Females on the other hand get a decrease in the production of oestrogens which may lead to osteoporosis and susceptibility to fractures.

Effects on the respiratory system

Some health care personnel fear this effect of morphine especially on the elderly and might have resulted in the inappropriate administration of the drug to patients. Studies on patients at the PACU have shown that respiratory depression associated with the administration of morphine improves even in the elderly if there is direct supervision of continuous positive airway pressure.[16] This seemingly untoward effect of the administration of morphine on the respiratory system can be capitalised on in the management of certain conditions like acute respiratory distress from pulmonary oedema.[33] Apart from this respiratory effect that opioids may have some opioids also may have some antitussive effects. Opioids like codeine even though may have a weak analgesic effect because of the low affinity to the μ-receptor may also have a cough suppressive effect.[33]

Effects on the GI system

The opioid receptors that opioid analgesics bind for pain relief are a special type of proteins which are G protein-coupled receptors. When these receptors are activated, there is hyperpolarisation. This hyperpolarisation then lowers neuronal excitability.[73] The effects are observed on inhibitory, excitatory, and secretomotor neurons in the entire GI tract. Consequently, opioid analgesics mediate a wide range of effects on organs across the GI system resulting in notable GI effects when patients are put on opioid medications for postoperative pain management.[33,73] Some of these GI effects such as constipation are even pronounced on the prolonged use of opioids in those with chronic pain.

Studies have demonstrated that the administration of opioids such as codeine, morphine and tramadol results in a significant delay in gastric emptying. Inhibitory neuron suppression leads to an increase in tone at the gastric antrum which is said to be responsible for the delay. There is also a notable increase in the transit time in the small intestines.[73] The result of the activation of the opioid receptors on the small intestine is the impairment of neural integration required for ordered motor action. It also possibly impacts the CNS and promotes sympathetic output to the intestine.[73] The resultant effect of this is non-

peristaltic contractions with high amplitude leading to an increase in the intestinal transit time.

The most common side effect of opioid analgesia is constipation. Opioid-induced constipation occurs in 15-70% of patients taking them for pain management with the actual rate determined by the kind of opioid the individual is taking.[73] Studies have indicated that opioid-induced constipation is usage and frequency-dependent. It is therefore common in persons that take opioid medications for a long time. About 0.2-6% of the population develop persistent abdominal pain on taking opioids which worsens with increasing doses of the drug.[73] This phenomenon known as the Narcotic Bowel Syndrome may sometimes be confused with conditions like irritable bowel syndrome and inflammatory bowel disease.

Opioids cause vomiting in some people. When patients are put on opioids, it can cause the stimulation of the chemoreceptor trigger zone. Such persons may have to be given antiemetics to abate the vomiting. Morphine can produce vomiting in up to 30% of patients who receive it.[31, 73]

Opioid tolerance

When a patient takes opioids for a long time, they tend to develop adaptive changes. When this occurs, increasing doses of the drug are required to produce the same effect. This is referred to as tolerance.[73] Adverse physiological disturbances occur which may persist till compensation occurs. This phenomenon known as dependence may be adaptive or learnt. The adaptive uncoupling of G-proteins occurs which leads to desensitisation and subsequent downregulation of signal transmission to opioid receptors. There is an associated psychological effect from learnt dependence that may result in a withdrawal syndrome. When a person has a dependence on one opioid there is the tendency to develop cross dependence towards other opioids.[73]

2.4.2 Nonopioid Analgesics

This group of analgesics is widely used because of the ability to relieve pain and may also possess a wide range of anti-inflammatory properties. The effect of these nonopioid

analgesics is essentially due to a different mechanism of action and can also reduce opioid-related side effects.[21] The ability of NSAIDs to achieve good pain control and reduce the requirement for opioids and the opioid-associated side effects have been supported by several studies.[80] Since the latter part of the 20th century, it has been generally regarded that these drugs basically act by inhibition of the cyclooxygenase (COX) pathway with resultant prostaglandin (PG) synthesis inhibition.[74] The ability for this class to relieve pain as well as side effects that they produce have been linked to their inhibition of PG synthesis.[74]

Nonopioid analgesics when given together with opioids can give an additive or synergistic effect in postoperative pain management. Although the use of nonopioids is effective and safe for postoperative pain management, less literature supports the benefits of a combination of nonopioid analgesics and their associated side effects when used in the long term.[20,75,76]

Since balanced analgesia was proposed about 25 years ago, there have been combinations of nonopioid analgesics with opioids, with morphine being the point of reference, for the opioids.[77] This is in an attempt to reduce the requirement of opioids for postoperative pain management by combining different drugs for analgesia in an attempt to provide adequate pain relief and also to reduce opioid-associated side effects. There have been several formulations with different routes of administration that have been developed. Whilst some of these formulations can be used to manage acute pain after surgery, others cannot be used immediately as they may have a slower onset of action or the route may not be immediately available for use after surgery. These drugs may be used alone or they may be combined with other opioids especially morphine to manage acute pain from surgery.[77]

I.V formulations of nonopioid analgesics with rapid onset and higher plasma levels are currently available. This availability has encouraged their usage in postoperative pain management.[78] For instance, the administration of i.v. acetaminophen at incision closure has demonstrated improved postoperative pain scores, fewer side effects, reduced opioid-induced side effects and decreased use of opioids.[38]

Paracetamol and NSAIDs are the commonly used nonopioid analgesics. To a larger extend metamizole may also be used in managing acute postoperative pain.[79] It has been well

recognised that the analgesic effect on postoperative pain is the same for non-selective COX-2 inhibitors and NSAIDs.[79] When given alone for postoperative pain control, NSAIDs comparatively achieve better pain control than paracetamol.[80]

In several countries, NSAIDs are not used as the non-opioid drug of choice over paracetamol in multimodal analgesia despite the reported efficacy of the former over the latter for postoperative pain control because of the associated side effects.[80]

The risk for miscarriage in the first trimester of cyesis as well as the risk of cryptorchidism precludes the use of NSAIDs as the analgesic of choice in the first trimester of pregnancy. Aspirin also has effects on the fetus when used for pain control in the third trimester of pregnancy as it may cause oligohydramnios or lead to renal damage in the fetus.[80]

In recent times there have been concerns over the effect of some non-opioid analgesics such as NSAIDs on wound healing. However, there have not been large randomised control trials on this but studies in animals revealed a possible effect on bone healing.[80,81]

Metamizole is another non-opioid drug with comparative efficacy to NSAIDs that may be used to treat postoperative pain. This drug is not readily available across the globe and has received a mixed reaction on its use due to confusion on the possibility of causing agranulocytosis.[81] Whilst some countries have redrawn the license for its use, others suggest no justification from scientific reviews on the supposed agranulocytosis it causes and therefore recommends its use.[81] Compared to NSAIDs, Metamizole has insignificant cardiovascular, gastrointestinal and renal side effects.[81] It has been regarded as effective in managing acute postoperative pain with very good tolerance. In some countries, it is even used as the first line non-opioid parenteral analgesia because of its high efficacy balanced with its rare side effects.

2.5 Choice of postoperative analgesia.

The choice of analgesia is an essential component in postoperative pain management. When institutions have their postoperative pain management protocols or adopted from standard recommendations, clinicians are mostly guided in choosing analgesia for pain management. Choosing an appropriate analgesic can be influenced by several factors. The availability of a particular drug and knowledge on its efficacy is important in choosing an

agent tailored to the patient's need.[27] The mainstay for most surgeons in managing postoperative pain has remained opioids and it is widely used.[27] No standard management of postoperative pain is documented for use across Ghana.[41]

There is a wide range of drugs from which a prescriber can choose to manage postoperative pain. The World Health Organisation (WHO) pain ladder, which is a stepwise method to managing pain has been a guide in pain management by considering the intensity of pain that a patient has.[54] Although the choice of medication for postoperative pain control, should be individualized, there are guidelines that the prescriber needs to follow.[54] In general, the patient's health status is paramount and therefore considered first. Ideally, one needs to consider whether the pain being treated is mild, moderate, or severe in choosing the analgesic following the WHO pain ladder. The efficacy of the drug and the possible side effects are put into consideration.

Assessment of the risks associated with the pain is essential. Choice of analgesia can be influenced also by the availability of the type of medication used. Further, this is significantly influenced by the surgical procedure to be performed.[82] Upper abdominal incisions are painful and clinicians are more likely to choose drugs that are strong enough to control moderate to severe pain in such circumstances.

Paracetamol is the most widely used analgesia world wide and there have been concerns over the undue use of the drug in clinical practice in managing pain.[83] From observation, the drug is been used in clinical practice in the country as a stand-alone drug or in combination with morphine for postoperative pain. The choice of either i.m. morphine alone or combining it with i.v. paracetamol for managing postoperative pain may be influenced by factors such as the prescriber's familiarity with the drug and convenience in prescription.

2.6 Paracetamol and Morphine in postoperative pain treatment

2.6.1 Overview of morphine

Morphine is the most widely used opioid and has become the standard choice for postoperative pain management by most surgeons.[5] Compared to other opioids like

fentanyl, it has a relatively longer onset of action but its effects last longer and thus may be used preferably in achieving adequate postoperative pain control.[84] It is the standard against which other analgesics are measured. There has been no direct link between the usage of morphine and derangement of liver enzymes from hepatic injury due to the use of the drug.[85] It is on the WHO essential drug list of opioid analgesia for the treatment of postoperative pain. As a result of the potential to make patients feel a high sense of well-being and thus the possibility for abuse, it is a controlled substance.[85]

2.6.2 Pharmacology of morphine

Morphine is by nature a hydrophilic opioid that is naturally occurring in opium.[84] As a result of this hydrophilic property, there is a delayed penetration into the CNS. This is because a relatively high hydrophobic activity of an opioid gives it a rapid onset of action by transporting it quickly to its site of action.[84, 86] This explains why morphine has a relatively slow onset of action compared to other opioids like fentanyl. This further allows for very rapid redistribution of these drugs in the tissue making morphine last a little longer compared to these drugs.[84] Morphine takes 5 to 6 minutes to reach 80 percent of maximum concentration in the effect compartment following a single shot of i.v. administration.[84,87] It is based on this that the lockout period for the patient-controlled analgesia system was designed.

Morphine-6 glucuronide (M6G) is a metabolite of morphine that has a potency of up to about eight (8) times that of morphine.[84] This may cause respiratory depression in individuals with end-stage kidney disease because it is water-soluble and eliminated by the kidneys.[84] The metabolism of morphine may vary somewhat in individuals as well as μ-receptor affinity. The change in the efficacy of morphine and its metabolite M6G due to the change at the μ-receptor may result in requiring increasing doses of the morphine in certain individuals.[84, 88] However, some studies have suggested that this variability may be determined by variability in the sensitivity to pain.[84, 88, 89]

There have been suggestions for the use of a loading dose for morphine. [84, 90] Studies have however indicated that a loading dose of morphine has not been found to significantly reduce the pain but may rather increase the incidence of side effects.[91] Farsi and his

colleagues in their study demonstrated that when the dose is increased by 50% there is a resultant increase in the analgesic effect of morphine without any increase in the associated adverse effects.[92] When morphine is given orally, absorption occurs in the upper intestines because it requires an alkaline environment for absorption. Significant first-pass metabolism occurs with the oral administration of morphine. As a result of this, up to about six times the dose of parenteral morphine would have to be given orally to attain a similar effect to parenteral administration.[85] There has also been documentation of the variability of oral administration with food depending on the formulation type. When administered in the conventional preparation, absorption is increased with the concomitant intake of food.[85]

Opioid receptors in the brain, GIT, and spinal cord to which morphine binds, have been noted to mediate not only the analgesic effect but the side effects of the drug as well.[93] The analgesia produced by morphine is as a result of the interaction with the opioid receptors and the reticence of communication from the dorsal horn of the spinal cord. Subsequently, there is a decrease in the release of neurotransmitters associated with the transmission of pain.[93] Morphine is a strong opioid with a quick onset of action compared with non-opioid analgesics and a peak effect in 1 to 2 hours.

2.6.3 Dosing of Morphine

The sulfate form of morphine is most commonly utilised, but the hydrochloride and tartrate forms are also used in similar quantities. The salts are used to express doses. Oral, subcutaneous, intramuscular, intravenous, intraspinal, and rectal routes are all options for administration. There have been several recommendations on the dose of morphine to be given.[92]

There have not been many studies on what the ideal dosage of morphine should be to give adequate pain relief whilst keeping the opioid-related side effects to a minimum.[92] According to Bijur and his colleagues, the usual starting dose of 0.10mg/kg may not be enough to achieve effective pain control.[94] Anther study suggested that a dose of 0.10mg/kg can be compared with that of 0.15mg/kg as this does not provide significant pain relief with a difference of 0.8 on the average on the NMR.[95] Other studies have however indicated that a dose of 0.15mg/kg provided significant pain relief and considered this to be the threshold for dosing.[92] There is no significant difference when morphine is given

intramuscularly or subcutaneously at a dose of 0.15mg/kg.[96] After major abdominal surgery, i.m. morphine at a dose of 0.1mg/kg provided adequate pain relief compared to 2mg/kg of i.m. pethidine without any major difference in the side effects from a study in Bangladesh.[97]

The usual adult dose of 10mg 4-6 hourly given intramuscularly or subcutaneously should be adjusted in the elderly and patients with renal impairment. When given via the i.v. route, an adult dose of 2.5-10 mg may be needed titrating dose and interval against the response of the patient. In an opioid-naïve patient, rapid boluses may be unsuitable.[84, 98, 99]

2.6.4 Side effects of morphine

The common side effects of morphine are no different from the other opioids. Most of the issues raised with the use of morphine as a potent analgesic have been with its side effects which sometimes make it difficult for the patient to tolerate. Nausea and vomiting occurring a few hours after surgery can be very distressing to the patient.[100,101] Postoperative nausea and vomiting are the commonest side effects of morphine recorded in patients at the PACU.[27,84,102] This occurs between 5% to 15% of patients admitted to the PACU and may even be up to 80% after gynecological surgery.[84] Currently, there are no studies that have looked at the duration of nausea and the frequency of vomiting in patients who get PONV after receiving morphine for the management of postoperative pain.[84] Some patients may need antiemetics for the PONV. There have been various actions in an attempt to minimize the incidence of PONV in patients who receive morphine for postoperative pain management. One of these is the use of multimodal analgesia with the expectation that the addition of the non-opioid analgesia will offer morphine sparing effect and the reduction of morphine to control. This then will help in minimizing the incidence of PONV.[21] There have been studies that have suggested that dexmedetomidine, an α2-adrenoreceptor agonist, can reduce morphine requirement and reduce pain scores when administered intraoperatively. This can reduce the incidence of nausea and vomiting associated with the use of morphine and also the dose of required opioids.[103,104,105,183]

Respiratory depression is probably the most dreaded and fatal side effect with the administration of morphine.[84,106,107] The interaction of morphine with ventral medullary opioid receptors was once believed to cause respiratory depression in patients who receive

morphine for pain management. However, current evidence has revealed that the preBötzinger complex in the medulla is the location responsible for causing the reduction in the respiratory rate leading to respiratory depression.[107,108] In most instances, the ventilatory rate has been a more reliable means of checking respiratory depression rather than the use of the change in the SpO2 level. Respiratory depression is said to have occurred when the SpO2 is ≤85% to 94%. For patients who may be on morphine and receiving supplemental oxygen, an SpO2 of 95% should be considered for respiratory depression.[84] Patients who have a respiratory rate of 12 cycles per minute may need titration with morphine stopped. If the respirator rate is <10 with accompanying impaired consciousness, then the effect has to be reversed with naloxone.[84] This reversal is possible because naloxone is a competitive opioid receptor antagonist thus making it possible for it to counteract the action of morphine and reverse the morphine-induced respiratory depression.[109]

Naloxone has a short half-life and re-narcotisation may occur in some individuals even when they get some initial relief. Notwithstanding, there have been reports of naloxone-associated symptoms such as opioid withdrawal effect, sweating, pulmonary edema, behavioural changes and cardiovascular problems.[110] As a result of this, there is the recommendation of a starting dose of i.v. or i.m naloxone from 0.04 to 0.4 mg whilst the patient is monitored for any symptoms related to the reversal.[110] Some authorities recommend starting naloxone with the lowest dose possible and titrated against the patient's response to the reversal.[110,111] The reversal of respiratory depression by naloxone also goes with the reversal of the analgesic effect of morphine.[106]

One of the common reasons why morphine has been discontinued as the drug for postoperative pain management is the sedative effect. This occurs about 60% of the time and there is no documentation of a direct link between sedation and effective pain relief.[84]

Postoperative ileus may occur with the administration of morphine and may even result in a longer hospital stay.[27,102,112]

Other side effects that may be encountered with the use of morphine include hypotension and pruritus [27,102]

2.6.5 An Overview of Paracetamol

Paracetamol is the most commonly used over-the-counter medicine in the world, forming Step One of the WHO analgesic ladder.[113] Paracetamol is the most widely prescribed analgesic for acute pain management.[114] Its use had even become popular in the 1950s when it was advertised as a safe alternative to phenacetin-containing analgesics.[115] This was after phenacetin was associated with the development of upper urinary tract cancers and raised safety concerns among scientists.[116] It plays an essential role in multimodal analgesia due to its good safety profile and fewer medication interactions as compared to others such as aspirin.[113,116, 117]

When administered in extremely high doses, paracetamol may produce some serious adverse effects such as hepatotoxicity; however, harm from long-term therapeutic use is unknown.[117] Oral or rectal administration of paracetamol produces analgesia within 40 minutes and reaches a maximum effect within one (1) hour.[113] Bioavailability ranges from 63 to 89 percent for oral route and 24 to 98 percent for rectal route administration. This makes it difficult to predict the onset and duration of action for these routes of drug administration.[113] Intravenous(i.v.) paracetamol has been introduced into clinical practice and gaining popularity for perioperative use in the last decade due to its superior onset of action compared to the aforementioned routes. The i.v reparation has been used together with some other classes of analgesia as multimodal analgesia for pain management especially, postoperatively. It has an onset of action of 5 minutes and peaks within 40 to 60 minutes, with a duration of 4 to 6 hours .[113] I.v. paracetamol is easy to administer and may be used when enteral administration is not available or where a quick onset of action is needed, making it an excellent alternative for analgesia in the perioperative pain management regimen. [113]

2.6.6 Paracetamol's Mechanism of Action

The mechanism of action of paracetamol is still unclear but thought to be a highly selective inhibitor of cyclooxygenase-2 (COX-2).[27,117,118] Apart from this there has been another theory on the central mechanism of paracetamol in controlling pain. This theory is talks about the inhibition of the nitric oxide pathway. This inhibition is through N-methyl-d-

aspartate (NMDA) and substance P with a peripheral effect also occurring through the reduction in the synthesis of prostacyclin.[92] Paracetamol has opioid-sparing effects and lacks interference with platelet function.[27,119] Onset of action has been noted to be slow as compared to opioid analgesics. Primary metabolism of the drug occurs in the liver, hence, contraindicated in liver disease. Scientific evidence suggests that paracetamol's mode of action comprises several interconnected central mechanisms, including effects on prostaglandin synthesis, serotonergic, opioid, nitric oxide (NO), and cannabinoid pathways.[113,117] Nonsteroidal anti-inflammatory medicines (NSAIDs) have traditionally been used to inhibit cyclo-oxygenase (COX) and prevent the conversion of arachidonic acid to prostaglandin (PG) G2.[117]

Even though it is believed that paracetamol inhibits COX-mediated prostaglandin formation, unlike NSAIDs, paracetamol lacks anti-inflammatory effects and has not been shown to lessen inflammation.[113]

The COX enzymes execute their function by converting PGG2 to prostaglandin H2 (PGH2) synthase. This is then transformed by the tissues to numerous PGG derivatives to suit their metabolic needs.[120,121,122] When the cellular environment is deprived of arachidonic acid and peroxides, paracetamol inhibits the peroxidase (POX) activity of the COX isoenzymes, primarily COX-2.[120,121,122] As a result, paracetamol is essentially a strong PG synthesis inhibitor that inhibits the normal regeneration of POX while the cell is intact.[113] Following cellular injury, the concentration of hydroperoxide rises and prostaglandin is least inhibited. This peroxide-dependent COX inhibition explains why paracetamol has different actions in the brain, where peroxide concentrations are substantially lower as opposed to peripheral areas where inflammation has occurred with large amounts of peroxides.[121]

Another mechanism of action involves the inhibition of anandamide reuptake, which leads to the stimulation of cannabinoid receptor CB1 by a paracetamol metabolite, N-arachidonoylphonamide (AM404), which is produced by the conjugation of deacetylated paracetamol and arachidonic acid, and the direct activation of a capsaicin receptor metabolite, transient receptor potential cation channel vanilloid type (TRPV1).[123] The central generation of AM404 suppresses the synthesis of prostaglandins in the brain,

resulting in paracetamol's antipyretic effect, although the peripheral activity is uncertain.[113] Nausea and vomiting are coordinated in the cortex and the brain stem respectively. Very close to the medulla oblongata is the vomiting centre. The cortical centres are affected through the interaction with the medulla oblongata by pain via several neurotransmitters. This interaction contributes to PONV.[183] Effective analgesia by paracetamol through its central action may affect this interaction and prevent the initiation of the stimulus that is responsible for the PONV. Furthermore, recent data suggests an indirect modulation of the serotonergic system through the EP3 receptor.[183] This is a major receptor for Prostaglandin E_2 found in neuroamine neuron types in the medulla oblongata. Hence, paracetamol is able to reduce PONV. There have also been ample evidence supporting the ability of paracetamol to cause an increase in cannabinoid tone suppressing vomiting caused by chemoreceptor trigger zone.[183] This may be the reason why some surgeons add paracetamol to opioids such as morphine in multimodal analgesia in patients who have undergone surgery in order to reduce or prevent the incidence of opioid-associated nausea and vomiting.

2.6.7 Efficacy of Paracetamol

Paracetamol is a very useful first-line analgesic that acts in synergy with other kinds of analgesics to improve analgesic efficacy while reducing the negative effects of the adjunct medication.[113]

Paracetamol has been used in a variety of surgical procedures as well as in the treatment of both acute and chronic pain. In comparison to typical doses of NSAIDs and opioids, paracetamol has shown fewer side effects while staying effective.[115] This has encouraged the use of paracetamol in a multimodal analgesic regimen. Further to this, paracetamol is thought to provide opioid-sparing benefits such as reduced incidence of respiratory depression, nausea, and vomiting, as well as improved patient satisfaction.[124]

Although i.v paracetamol has a faster onset of action than oral or rectal paracetamol, there is no significant difference in total efficacy when delivered via any of the methods.[125]

2.6.8 Dosing of Paracetamol

The Medicines and Healthcare Regulatory Authority (MHRA) accepted and validated the same paracetamol dose for all modes of administration for individuals weighing more than 50kg. The recommended dose is 1g up to four times in 24 hours, particularly in patients with creatinine clearance of more than 30ml/min.[113]

Despite the fact that paracetamol has a better lipid solubility and low protein binding, the MHRA has never approved it for modified doses.[113] Regardless, pharmacokinetic data show that a single loading dose of 2g, followed by 1g administered every 6 hours, has made its way through clinical practice and that evidence-based practice has shown that 2g loading dose in postoperative analgesia, adult patients have demonstrated lower pain scores and longer duration of pain relief with no increase in side effects or toxicity markers.[113]

2.6.9 Paracetamol Pharmacokinetics

Paracetamol is metabolized mostly by the production of conjugates with glucuronide and sulphate, and is eventually eliminated through the urine.[117] When therapeutic doses of paracetamol are administered, approximately, 10% is metabolized by cytochrome P450 (CYP) enzymes to form n-acetyl-p-benzoquinoneimine (NAPQI). NAPQI then conjugates with glutathione within the cells and is excreted as cysteine and mercapturic acid conjugates, with less than 5% excreted unchanged.[123] However, when glutathione levels are low, as in paracetamol overdose, NAPQI produces acute hepatic necrosis by interacting with cellular membrane molecules. [113]

Paracetamol excretion from the body may significantly vary depending on the clinical state of the individual. When compared to healthy people, paracetamol elimination is delayed and glucuronide and sulphate conjugates elimination is threefold slower in cases of severe renal impairment with creatinine clearance of less than 10-30ml/min.[113]

2.6.10 Systemic Effects of Paracetamol

Cardiovascular System

The research on the relationship between paracetamol and the incidence of cardiovascular illnesses is limited when compared to NSAIDS. However, studies could be conducted in this field due to the comparable mechanism of action of paracetamol and NSAIDS, both of which are related with hypertension.[126] In one study, it was reported that administering paracetamol to hypertensive individuals raises blood pressure by 4mmHg.[117] It has been established that a 2mmHg increase in systolic blood pressure is associated with a 7% rise in the risk of death from coronary artery disease and a 10% rise in the risk of stroke.[127] Hypotension, on the other hand, is noted as a rare side effect of paracetamol.[113]

Gastrointestinal System

Overdose of paracetamol has been extensively documented to produce acute effects on the liver, with the most prevalent concerns being GI blood loss and liver toxicity.[128,129] Prolonged use of paracetamol within the therapeutic dose range may cause liver damage. This hepatic damage from prolonged use may be due to glutathione depletion, chronic alcoholic activation of the cytochrome P450 enzyme, or concomitant use of paracetamol with other medications.[130] The use of paracetamol is associated with dyspepsia and nausea to some degree. There is no proof of GI bleed associated with the use of paracetamol.[117]

In spite of the proof of paracetamol's safety, epidemiological studies have confirmed that there is an increasing potential risk of upper GI hemorrhage with a daily dose greater than or equal to 2g together with NSAIDs. This observation might be found to be due to an increase in the inhibition of cyclooxygenase, similar to that seen in persons on high-dose NSAIDs or those on multiple NSAIDs, who are similarly at elevated risk.[131] Despite the fact that paracetamol is well tolerated in patients with hepatic insufficiency and liver cirrhosis in the authorized therapeutic dose range, it is administered with caution. [113]

Renal System

Acute kidney injury occurs in 1-2 % of paracetamol overdose patients, and it is more common in cases of paracetamol-induced hepatotoxicity.[117] Moderate to long-term paracetamol use has been connected to end-stage renal disease. The mechanism is linked to glutathione reduction, necessitating optimization of hydration and nutrition in patients receiving regular doses of paracetamol.[113]

While the nephrotoxicity caused by paracetamol is unclear, it is strongly linked to the local production of NAPQI or other harmful metabolites by CYP or COX enzymes.[117] Despite the association of renal toxicity from paracetamol with glutathione depletion, it has been established that N-acetylcysteine administration does not affect the peak concentration of creatinine. This implies that glutathione deficiency is not the only cause of nephrotoxicity associated with paracetamol intake.[117]

Respiratory System

Paracetamol administration may have some untoward effects on the respiratory system in some patients. According to epidemiological research, regular use of paracetamol is closely connected with morbidities such as wheezing, rhinitis, and asthma in both adults and children.[113]

Some concerns have been raised about the findings from observational studies that show a link between paracetamol use and asthma diagnoses or exacerbations.[132,133] The product labelling for paracetamol clearly states that it can cause breathing difficulties and bronchospasm in people who are at a higher relative risk of experiencing analgesic asthma.[113]

2.6.11 Combining morphine and paracetamol

Clegg-Lamptey and Hodasi bemoaned the poor postoperative pain management in surgical patients and recommended an increase in opioid use and a multimodal approach.[134] This, they noted, will not only relieve the patient of postoperative pain but will also enhance their recovery. However, there is no objective data in the subregion to back such a recommendation. Bandey and Singh concluded that intravenous use of paracetamol is effective and safe for postoperative pain management compared with tramadol. Their work focused on laparoscopic surgery and thus such a conclusion cannot be readily extrapolated to open abdominal surgeries.[114]

Intravenous paracetamol has been used in major surgeries such as lumbar discectomy with satisfactory results.[118] In contrast, Alimian et al found i.v. paracetamol to be ineffective in the first six (6) hours of postsurgery in managing pain after elective laparotomy but it is as effective as morphine after eight (8) hours of postsurgery.[135] Martinez *et al* do not

recommend giving acetaminophen alone to manage postoperative pain but should include an NSAID or nefopam which makes it superior to a stand-alone non-opioid analgesic.[22] In another study, the authors found paracetamol and morphine to be equally effective in providing pain relief.[136]

Several studies have shown different effects when morphine is combined with other forms of analgesia. The synergy between paracetamol and morphine was demonstrated in a study by Zeidan *et al*.[92] In their study, the authors found paracetamol and morphine to have additive effect interaction in managing postoperative pain. This additive effect decreased the occurrence of side effects of both drugs. In patients who have undergone major surgery, Maund *et al* found a reduction in the consumption of morphine within 24 hours for those on PCA if morphine is combined with i.v. paracetamol.[119]

In the management of postoperative pain, i.m. morphine and i.v. morphine are equally efficacious.[137] Intramuscular morphine has an absorption peak of 10-20 minutes.[138] For adults, the usual route of administration of morphine is i.m. or subcutaneous but may be given i.v. when a rapid onset of action is desired.[139] In a low-resource setting like Ghana, naloxone and resuscitative equipment are not readily available in the event of severe respiratory depression with rapid administration, hence the i.m. route used as a safe alternative for this study.[139]

A study in India compared the efficacy of a combination of i.v. paracetamol and fentanyl versus fentanyl alone in managing postoperative pain after laparoscopic cholecystectomy. However, in that study, the paracetamol was given intraoperatively before extubating the patients and its effect measured post-extubation. The study was not clear on the randomization process in generating the randomization list of participants. There could be some bias in the randomization and there could also be imprecision in the use of the VAS for the pain assessment.[181] The study also assessed paracetamol as preemptive analgesia as against its use in actively alleviating post-operative pain in combination with opioids.

Similarly, another study looked at the combination of fentanyl and i.v. paracetamol against fentanyl in the management of pain after total hip replacement.[182] In that study which was carried out in Japan, the study design was similar to the current study with the administration of 1g qid of paracetamol together with an opioid compared with an opioid

only. The study further assessed the pain scores using NRS except that fentanyl was the opioid in use unlike morphine in this study. The study found that a combination of fentanyl with paracetamol reduced the total fentanyl requirement up to 24 hours after surgery. The recording of the score in that study was done by staff on the ward who were not blinded to the groups the patients were allocated. Hence, the assessors could know the drugs that the patients received for the pain management. This could have introduced some bias in the data collection.

2.7 Analgesia and length of stay

Adequate pain management can enhance recovery, reduce complications, and lead to early discharge. Multi-modal analgesia has been found to reduce the length of hospital stay and the cost of surgery.[140,141,142] The effect of analgesia on the length of stay has been variable in the findings by some studies. Some of these studies have regarded the length of stay after major abdominal surgery as multifactorial and not necessarily driven solely by the effect of adequate analgesia.[142] Whilst some studies have found adequate analgesia and the type of analgesic a patient receives after surgery affecting the length of hospital stay, others did not see a shortened length of stay based on the type of analgesia.[142]

Some research works indicate that multi-modal analgesia provides adequate pain relief with resultant effect in enhanced recovery and early discharge after surgery. However, there is still controversy over which of the modalities is optimum.[141] In their meta-analysis, Marret *et al* demonstrated that patients who received epidural morphine after colorectal surgery had a reduced length of stay as compared to their counterparts that received .i.v. morphine.[143] Hughes et al found that the type of analgesia does not have any significant effect on the length of stay.[141] Similarly, according to Kehlet and Holte, analgesia with epidural morphine improved other areas of recovery such as bowel function but did not show any positive effect on length of stay.[144] They further suggested the integration of epidural analgesia into a multimodal mode may show a possible reduction in the length of stay after surgery. In the analysis of the effect of analgesia using i.v paracetamol with morphine as against oral paracetamol with i.v. morphine, it was demonstrated that those in the i.v paracetamol group had a shorter hospital stay after abdominal hysterectomy.[142]

More studies have demonstrated a short length of stay in patients who received morphine with i.v. paracetamol for abdominal and orthopaedic surgeries.[145,146,147].

There have been studies that reported that when patients receive morphine alone after laparotomy, they are less likely to meet the criteria for admission to go home early as compared to those who receive multimodal.[148] Since the late 20th century when fast-track abdominal surgery was introduced, early discharge, which is a component of the composite of the perioperative care to enhance recovery has received attention. This surgery package makes use of the multimodal approach to attain optimal pain relief and to shorten the length of stay.[149] This has also been replicated in various gynaecological surgeries and the results indicated a short length of stay for those who had good pain control from multimodal analgesia.[149,150] Maheshwari *et al* reported early discharge of patients after getting adequate pain management after surgery using multimodal analgesia.[151]

2.8 Administered analgesia and postoperative complications

The issue of postoperative complications associated with the analgesic given has been linked to the achievement of adequate postoperative pain as this is expected to allow relief to get the patient out of bed.[152] Early mobilization of the patient helps to prevent postoperative immobilization that is associated with complications due to prolonged stay in bed. When intermittent opioid therapy and patient-controlled analgesia are compared it is noted that venothromboembolism and prolonged length of stay complications are not improved with patient-controlled analgesia.[144] Stress response can have a major impact on the immunity of the patient after major surgery. If pain is not adequately controlled, it triggers the stress response through the neuroendocrine response with the resultant catecholamine secretion. This can cause a hypermetabolic state, affect the levels of anticoagulants with the propensity to cause venothromboembolism.[153] There is an insignificant effect on the stress of surgery when NSAIDs are given for pain control.[144] When i.m. morphine was compared with i.v. paracetamol in postoperative pain management, there were lower side effects in the group that received paracetamol with no significant statistical difference between the pain scores.[144] Similarly, there were no differences in the side effects and analgesia from a study that compare pethidine, tramadol

and morphine. Another study found paracetamol to be more effective in postoperative pain control than narcotics.[144] No significant difference was found in unplanned 30-day readmissions in patients given Morphine Fentanyl, and hydromorphine in a study be Elsamadicy *et al*.[140] There was a similar prevalence of postoperative complications in all cohorts.[140]

CHAPTER THREE

METHODOLOGY

3.1 Study Design and type

The study was a prospective single-blinded randomised controlled trial (RCT) that compared the efficacy of unimodal i.m. morphine with bimodal administration of i.v. paracetamol and i.m. morphine in managing postoperative pain after emergency abdominal surgery.

3.2 Study Setting

The research was conducted in Komfo Anokye Teaching Hospital (KATH) in Kumasi, Ashanti Region. KATH is the second largest health facility in Ghana with a bed capacity of about 1200. The hospital receives referrals from other hospitals in Kumasi and outside Kumasi. The hospital is bounded on the east by the main Kejetia dual carriage; on the west and south by 4BN Infantry Uddara Barracks and the Central Police Barracks and on the north by the Bantama Township.

The hospital has a staff strength of about four thousand (4,000), comprised of administrative, medical, paramedical, and auxiliary personnel providing various services

in the healthcare and health delivery program. Every year, about fifteen thousand (15,000) in-patients and one hundred and forty-two thousand (142,000) out-patients are treated. The hospital's organizational services are divided along the lines of diseases, age, and gender. Furthermore, the hospital includes twelve directorates, ten (10) of which provide clinical services and two (2) of which provide non-clinical services.

The Komfo Anokye Teaching Hospital (KATH) General Surgery Unit is made up of five (5) teams. Each team consists of six (6) team members on average, led by a consultant, and includes at least one post membership resident, junior residents, and house officers. Each team is responsible for one (1) weekday emergency duty and one (1) weekend emergency duty every fifth weekend. Each team handles patients ranging from breasts to thyroid disease, soft tissue swellings and infections, visceral surgery, and limb amputations due to causes other than trauma. According to KATH theatre records, general surgery teams perform an average of thirty (30) emergency abdominal procedures every month. This ranges from infectious causes, malignancies to trauma. Patients were recruited into the study in the KATH Main Operating Theatre over a period of 4 months.

3.3 Sample size

The desired sample size was calculated by using Cochran's formula. With a confidence interval of 95%, an accuracy of 10% and a power of 90%, the sample size was calculated as:

$$n = \frac{z_{\alpha/2}^2 * (p) * (1-p)}{e^2}$$

Where;

n= Sample size

Z= Z score (reliability coefficient) of 1.96 at 95% CI

p= prevalence of emergency abdominal surgery of 48.1% (0.481) using that of Zaria, Nigeria,[154] since the exact number of patients presenting with acute abdominal conditions and subsequently those who will require surgery is not known in Ghana.

q = 1-p (proportion of the target population not having the characteristics)

e = degree of accuracy (assumed 0.1)

$$n = \frac{1.96^2 \times 0.481\ (1 - 0.481)}{0.1^2}$$

$$n = \frac{3.8416 \times 0.481(0.519)}{0.01}$$

$$n = \frac{3.8416 \times 0.2497}{0.01}$$

$$n = \frac{0.9590}{0.01}$$

$$n = 95.90$$

$$n = 96$$

Ten (10) percent of the sample frame was added to allow for possible attrition. Thus, a total of 108 participants were estimated for the study.

3.4 Study Population

The study population consisted of patients from 18 to 80 years who underwent emergency abdominal surgery at the main operating theatre of KATH. Participation in the study was voluntary.

3.4.1 Inclusion Criteria

- Patients aged from 18 to 80 years.
- Patients who underwent emergency abdominal surgery

- Anticipated abdominal incision of at least 5cm long including appendicectomy
- Patients who consented to take part in the study

3.4.2 Exclusion criteria

- Patients allergic to paracetamol or morphine
- Patients with impaired hepatic function or clinical features of liver disease
- Patients with renal impairment and CrCl < 60ml/min
- Patients with chronic opioid dependence
- Patients who were critically ill and needed ICU care
- Patients with a neuropsychiatric condition that could impair pain assessment

3.5 Data collection tool/instrument

A structured questionnaire was designed on an electronic data capture system, REDCap, to collect information electronically. Both close-ended and open-ended questions were asked. Study variables collected included socio-demographic characteristics of the participant such as age, sex, last educational level, marital status, occupation, religion, ethnicity, and family system. Other variables collected were pain assessment score and outcome of surgery such as time of first bowel movement, time of first oral intake, time of ambulation, postoperative nausea, postoperative vomiting, diagnosis of pneumonia, diagnosis of DVT, and length of hospital stay. The Numeric Rating Scale (NRS) was used to assess the intensity of pain. Data collection for each participant was completed on the day and time of discharge.

3.6 Method for data collection

Patients who underwent emergency abdominal surgery during the study period using general anaesthesia with endotracheal intubation who satisfied the eligibility criteria were enrolled in the study after obtaining informed consent. Considering the average of 30

emergency abdominal surgeries performed by the General Surgical Teams in KATH per month according to hospital records, data was collected over 4 months. Patients with acute abdomen reporting at the Emergency Medicine and Surgery Directorates of KATH were recruited for the study. The purpose of the study and its benefits as well as the rights of the respondents and the procedure involved were explained to all participants. Participants were assured of anonymity and confidentiality such that, their names and residence were not inquired. Informed consent was then sought before the questionnaire was administered.

Participants were assigned to an arm of the study by a random process to avoid sampling bias. The two arms of the study were evenly distributed in envelopes and put in a container. Before going to the operating room, each participant was made to pick an envelope, and upon opening, they were randomised to the selected arm.

Participants who were randomised into the morphine-alone arm received i.m. morphine 10mg 6hourly x 48 hours. The other group received i.v paracetamol 1g 6hourly x 48 hours and i.m. morphine 10mg 6hourly x 48 hours. In each of the arms, the first dose was given within ten (10) minutes of receiving the patient to the recovery ward. Patients above 60 years old received morphine dose of 5mg 6hourly (50% of the regular dose to adults).[155]

House officers were trained in using the NRS and CCPS (in case a patient could not appreciate the NRS for the assessment of pain) as outcome assessors. Outcome assessors were blinded to the analgesic administered to participants. The NRS was used to assess the participants level of pain at one (1) hour after the administration of the first dose of the analgesic. Reassessment of pain was done at three (3) hours, six (6) hours, 12 hours and 24 hours after the administration of the first dose. On the NRS, zero (0) was no pain, 1-3 was mild pain, 4-6 was moderate pain and 7-10 was severe pain. Unsatisfactory pain relief was defined as an NRS score of four (4) or more. Rescue analgesia, in this case, was given to participants who scored four (4) on the NRS and did not have analgesic being infused at the time of the pain assessment. Any rescue analgesia given was determined by the attending physician based on the patient's condition and was recorded accordingly.
The questionnaire was administered through face-to-face interaction with study participants. The health information records (HIR) of participants were explored for

relevant information such as any rescue analgesia given, the dose of rescue analgesia given, a surgical procedure performed, clinical diagnosis, complication from prolonged stay such as clinical diagnosis of DVT and date of discharge.

3.7 Statistical Analysis

Data were extracted from REDCap onto STATA 13, StataCorp, Texas 77845 USA, for analysis. Variables with significant differences to the outcome of the effectiveness of bimodal analgesia with unimodal opioid analgesia in post-emergency abdominal surgery pain management were used as predictors in a multinomial logistic regression. Information on the socio-demographics of the patients was presented using percentages, frequencies, means, standard deviations, pie charts, and tables. Chi-square test and odds ratios were used to determine the relationship between dependent variables: pain scores (at one hour, three hours, six hours, twelve hours and twenty-four hours following the administration of the first dose of the analgesic), time of ambulation, time of first bowel movement, postoperative nausea and vomiting, postoperative pneumonia, clinical diagnosis of DVT as well as the length of hospital stay and independent variables which are the bimodal analgesia group (i.m. morphine and i.v. paracetamol) and unimodal (i.m. morphine only) group. Levene's test was done to determine whether groups have equal variance with the pain scores. Post hoc analysis was done to determine which of the interventions contributed significantly to pain management. Statistical significance for all testing was set at a 95% confidence interval.

3.8 Ethical Consideration

Ethical clearance was given by the KATH IRB before the study commenced and registered with Pan African Clinical Trial Registry (PACTR), and Food and Drugs Authority (FDA), Ghana. Participants' anonymity was maintained and informed consent was sought before each questionnaire was administered. All data sought from participants were used strictly for the study. The researcher had no conflict of interest in the conduct of this study.

CHAPTER FOUR

RESULTS

4.0 Introduction

A total of 114 patients were assessed for eligibility but 110 patients satisfied the eligibility criteria and were recruited into the study to assess the response to analgesia in managing postoperative pain after emergency abdominal surgery at KATH. Data from 108 patients were, however, analysed; two patients (1.8%) were omitted from the analysis because of inadequate data.

4.1 Demographic Status of Patients

The demographics of the participants covered age, gender, educational status, occupational status, marital status, religion, ethnicity, and family system. Out of the 108 participants, 81 (75%) were males and 27 (25%) were females. The age distribution of the 108 participants ranged from 18 years to 80 years with an average age and standard deviation (SD) of 35.50 and 16.16 respectively.

A greater number of the participants were either less than 30 years (44.44%) or between 30 to 59 years (44.44%). Those who were 60 years and above were 12 (11.11%). More than half of the participants, 71 (65.74%) were Senior High School (SHS) graduates and 11 (10.19%) were graduates of Tertiary Schools. The majority, 57(52.78%), were single and 45 (41.67%) were married.

Table 4.1 Distribution of Groups and Socio-Demographic characteristics

Variable	Morphine N=54 (%)	Morphine and Paracetamol N=54 (%)	P value
Age group (Years)			**0.001**
Less than 30years	36 (66.67)	12 (22.22)	
30-59years	12 (22.22)	36 (66.67)	
60 years and above	6 (11.11)	6 (11.11)	
Gender			0.120
male	44 (81.48)	37 (68.52)	
female	10 (18.52)	17 (31.48)	
Educational status			0.257
None	3 (5.56)	8 (14.81)	
JSS_JHS	6 (11.11)	9 (16.67)	
SSS_SHS	38 (70.37)	33 (61.11)	
Tertiary	7 (12.96)	4 (7.41)	
Marital status			**0.002**
Single	38 (70.37)	19 (35.19)	
Married	13 (24.08)	32 (59.26)	
Co-habitation	1 (1.85)	2 (3.70)	
Widowed	2 (3.70)	1 (1.85)	
Occupational status			**0.023**
Civil Servant	3 (5.56)	4 (7.41)	
Farmer	3 (5.56)	10 (18.52)	
Retired	2 (3.70)	0 (0.00)	
Self-Employed	18 (33.33)	24 (44.44)	
Student	8 (14.81)	9 (16.67)	
Unemployed	20 (37.04)	7 (12.96)	
Ethnicity			0.126
Akan	52 (96.30)	46 (85.19)	
Ewe	0 (0.00)	1 (1.85)	
Mole-Dagbani	2 (3.70)	7 (12.96)	

Table 4.2 shows the distribution of the type of surgeries done. Those captured under 'Other abdominal surgeries' include surgeries such as splenectomy, emergency cholecystectomy, repair of traumatic bladder rapture, laparotomy for evisceration of bowel, ventral wall hernia repair due to obstruction that did not have more than five (5) patients each.

Table 4.2 Distribution of types of surgeries (N=108)

Type of Surgery	**Number**
Appendicectomy	51
Small bowel surgery	16
Gastric surgery	14
Large bowel surgery	9
Adhesiolysis	5
Others abdominal surgeries	13

Nine (9) of the surgeries performed were due to malignant conditions while the remaining 99 were as a result of benign conditions.

Figure 4.1 below shows the history of previous surgery done. Ninety-eight of the participants (91%) had undergone some surgical procedure before this study.

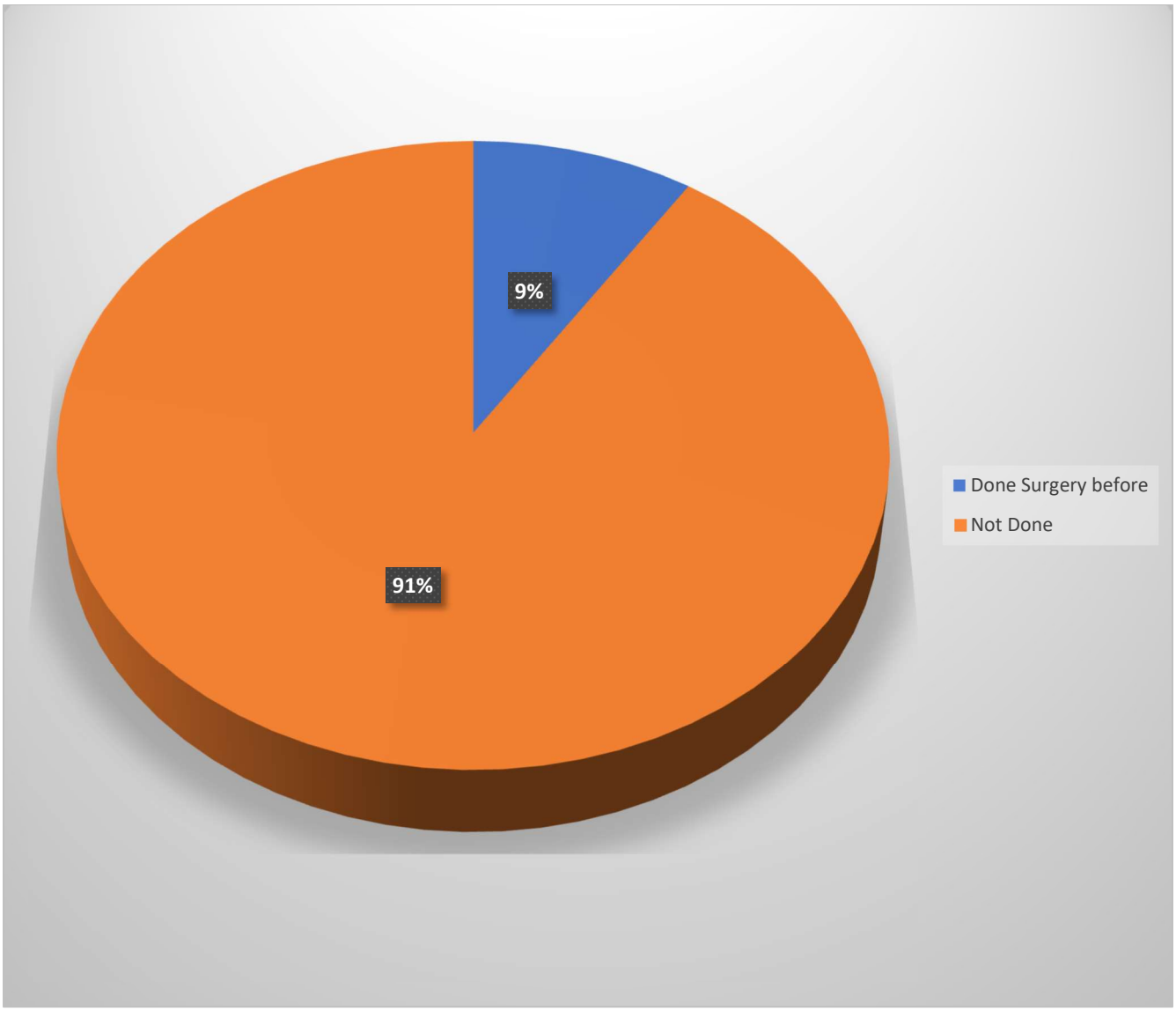

Figure 4.1 Distribution of Previous surgery done

Figure 4.2 shows that 10% of those that had previous surgery before the current one admitted that their pain was poorly managed.

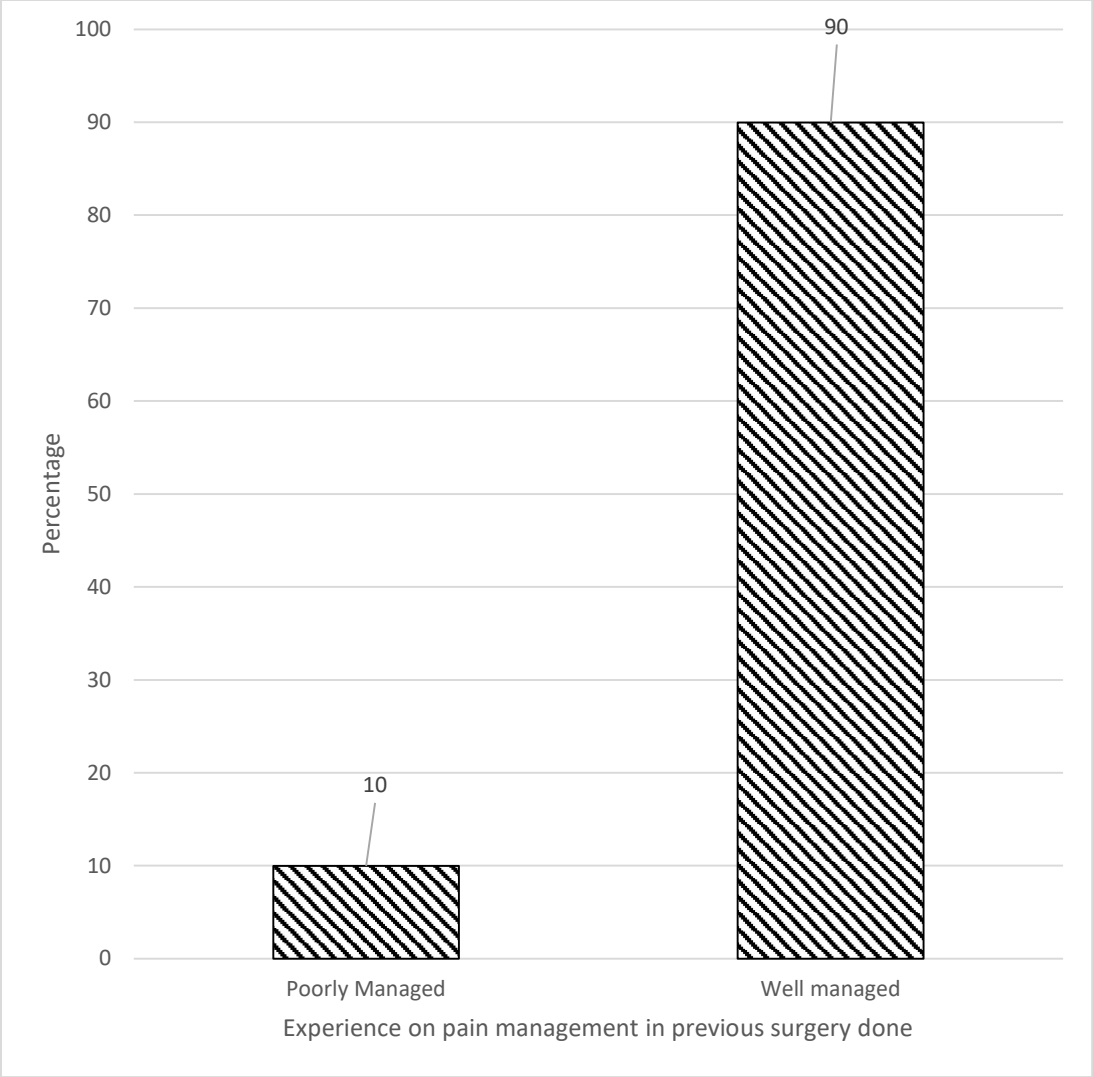

Figure 4.2 Distribution of participants' experience on pain management in previous surgery done

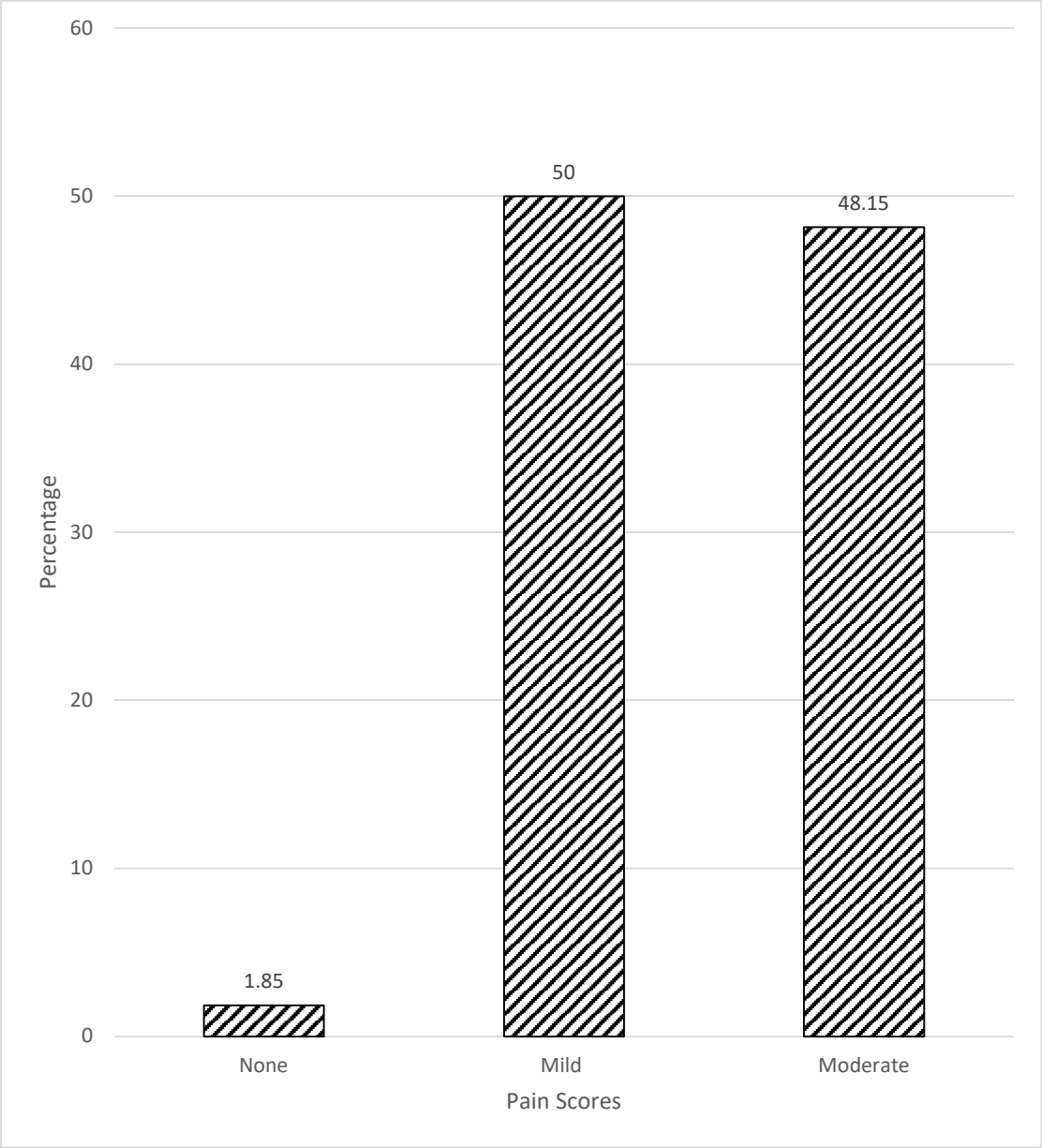

Figure 4.3 Distribution of pain assessment at one hour

Figure 4.4 below shows the distribution of pain assessment score at three hours after first dose of analgesia

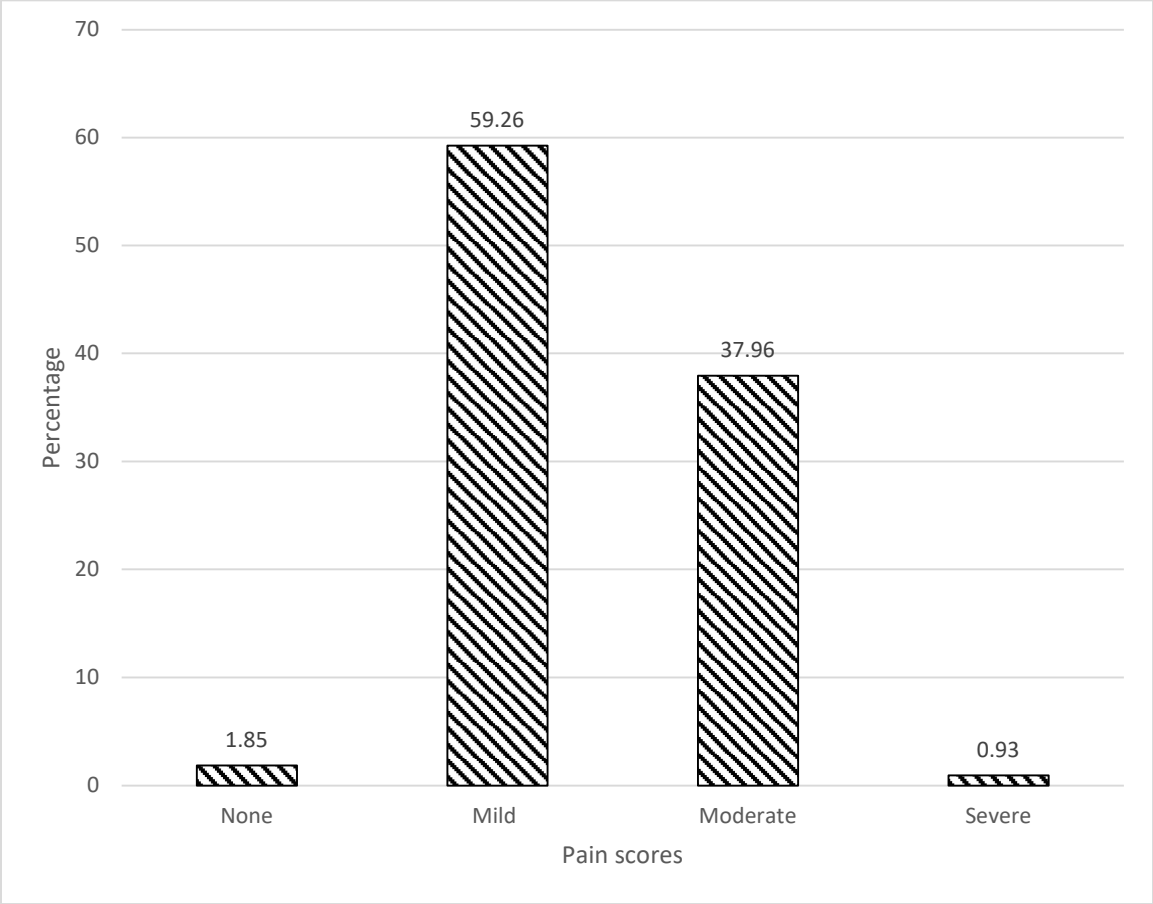

Figure 4.4 Distribution of pain assessment at three hours

Figure 4.5 below shows the distribution of pain assessment score at six hours after first dose of analgesia.

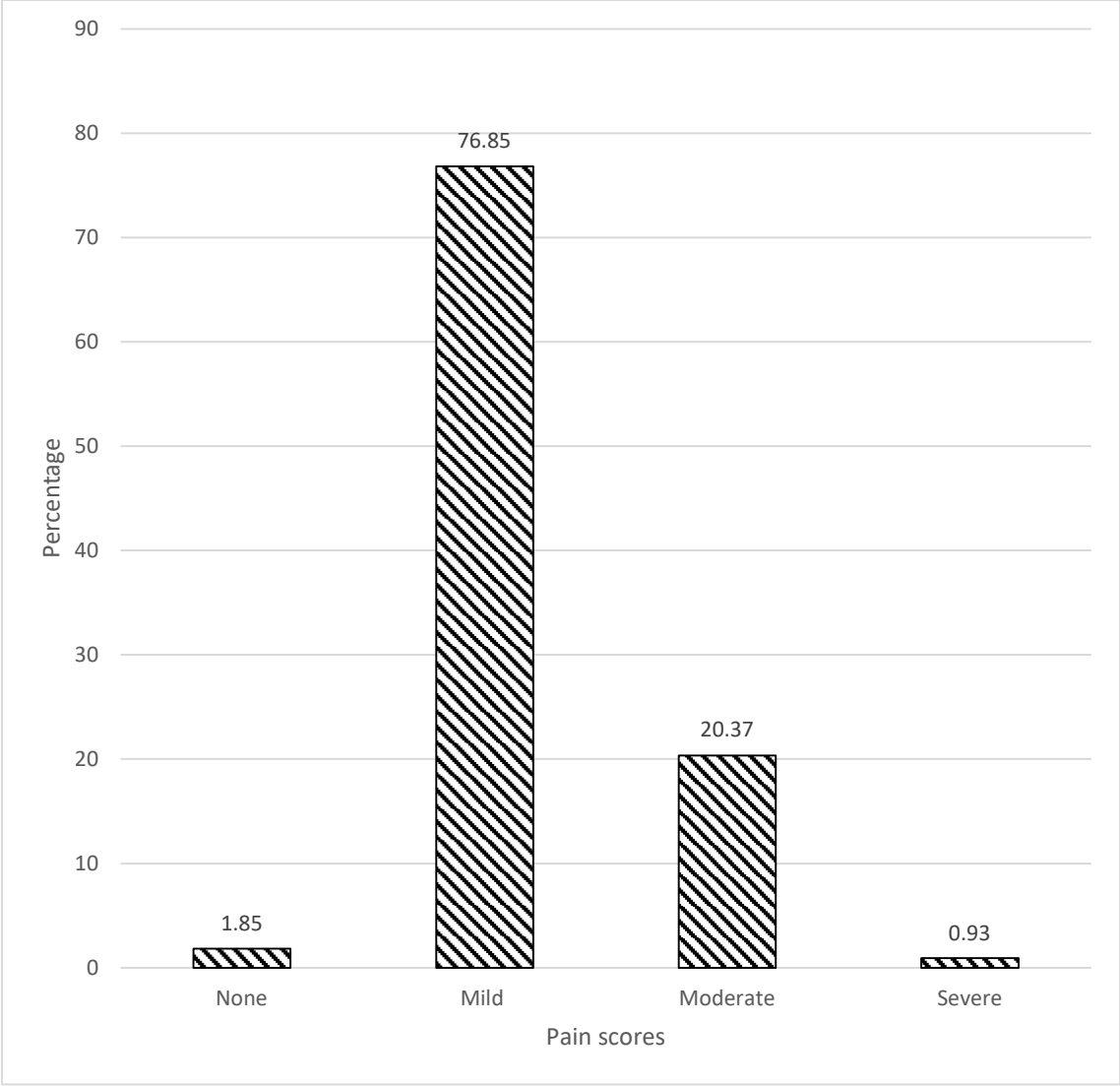

Figure 4.5 Distribution of pain assessment at six hours

Figure 4.6 below shows the distribution of pain assessment score at twelve hours after administration of the first dose of analgesia.

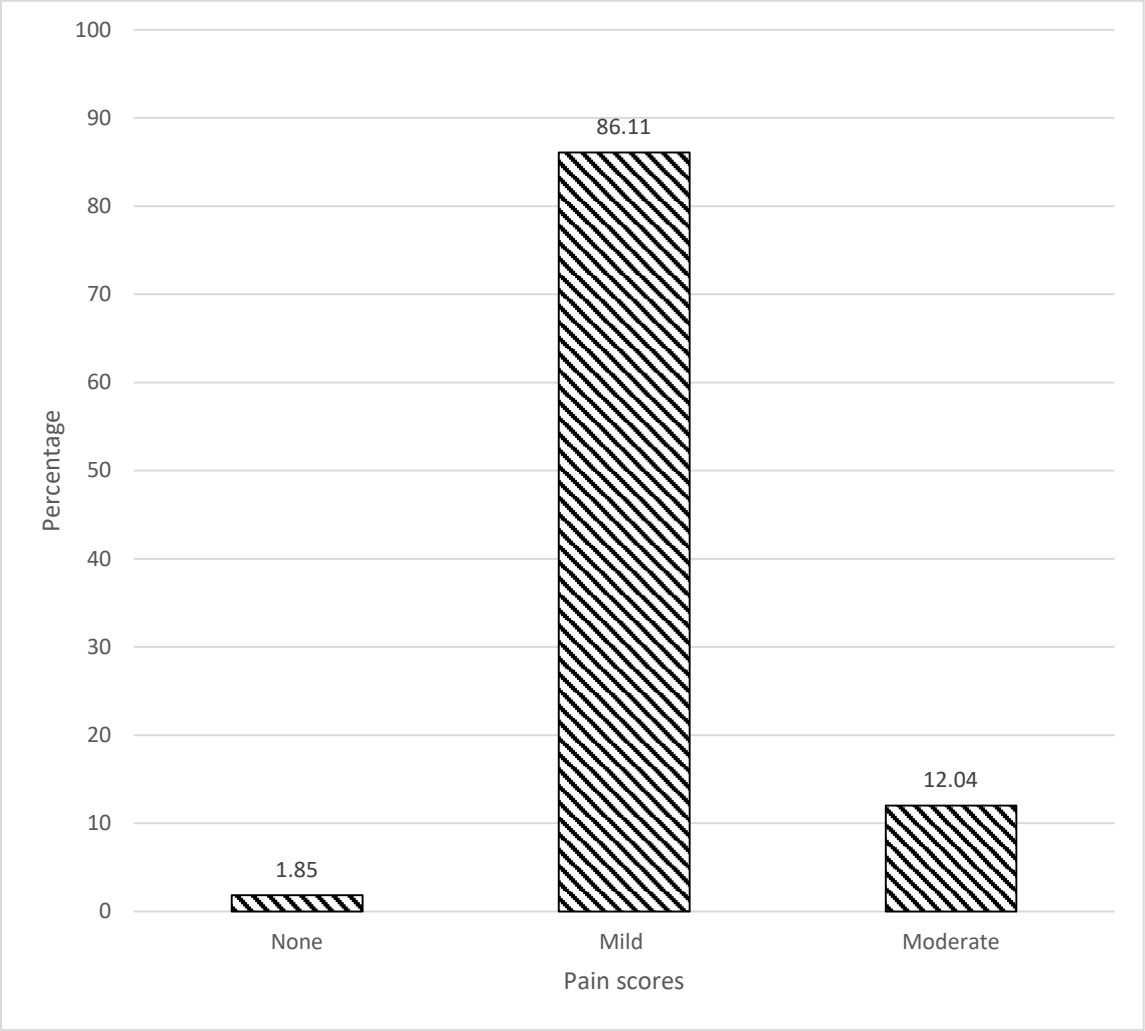

Figure 4.6 Distribution of pain assessment at twelve hours

Figure 4.7 below shows the distribution of pain assessment score at twenty-four hours after the administration of the first dose of analgesia.

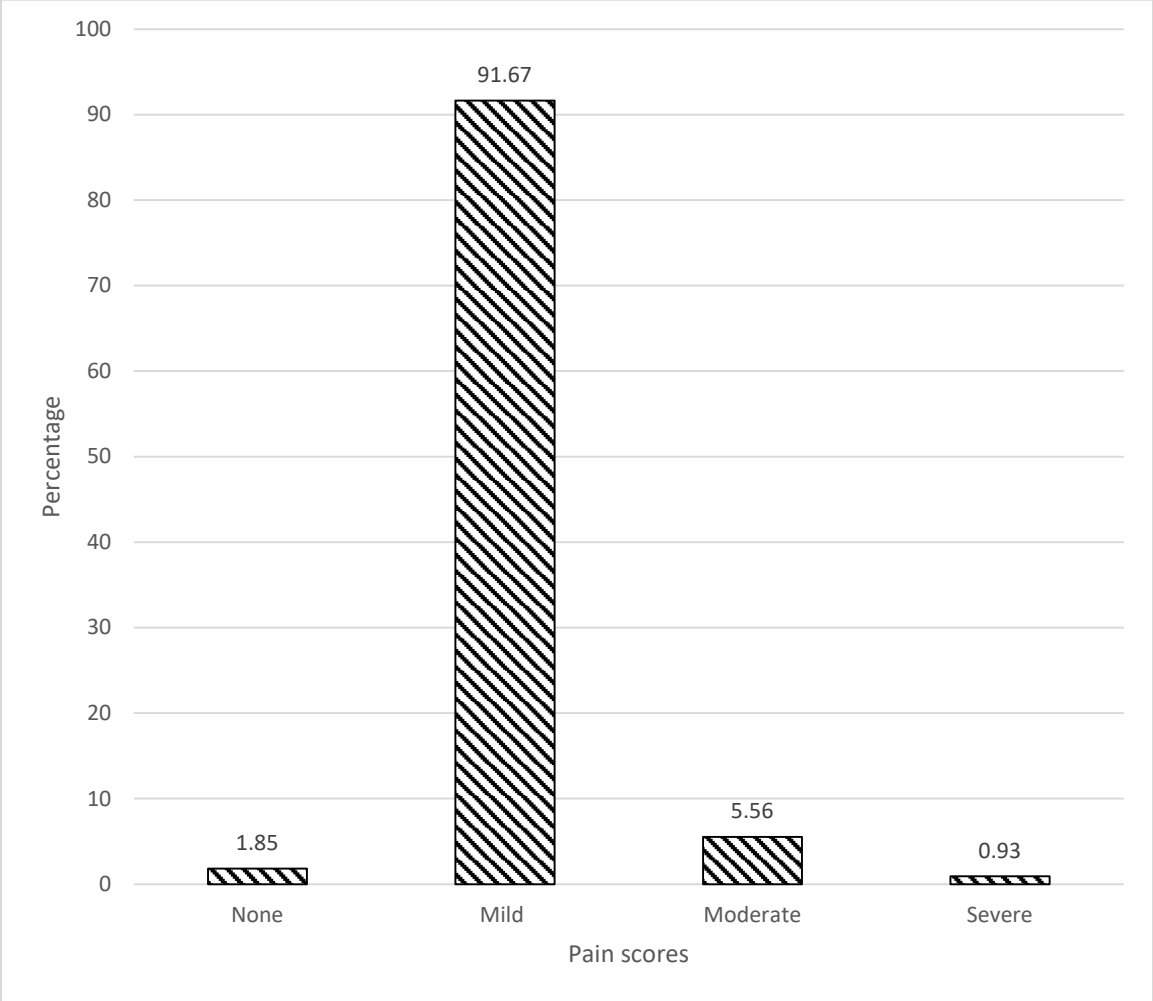

Figure 4.7 Distribution of pain assessment at twenty-four hours

Table 4.3 below shows the distribution between the two groups and the mean pain scores with minimum and maximum scores recorded.

Table 4.3 Distribution of Mean Pain Scores in the two groups

Variable	Mean pain score (± SD)	Minimum	Maximum	P value
Pain Score at one hour				0.68
Morphine	3.35 (1.01)	0	5	
Morphine and Paracetamol	3.66 (0.86)	2	6	
Pain Score at three hours				0.72
Morphine	3.01 (1.12)	0	6	
Morphine and Paracetamol	3.35 (1.08)	2	7	
Pain Score at six hours				0.02*
Morphine	2.38 (0.87)	0	5	
Morphine and Paracetamol	3 (1.22)	1	7	
Pain Score at twelve hours				0.002*
Morphine	2.25 (0.73)	0	4	
Morphine and Paracetamol	2.6 (1.07)	1	6	
Pain Score at twenty-four hours				0.001*
Morphine	1.92 (0.63)	0	3	
Morphine and Paracetamol	2.44 (1.11)	1	7	

Twelve of the participants at different times of the assessment received injection diclofenac as rescue analgesia because of pain score of at least four (4) when they did not have pain medication due or receiving it at the time of assessment. Seven (7) of them were in the bimodal group and the remainder in the unimodal group.

Chi-Square test was done to assess if there was any relationship between the administered analgesic (Morphine and Morphine plus Paracetamol) and socio-demographic characteristics. There was a statistically significant relationship between age, marital status, and occupational status with groups P values (0.001), (0.002), and (0.023) respectively. However, there was no statistically significant relationship between gender, educational status, and ethnicity with groups (Table 4.4).

Non-parametric statistical tests were used accordingly. Kruskal–Wallis test was used to test the differences in the pain scores and demographics. From Tables 4.4, the mean pain score at 1 hour after the first dose of postoperative analgesic given was 3.50 (0.95). There was a significant difference in pain scores (at 1, 3 6, 12, and 24 hours after the first dose of postoperative analgesic was given) between age groups of the patients, educational level and occupational status. Patients aged between 30 to 59 years had higher mean pain scores than those aged less than 30 years and at least 60 years ($P < 0.05$).

Table 4.4 Demographic characteristics of the study patients with differences in Pain Scores and timing of pain assessment (N = 108)

Variables	PAS 1hour		PAS 3 hour		PAS 6 hours	
	Mean (SD)	P value	Mean (SD)	P value	Mean (SD)	P value
Age group (Years)		0.4963		0.674		**0.01***
Less than 30years	3.47 (0.92)		3.12 (1.19)		2.39 (1.04)	
30-59years	3.58 (0.89)		3.25 (1.02)		2.95 (1.14)	
60 years and above	3.3 (1.30)		3.16 (1.19)		2.83 (0.93)	
Gender		0.0831		0.452		0.08
Male	3.41 (0.99)		3.13 (1.18)		2.59 (1.10)	
Female	3.77 (0.75)		3.33 (0.87)		3 (1.07)	
Educational status		**0.02***		**0.001***		**0.005***
None	4 (0.89)		3.63 (0.80)		3.18 (0.98)	
JSS/JHS	3.7 (0.59)		3.86 (0.83)		3.13 (0.74)	
SSS/SHS	3.4 (1.02)		2.91 (1.16)		2.60 (1.18)	
Tertiary	3 (0.63)		3.54 (0.68)		2.18 (0.75)	
Marital status		0.7622		0.162		0.069
Single	3.47 (0.90)		3.08 (1.07)		2.49 (1.03)	
Married	3.48 (0.96)		3.2 (1.14)		2.84 (1.14)	
Co-habitation	3.66 (1.15)		4.3 (0.57)		3.33 (1.15)	
Widowed	4.33 (1.52)		3.66 (1.52)		3.66 (1.15)	
Occupational status		**0.02***		0.063		0.064
Civil Servant	3.14 (0.37)		3.85 (0.37)		2.28 (0.75)	
Farmer	3.69 (6.30)		2.92 (0.95)		2.69 (0.94)	
Retired	2		2		2	
Self-Employed	3.71 (1.04)		3.40 (1.26)		3.04 (1.24)	
Student	3.52 (0.62)		3 (0.93)		2.23 (0.66)	
Unemployed	3.29 (1.10)		3 (1.07)		2.59 (1.15)	
Religion		0.1323		0.270		0.072
Christianity	3.49 (0.96)		3.16 (1.11)		2.66 (1.10)	
Islam	4		3.75 (0.95)		3.5 (1.0)	
Ethnicity		0.6809		0.977		0.480
Akan	3.5 (0.89)		3.20 (1.09)		2.69 (1.09)	
Ewe	3		3		2	
Mole-Dagbani	3.44 (1.50)		3 (1.41)		2.77 (1.30)	

Variables	PAS 12 hours		PAS 24 hours	
	Mean (SD)	P value	Mean (SD)	P value

Age group (Years)		0.087		**0.03***
Less than 30years	2.22 (0.85)		2 (0.94)	
30-59years	2.58 (0.98)		2.37 (0.89)	
60 years and above	2.66 (0.88)		2.16 (1.02)	
Gender		0.27		**0.03***
Male	2.37 (0.92)		2.33 (0.55)	
Female	2.62 (0.92)		2.45 (0.52)	
Educational status		0.08		0.121
None	2.72 (0.78)		2.45 (0.52)	
JSS_JHS	2.73 (0.79)		2.4 (0.73)	
SSS_SHS	2.35 (1.00)		2.12 (1.06)	
Tertiary	2.27 (0.64)		2 (0.44)	
Marital status		**0.01***		0.079
Single	2.31 (0.92)		2.10 (1.01)	
Married	2.46 (0.89)		2.2 (0.84)	
Co-habitation	3 (1.0)		3 (1.0)	
Widowed	3.66 (0.57)		2.66 (0.57)	
Occupational status		0.069		**0.007***
Civil Servant	2.42 (0.53)		2	
Farmer	2.38 (0.65)		2.38 (0.65)	
Retired	2		1	
Self-Employed	2.64 (1.03)		2.30 (1.11)	
Student	1.94 (0.42)		1.70 (0.68)	
Unemployed	2.48 (1.12)		2.33 (0.91)	
Religion		0.925		0.485
Christianity	2.42 (0.91)		2.16 (0.91)	
Islam	2.75 (1.5)		2.75 (1.5)	
Ethnicity		0.817		0.979
Akan	2.44 (0.89)		2.18 (0.91)	
Ewe	2		2	
Mole-Dagbani	2.33 (1.32)		2.22 (1.30)	

As indicated in Table 4.5, there was no statistical difference between the means of the length of incision and pain scores except pain score at one hour (P-value 0.05). Moreover,

participants with higher pain score had a longer length of incision whiles those with mild pain scores had a shorter length of incision.

Table 4.5 Pain Scores of the study patients with differences in Length of Incision (N = 108)

Variables	Mean Length of incision in cm (± SD)	P value	Chi square
Pain Score after one hour		**0.05***	5.86
None	15		
Mild	12.16 (5.62)		
Moderate	14.15 (4.81)		
Pain Score after three hours		0.285	3.791
None	15		
Mild	12.95 (5.82)		
Moderate	13.14 (4.13)		
Severe	25		
Pain Score after six hours		0.247	4.137
None	15		
Mild	12.91 (5.55)		
Moderate	13.45 (3.67)		
Severe	25		
Pain Score after twelve hours		0.330	2.214
None	15		
Mild	12.90 (5.31)		
Moderate	14.84 (5.19)		
Severe	-		
Pain Score after twenty-four hours		0.157	5.199
None	15		
Mild	12.90 (5.34)		
Moderate	15		
Severe	25		

Table 4.6 showed the mean length of incision between the two groups comparing patients who had appendicectomy with incision through the McBurney's point as well as those who had a midline incision for laparotomy for other pathologies. There is no significant difference statistically in the length of incision between the two groups.

Table 4.6 Mean length of incision among the two groups in cm (N = 108)

Variable	**Mean Length of incision (cm)**		**P value**
	Morphine	**Morphine + paracetamol**	
Appendicectomy	6.44	7.90	0.485
Laparotomy	13.24	14.89	0.092

Table 4.7 below shows the length of stay of participants for each of the groups. The total number of participants assessed for the length of stay as indicated on the table is 103 instead of the total 108. This is because five (5) of the participants died before they were discharged. Thus, the number (N) being 103.

Table 4.7 Groups of study patients with differences in Length of Stay (Days) (N = 103)

Variable	Mean length of stay in days (± SD)	P value	Chi square
Groups		**0.33**	**0.931**
Morphine	5.70 (3.14)		
Morphine and Paracetamol	6.69 (4.55)		

Table 4.8 shows the relationship between the analgesic administered and the time of first bowel movement (in hours), and time of ambulation (hours). This excluded five (5) participants; three (3) from morphine alone group and two (2) from morphine and paracetamol group who died before bowel movement could be ascertained. There was statistical significance between the analgesic given and the time of bowel movement (P-value=0.03).

Table 4.8 Analgesic administered and the time of first bowel movement

	Morphine	Morphine and Paracetamol	X^2	P-value
Time of first bowel movement			**7.03**	**0.03***
Less than 24hours	4 (7.84)	0 (0.00)		
24 hours-72hours	33 (64.71)	28 (53.85)		
Above 72hours	14 (27.45)	24 (46.15)		

Table 4.9 shows the relationship between the analgesic administered and the time of ambulation (hours). There was statistical significance between the analgesic given and the time of ambulation after surgery (P-value=0.01).

Table 4.9 Analgesic administered and the time of ambulation.

	Morphine	Morphine and paracetamol	X^2	P-value
Time of ambulation after surgery			**11.77**	**0.01***
Less than 24hours	4 (7.84)	2 (3.85)		
24 hours-48hours	26 (50.98)	15 (28.85)		
49hours-96hours	16 (31.37)	16 (30.77)		
Above 96hours	5 (9.80)	19 (36.54)		

Table 4.10 shows the distribution of nausea and vomiting with the administered analgesic. Majority of those who had nausea and vomiting were in the morphine only group.

Table 4.10 Distribution of Groups and nausea and vomiting (Colum %)

Variable	Morphine N=14 (%)	Morphine and Paracetamol N=3 (%)	P value	Chi square
			0.02*	7.825
Side Effects				
Nausea only	11 (78.57)	1 (33.33)		
Nausea and vomiting	2 (14.29)	0		
Vomiting only	1 (7.14)	2 (66.67)		

No patient developed DVT. Only one participant, who was in the morphine plus paracetamol group, was diagnosed with pneumonia.

CHAPTER FIVE

DISCUSSION

5.1 Demography

The data from this study shows that a small proportion of the participants were beyond 60 years old, which is a reflection of the youthful population of the country. The elderly population within the study was evenly distributed between the two arms. Participants above 60 years on average reported less pain compared to those between 30-60 years, despite receiving half the dose of morphine for treatment of their postoperative pain. Generally, elderly patients may be expected to report less postoperative pain similar to other forms of acute pain in general. The perception of pain in older people can be affected by physiological changes that occur with aging.[156] Having ruled out dementia by excluding all patients with a likely neuropsychiatric condition that could affect pain perception from this study, it is likely that physiological changes that go with aging could have contributed to the relatively low pain scores. Further, elderly patients may suffer from a couple of conditions like musculoskeletal pain and may have chronic background pain. This could make them accept pain as a normal part of aging and are more likely to tolerate pain. There is also the possibility of actual adequate pain alleviation with the analgesics they received.

There was a statistically significant difference between the mean ages of the two groups (P=0.001) with the mean age for the morphine alone group being 31.18 years and 39.83 years for the paracetamol plus morphine group. The mean ages for the two groups were still lower than forty years with even distribution of the ages above 60 years. With the equal distribution of the elderly population among the two groups the possible effect of aging on the response to pain would have been equal among the two groups. In a similar study on postoperative pain by Beloeil *et al*, males formed 64% of the study population which is similar to the distribution of the sexes in this study, of which males formed a 75% of the participants.[157] There was no statistical difference between the sex distribution among the two groups in this study.

The mean pain scores in males were generally lower in males than in females. This was even statistically significant at 12 and 24hours post-administration of the first analgesic dose. This finding is consistent with findings from other authors that found women to be

more sensitive to pain than men and are thus at risk of clinical pain.[158] Women are thus expected to express relatively higher postoperative pain as on the assessment score. Further to this, 98 out of 108 (90.7%) of the study participants were of Akan origin. Among the Akans of Ghana, males are expected to bear pain relatively better than females. Thus, males within the Akan community are not expected to outwardly express pain but to bear it. This may also have accounted for the lower mean pain assessment score in the male participants in this study.

The majority of the respondents were Akans and a few of them were Mole-Dagbanis because of the setting of the study. The catchment area of KATH predominantly is made up of Akan communities even though some referrals come from the Northern part of the country. Among the Akans of Ghana, a male is expected to tolerate pain and not to outwardly express it. Pain tolerance can be affected and to a larger extent be influenced by culture or ethnicity.[36,41] The people from Northern Ghana are generally regarded as hardy in terms of pain tolerance.[41] They are therefore likely to bear pain much better relative to those of Akan descent.

The finding that there was no statistical relationship between ethnicity and pain score is inconsistent with findings from certain studies that suggest that pain perception is influenced by an individual's culture and ethnicity.[36,41] This is may possibly be because a larger proportion of participants were Akans and only one (1) was an Ewe and nine (9) were Mole-Dagbanis. The smaller numbers of the other tribes in the study, likely due to the study setting, might not have been enough to statistically correlate between ethnicity and response to pain in this study. The other possibility is that such persons might have lived among the Akans for a longer period and adapted to similar pain perceptions as those in the communities within which they live.[44]

A student was more likely to have mild pain at 12 and 24 hours post-administration of the first dose of analgesia they showed mild pain at these pain assessment hours with a p-value of 0.007. It is however not clear from this current study why a student was more likely to have recorded low pain scores at those periods.

5.2 Postoperative pain

Postoperative pain is severe in the first six (6) hours of surgical procedure.[3] It is therefore expected that most patients should have maximal pain when pain is not adequately managed within the first six (6) hours after a major surgery like abdominal surgery. That may explain why some participants had severe pain at three hours as a few of them may start having the effect of their analgesia having gone beyond its maximum effect and may begin to wear of gradually with about 0.93% of them having severe pain at the time of assessment. About 0.93% of the participants at 6 hours of assessment had severe pain. This could be because the effects of paracetamol or morphine at this point expected had worn off after the initial administration. Participants at this point of pain assessment would thus be about receiving the next dose of medication or would have received the medication the medication and yet to achieve the full effect of it. As a result, patients with low pain threshold were then likely to express more pain at that point of assessment. Similarly, at 24 hours, patients would be due to receive the last dose of the first day's prescription of analgesia. Therefore, at the time of assessment at 24 hours point, it would be 24 hours after receiving the first dose of analgesia or they would have just received medication and yet to get its full effect, thus, about 0.93 % of the participants having severe pain at this point of assessment.

A greater number of the participants had no prior surgery before this study. Of the minority that had undergone some form of a surgical procedure previously, 90% believed their pain was well managed. This finding was likely to indicate that previous bad experience of surgical pain management was not likely to have affected the perception of pain by participants in this study.

Half of the participants of this study had mild pain upon the assessment of pain at the first hour after receiving the first dose of analgesic at the recovery ward, irrespective of the analgesic received. This can be because each group had received at least i.m. morphine which has a peak absorption at 10-20 minutes with its peak action for analgesia at 1-2 hours after administration.[138] Thus, the possibility of peak analgesia at the first hour of assessment resulting in low pain scores at that time. Less than half of the participants (38.89%) had moderate or severe pain at the 3 hours assessment point. This is consistent with findings

reported by Askar et al that by the first hour, the analgesic effect of morphine had started and reached substantial levels at 4 hours postoperatively.[159] Similar to this finding is what Svensson et al reported. In their study, 39% of patients who had undergone major elective surgical procedures had moderate or severe pain at 4 hours postoperatively.[160]

At the one (1) hour pain assessment point, patients with a longer mean length of incision (15 cm) had no pain. However, severe pain at 3, 12 and 24 hours assessment points was associated with a mean incision length of 25cm even though there was no statistical significance. Participants who received morphine only on average had a length of incision that was statistically significant to that of the bimodal group. This could have influenced the extent of pain perceived by participants in each group. The extent of nociception stimulation and action through tissue destruction at the incision may have an effect on pain perceived.[24] Results from studies looking at the correlation between the length of incision and postoperative pain have been variable. Nicholls-Dempsey and Abenhaim reported no impact of length of incision on postoperative pain in women who had caesarean sections in the first 48 hours after surgery.[36] Patients who get relatively shorter incisions may need some more tissue stretching and retraction to aid in exposure which could explain why within the first hour mild and moderate pain is associated with lower means of incisional length and compared to those with no pain.

5.3 Response to morphine

The mean pain assessment score using the NRS at one hour of the administration of the first dose of analgesic was 3.35 and 1.92 in 24 hours, indicating that there was mild pain on average for participants in this group. Some participants in this group had reported mild pain at all the intervals of assessment after administration of the first dose of analgesia postoperatively. This finding is consistent with that of other authors regarding the effect of using morphine alone in managing postoperative pain despite the recommendations of using a multimodal approach.[134] However, with some participants having a mean NRS score of above 4, they had to be given rescue analgesia that was decided by the attending

physician. In a study comparing paracetamol and morphine in elective surgery, Alimian et al reported that some of the participants who received morphine only in their study had to be given rescue analgesia at a point even though the required cumulative dose was less compared to their compatriots in the paracetamol only arm.[135]

Patients who received morphine alone had a relatively lower mean pain score as compared to those that received morphine with paracetamol. This lower mean pain scores in the morphine alone group may be explained by the fact that this group also on average had a lower mean length of incision though not statistically significant. The noxious stimuli by nociceptors may correspond with the extent of tissue damage from the incision made. This may be because a shorter incision is likely to cause less tissue damage and hence not as much stimuli to the nociceptors. This may then cause relatively less pain that may then have been controlled with the administration of the opioid-alone analgesic.

Some studies have found morphine-alone to be comparable in managing postoperative pain just as multi-modal approach with morphine. In a double-blinded randomised trial, Cepeda et al found a similar postoperative pain intensity in patients that received morphine-alone as compared to those who received both morphine and ketorolac.[161]

5.4 Response to morphine and paracetamol

The administration of another analgesic together with morphine usually is aimed at providing better pain control than the individual agents will do. This is because of the expected additive or synergistic effects of these combinations.

The minimum NRS score recorded for those in the bimodal group was 1 and the maximum was 7, with a mean NRS score below 4 throughout the assessment hours of this study. This indicates a good pain control with just seven participants in this group requiring rescue analgesia at a point within 24 hours of surgery. Bandey and Signh concluded that paracetamol was effective for postoperative pain management as compared to tramadol, an opioid. Therefore, combining it with an opioid could give a synergistic effect and give adequate pain control as seen. Similarly, Alimian et al found paracetamol to be as effective as morphine in managing postoperative pain, albeit, after 8 hours.

Synergism in pain management is explored by clinicians in giving optimum pain management to patients. This expected additive or a synergistic effect is not always achieved. While the combination of morphine and NSAIDs has shown synergy, the combination of morphine and nefopam or tramadol shows an infradditive effect.[41] Several studies have suggested the additive effect in combining morphine and paracetamol. An additive effect between morphine and paracetamol was demonstrated by Zeidan et al.[93] Similarly, Maund et al found a reduction in the requirement for morphine in patients on PCA when combined with i.v. paracetamol.[119]

Considering the possible additive effect of the combination of paracetamol and morphine in managing postoperative pain in emergency abdominal surgery, it would be expected to provide better pain control than morphine alone. The findings from this study however suggested otherwise. The mean pain scores at all points (pain assessment times) in pain assessment for the group that received morphine alone were comparatively lower than those that received a combination of morphine and paracetamol. Adeniji et al reported superiority of bimodal analgesia over unimodal analgesia. They found the combination of parenteral pentazocine or tramadol with piroxicam to be better at pain control than the unimodal mode for these analgesics in post-caesarean section pain management.[8] Further, Alimian et al recommended the use of paracetamol and morphine for postoperative pain management to abate opioid-related complications in postoperative pain management.[135] One possible explanation would be the timing of the combination of paracetamol and morphine. If the administration of the drugs was done such that paracetamol is given first, probably, at the time of assessment the effect of the morphine might not have been fully attained. It is also possible that the addition of the paracetamol to morphine for postoperative pain management did not give an additive or synergistic effect as might be expected in a multimodal form of analgesia. In a meta-analysis of some randomised controlled trials, the administration of i.v. paracetamol to morphine was noted to have significantly reduced morphine consumption by patients but failed to reduce morphine-related side effects.[162] A similar finding could therefore have been that obtained in this study.

5.5 Administered analgesic and length of stay

Provision of optimal analgesia does not only relieve the patient of discomfort from surgery but also affects the length of hospital stay.[163] A shorter length of hospital stay for the postoperative patient has received a critical look in recent times because of its relation to bed turnover and the overall cost of management. The ripple effects of this can trigger a backlog causing the artificial non-availability of beds in most emergency departments in some hospitals in the country. Good postoperative pain management can shorten the length of hospital stay for patients.[27]

The current study showed no statistical difference between the length of stay in the hospital after an emergency abdominal surgery and whether a participant received a unimodal (morphine only) or bimodal (morphine and paracetamol) analgesia. This finding is consistent with a Cochrane review by Guay et al which showed no difference in the length of stay between patients who received epidural analgesia and those who received i.v. opioids.[164] The length of stay for participants in this study who received morphine alone was shorter as opposed to the findings by De Roo *et al* who had a mean length of stay of 5.96 days for patients who received opioid alone in their study. Some authors have linked a shorter hospital stay to multimodal analgesia. De Roo *et al* suggested an earlier recovery and a shorter hospital stay with a multimodal approach to postoperative pain management.[165] However, the number of days for the mean length of stay was closer to the 5.70 days obtained in the current study.

5.6 Analgesic administered and time of first bowel movement

Postoperative ileus has been recognized as one of the significant side effects of opioid analgesics.[27,166] This occurs when there is paralysis of the musculature of the intestines beyond 72 hours after surgery. Apart from the ileus that may be induced by the handling of bowel in abdominal surgery, the use of opioid analgesics has been linked with postoperative ileus, which sometimes just like the fear of addiction precludes its use by some clinicians.[30,112] The findings in this study suggest an early bowel movement in the morphine alone group as opposed to morphine with paracetamol group (P-value=0.03).

While none of those who received morphine with paracetamol had moved their bowel within 24 hours, 4 (7.84%) of those who received morphine only had moved their bowels within that same period. Nearly half of those who received bimodal analgesia moved their bowels after 72 hours. This is somewhat inconsistent with reports that administration of additional analgesia will not only improve upon pain score but will also offset some of the undesirable side effects of opioid administration.[167] From this study, over a quarter of patients who received morphine only for postoperative pain management (27.45 %) and close to half of those who received morphine with paracetamol (46.15%), had their first bowel movement beyond 72 hours after surgery.

In a meta-analysis of randomized controlled trials, Remy et al stated that the side effects of morphine are not significantly reduced by the administration of 1g qid of i.v. paracetamol as this does not have up to 10mg sparing effect of morphine consumption in 24 hours period.[162] In this current study, patients who received a bimodal analgesia received 1g qid of i.v. paracetamol. Relating this to the aforementioned findings from Remy et al, it can be expected that patients in the combination group may not have had the opioid-sparing effects from the paracetamol addition. Hence, there was no impact on the opioid effect on the bowel in this group as might have been possibly expected.

In another study, Orderda et al stated that 26% of patients who receive opioids for postoperative pain develop constipation in the fortnight after the surgery.[168] Of the patients that undergo abdominal surgeries, 20% develop postoperative ileus.[112] The resultant ileus from the opioid administration compounds that from the effect of handling of the bowel during surgery. This does not only result in abdominal discomfort but the resultant delay in the intestinal content propulsion affects the starting of feeding and upsets the absorption of oral medications.

5.7 Analgesic administered and time of ambulation

Ambulation after surgery improves recovery and reduces the complication associated with immobility. When patients are in pain after surgery it significantly limits their mobility.[166] The use of narcotics for postoperative pain control has been associated with a patient not likely to ambulate soon after surgery.[169] From this study, the number of participants that

had mobilised out of bed within 24 hours in the morphine alone group was twice the number in the morphine plus paracetamol group (P-value=0.01). About half the number in the unimodal group having got out of bed by 48 hours as compared to about a quarter in the bimodal group, it was noted that those in the unimodal group mobilised early (P-value=0.01). This finding contradicts what has been reported from some studies for multimodal analgesia. Further, patients who received morphine alone had a lower mean pain assessment score. It is thus not unexpected that with less pain, they mobilised relatively earlier than their compatriots in the bimodal group did.

In this study, participants who were in the bimodal analgesic group on average had longer incisions as compared to those in the morphine alone group. This could have been because such patients generally needed a wider incision for better exploration of the abdomen at surgery because of the extent of intraabdominal disease. This could mean such patients generally would have been relatively sicker than their counterparts at the time of surgery and less likely to mobilise early after surgery irrespective of the relief of pain.

5.8 Nausea and Vomiting

Nausea and vomiting have long been recognized as side effects of opioids and in some cases have influenced the decision to use opioids for pain management in some instances. In this study, 16% of participants had nausea, vomiting, or both nausea and vomiting. This proportion of participants presenting with nausea and/or vomiting is lower than what has been reported by some authors for patients who were given epidural morphine for postoperative pain management. Tzeng et al reported that 52% of patients reported postoperative nausea and vomiting (PONV) after receiving epidural morphine for postoperative pain treatment and in some series, 30-56% of participants had nausea and vomiting.[170]

This study showed that patients receiving morphine only for postoperative pain management were likely to have nausea or, nausea and vomiting (P=0.02). This finding may be explained by the fact that, combining paracetamol with morphine reduces the well-known side effects that may be produced by morphine alone. Paracetamol has some

antiemetic effect.[183] However, this assertion has not also been confirmed from several studies that had combined these two analgesics and looked at the opioid-related side effects.[41] A metabolite of paracetamol, AM404, has antiemetic effect through its inhibition of anandamide reuptake. High levels of anandamide are said to decrease the incidence of emesis.[124] However, the antiemesis effect of paracetamol is even more pronounced when given preoperatively than when the pain starts.[124]

In contrast to the findings from this study, some systematic reviews and mixed treatment comparison analyses did not see any effect of i.v. paracetamol on reducing postoperative nausea and vomiting when administered together with morphine.[119,124] Apfel et al reports that systematic reviews and meta-analysis from previous studies showed that opioid requirements were reduced with the use of acetaminophen for postoperative pain management. This, however, did not translate to a reduction in postoperative nausea and vomiting.

Pain has been elucidated as one of the risk factors for postoperative nausea and vomiting.[124] The reduction of the level of pain by additional analgesia to morphine in the multimodal group is expected to reduce pain and hence the risk for postoperative nausea and vomiting. However, in this study, the mean pain scores were relatively high in the group with bimodal analgesia than in those who received only morphine.

5.9 Analgesic administered and complications of immobility after surgery

This study also assessed complications that may be associated with prolonged immobility after surgery vis-a-vis the administered analgesia. There was no association between the administered analgesic administered and the development of DVT (diagnosed clinically) as none of the participants developed DVT. Early mobilization is key in preventing DVT.[171] This may be achieved by adequate pain relief to prevent unnecessarily prolonged stay in bed after surgery. The findings in the current study showed an average mild pain score at most of the assessment hours for the two groups. This indicates relatively adequate pain relief amongst the two groups that could have positively influenced early mobilization by the participants. Hence the possibility of no clinically diagnosed DVT among the

participants of either group. This, however, may not fully be responsible for no DVT among the participants since some of them might have been put on some other forms of DVT prophylaxis such as graduated TED stocking and pharmacological agents like heparin.

The finding of no DVT diagnosis from this study is in contrast to a finding of 5% in Uganda among patients after major abdominal surgery.[172] In that study, however, a doppler ultrasound was done for the patients on days 7 and 21 after surgery. The diagnosis of DVT in this current study was clinical and was up to the day the patient was discharged (mean length of stay of 5.7 days), hence, the possibility of missing some subclinical DVT could have occurred.

Further, only one of the participants in this study was diagnosed with pneumonia postoperatively. When pain is not adequately managed, especially after an upper midline abdominal incision, there is hypoventilation by the patient in an attempt to minimize abdominal movement with ventilation to reduce pain. This hypoventilation causes a decrease in vital capacity and alveolar ventilation leading to atelectasis and consequently causing pneumonia.[171] The incidence of postoperative pneumonia has been reported to be 5% in a study in China.[173] That study however did not directly relate the risks to the management of postoperative pain but other risk factors like diabetes mellitus, smoking, and cardiovascular diseases.

Wu et al have drawn an association between poor postoperative pain management and pneumonia.[21] The current study had only one participant diagnosed with pneumonia. This possibly could be that the participants had adequate pain management amongst both groups. They thus did not have to hypoventilate in an attempt to reduce abdominal movement that goes with respiration. Atelectasis may thus be minimal with less possibility of developing pneumonia as a result of hypoventilation from pain. Similarly, patients will mobilise out of bed early with less possibility of orthostatic pneumonia developing. The study however did not consider the possible effect of metabolic diseases, ASA state, diagnosis, incisional site and smoking on developing pneumonia after abdominal surgery.

CHAPTER SIX
CONCLUSION AND RECOMMENDATION

6.1 Conclusion

Receiving morphine alone or morphine with paracetamol provided adequate pain relief after emergency abdominal surgery even though those who received morphine alone had a lower mean pain score.

Whether a patient received morphine alone or morphine with paracetamol did not have any statistical difference in the length of stay.

Time of ambulation after surgery was shorter in those who received only morphine than those who received morphine and paracetamol.

A combination of morphine and paracetamol was less likely to give undesirable opioid side effects like nausea and vomiting. First bowel movement after surgery was earlier in those that received only morphine. Receiving paracetamol with morphine or morphine alone was not associated with developing pneumonia or clinically-diagnosed DVT.

6.2 Limitations

The pain assessment was for up to 24 hours and thus the effect of the pain management beyond this point till the patient was discharged could not be ascertained.

Diagnosis of no DVT was based on clinical findings and not supported by imaging. There could be some subclinical DVT that were missed because no routine imaging was done for participants. The study also did not document DVT prophylaxis (pharmacological and non-pharmacological) given to patients perioperatively.

6.3 Recommendations

Morphine alone or its combination with paracetamol gives adequate postoperative pain control in emergency abdominal surgery with the latter producing less nausea and vomiting.

It is recommended that a study with duration of pain assessment should be up to at least three days and follow up of complications up to 30 days should be carried out to gather wider data for analysis.

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APPENDICES

Appendix: 1 PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

INFORMATION SHEET

Title of Research:

POSTOPERATIVE PAIN MANAGEMENT IN EMERGENCY ABDOMINAL SURGERY: BIMODAL VERSUS UNIMODAL ANALGESIA

Name(s) and affiliation(s) of researcher(s):

This study is being conducted by Dr Frank Enoch Gyamfi of Directorate of Surgery, Komfo Anokye Teaching Hospital

Background:

Postoperative pain management in developing countries, and for that matter Ghana, has been suboptimal. This has largely been influenced by several factors which include tenuous concerns about the patient getting addicted to opioids, perennial unavailability of certain analgesics and patients inability to afford some drugs.

In Ghana, where <40% of the population are enrolled on the National Health Insurance Scheme (NHIS), affordability of some parenteral analgesics may be an issue for some patients. Such patients may not have a regular supply of the prescribed analgesia. This may make post-operative pain management poor.

Strict protocols on managing pain after surgery are not available for all health institutions in Ghana. Even when present, the knowledge of the doctor and the administering nurse on the analgesic may have a profound impact on postoperative pain management.

This study will assess the intensity of pain after patients have been given intravenous paracetamol and intramuscular morphine to assess which of these agents can manage postoperative pain very well

Purpose of research:

The purpose of this study is to compare the efficacy of i.v. paracetamol, i.m. morphine as a unimodal analgesic with bimodal administration of the two drugs in managing postoperative pain in emergency abdominal surgery.

Selection of participants:

The study population consists of patients from 18 to 80 years undergoing emergency abdominal surgery at the main operating theatre of KATH. Participation in the study is voluntary.

Procedure of the research, what shall be required of each participant and approximate total number of participants that would be involved in the research:

We will use lottery to divide participants in this research into 3 groups. One group will receive injection paracetamol after surgery for 2 days. The second group will receive injection morphine for 2 days and the third group will receive both morphine and paracetamol also for 2 days. A pain assessment scale will be used to assess your extent of

pain at regular intervals. If you are in too much pain a doctor will assess you and prescribe additional medication for you as and when necessary.

Neither you nor the staff who will assess you for pain will know the group that you are in and the drug that you have been given.

You will also be assessed for any complications whilst you are on admission. There will be no further follow-up by the research team after you have been discharged. In total 108 people are expected to participate in this study.

Risk(s):

The drugs being used for the study are routine pain medications given after surgery. However, if you have an unknown allergy to any of the drug, it may manifest if given to you. In case on adverse reaction to any of the medications, you will be given to necessary medical attention and withdrawn from the study.

Benefit(s):

There will be no monetary benefits. The goal of the research is to find out if any of the medication or combination is efficacious in treating your post-surgery pain. We hope the medication that you are given will adequately manage your pain. Since this is a research we cannot guarantee this.

Confidentiality:

All information collected in this study will be given code numbers. No name will be recorded. Data collected cannot be linked to you in anyway. No name or identifier will be

used in any publication or reports from this study. However, as part of our responsibility to conduct this research properly, we may allow officials from the Food and Drugs Board and ethics committees to have access to your records.

Voluntariness:

This research is entirely voluntary. Taking part in this study should be out of your own free will. You are not under obligation to do so.

Alternatives to participation:

If you choose not to participate, this will not affect your treatment in this hospital/institution in any way.

Withdrawal from the research:

You may choose to withdraw from the research at anytime without having to explain yourself. You may also choose not to answer any question you find uncomfortable or private).

Consequence of Withdrawal:

There will be no consequence, loss of benefit or care to you if you choose to withdraw from the study. Please note however, that some of the information that may have been obtained from you without identifiers (name etc), before you chose to withdraw, may have been modified or used in analysis reports and publications. These cannot be removed

anymore. We do promise to make good faith effort to comply with your wishes as much as practicable.

Costs/Compensation:

We greatly appreciate your participation in this research. However there is no direct monetary compensation for participation.

Contacts:

In case you have any question(s) concerning this study, please do not hesitate to contact Dr. Frank Gyamfi, the Principal investigator on 0556488299.

Further, if you have any concern about the conduct of this study, your welfare or your rights as a research participant, you may contact:

The Office of the Chairman,

Komfo Anokye Teaching Hospital Institutional Review Board (KATH-IRB),

Research and Development Unit, Kumasi.

Tel: +233 3220 00617.

Email address: kathirb@kathhsp.org or kathirb25@gmail.com

Appendix:2 CONSENT FORM

Statement of person obtaining informed consent:

I have fully explained this research to _____ and have given sufficient information about the study, including that on procedures, risks and benefits, to make an informed decision.

DATE: _____ SIGNATURE: _____

NAME: _____

Statement of person giving consent:

I have read the information on this study/research or have had it translated into a language I understand. I have also talked it over with the interviewer to my satisfaction.

I have read the description of the research or have had it translated into language I understand. I have also talked it over with the interviewer to my satisfaction. I understand that my participation is voluntary. I know enough about the purpose, methods, risks and benefits of the research study to decide that I want to take part in it. I understand that I may freely stop being part of this study at any time. I have received a copy of this consent form and additional information sheet to keep for myself.

DATE: _____ SIGNATURE/THUMB PRINT: _____

WITNESS' SIGNATURE (if applicable): _____

WITNESS' NAME (if applicable): _____

Appendix : Questionnaire

This research is in partial fulfillment of the requirement for the award of **Fellow of Ghana College of Surgeons**. This questionnaire is the tool being used to conduct a study on **''POSTOPERATIVE PAIN MANAGEMENT IN EMERGENCY ABDOMINAL SURGERY: BIMODAL VERSUS UNIMODAL ANALGESIA''**

All information provided shall be treated confidentially and will be used solely for academic purpose.

For further information, please contact 0556488299**.**

SECTION A: SOCIO DEMOGRAPHIC CHARACTERISTICS OF PATIENT

Please tick ☑ where appropriate.

STUDY ID …….STUDY ARM…….

1. Age: ……..years
2. Sex: ☐ Female ☐ Male
3. Last Educational Level: ☐ Primary ☐ Middle School ☐ JSS/JHS ☐ SSS/SHS ☐ Tertiary ☐ None
4. Marital Status: ☐ Single ☐ Married ☐ Co-habitation ☐ Widowed ☐ Other (Specify)……

5. Occupation: ☐ Civil Servant ☐ Self-employed

☐ Unemployed

6. Religion: ☐ Christianity ☐ Islam

African Tradition ☐ ☐ Other (Specify)……

7. Ethnicity: ☐ Akan ☐ Ewe

☐ Ga ☐ Mole-Dagbani

☐ Other (Specify) ……

8. Family system: ☐ Nuclear ☐ Extended

9. Residence: ☐ Rural ☐ Urban

10. Previous surgery ☐ Yes ☐ No

11. If Yes to 10, what was your experience of the postoperative pain

☐ Poorly managed ☐ Well managed

SECTION B: PAIN ASSESSMENT SCORE

12. One hour…….Three hours……six hours……Twelve hours…… twenty-four hours…….

13. Rescue analgesia given ☐ Yes ☐ No

14. If yes to 13 Name of drug and dose……

SECTION C: OUTCOME OF SURGERY

15. Operation performed……

16. Length of incision……

17. Cause for surgery ☐ Benign disease ☐ Malignant

18. Time of ambulation…….

19. Time of first bowel movement……..

20. Time of first oral intake……

21. Post operative nausea ☐ Yes ☐ No

22. Post operative vomiting ☐ Yes ☐ No

23. Diagnosis of pneumonia ☐ Yes ☐ No

24. Clinical diagnosis of DVT ☐ Yes ☐ No

25. Length of Stay …….