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The Effect of a Novel Multimodal Therapeutic Protocol on Patient Reported Post-Neurosurgical Pain Scores, versus the Current Postoperative Analgesic Practice Employed at a Local South African Hospital – An Investigator-Initiated Randomized Controlled Trial.

By

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Declaration

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First and foremost, I would like to give all the glory to God. He is my strength and my foundation, and without His mercy I would not be where I am today.

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Table of Contents

Abstract

Background: There is a high incidence of moderate to severe postoperative pain in patients undergoing neurosurgery. Post-craniotomy headache (PCH) remains undertreated due to the cautious use of opioids in this surgical population. Various alternative analgesics such as acetaminophen and scalp blocks are widely utilized for the treatment of PCH, but this is often inadequate. Although a multimodal approach to the management of PCH may be effective in improved pain relief, only a limited number of randomized controlled trials have explored this.

Aim: This study aims to investigate whether or not a multimodal analgesic regime, consisting of gabapentinoids and non-steroidal inflammatory drugs (NSAIDs) provides superior pain relief in patients undergoing elective craniotomy compared to the standard of care analgesia utilized at a local South African hospital.

Methods: Twenty-seven patients, 18 years or older, scheduled for elective craniotomy for the management of their epilepsy were recruited into this clinical trial. Enrolled participants were randomized into one of two groups. The experimental group received oral 150mg pregabalin one hour before surgery, IV 40mg parecoxib at surgical closure, and oral 150mg pregabalin two hours after surgery. The control group received a matching placebo at these respective time points. Postoperatively, all patients received standard of care analgesia consisting of 24 hours IV paracetamol and additional analgesia as required (prn). Pain assessments using the numerical rating scale (NRS) and visual analogue scale (VAS) were performed at 1 hour, 8 hours, 24 hours, 48 hours and 72 hours postoperatively. Additional analgesia consumption, postoperative nausea and vomiting, as well as the incidence of any adverse events were captured.

Results: Patients who received placebo showed an average trend of higher mean NRS pain scores compared to patients receiving pregabalin and parecoxib, although there was no significant difference (p = 0.218) in the maximum mean NRS pain scores between the experimental and control groups. However, patients who received pregabalin and parecoxib consumed significantly less dihydrocodeine than those who received placebo (p = 0.029). No significant differences were identified in use of other additional opioids and non-opioid analgesia during the first 24 postoperative hours.

Conclusion: There is insufficient evidence to confirm that the perioperative use of pregabalin and parecoxib reduces PCH in patients undergoing elective craniotomy. The study medication did, however, result in a significant reduction in the use of postoperative dihydrocodeine, although it was also associated with higher rates of reported blurred vision and dizziness.

Keywords: craniotomy, perioperative, pain, multimodal, analgesia, pregabalin, parecoxib, numerical rating scale, visual analogue scale.

List of Abbreviations

ALT – Alanine Aminotransferase
APS – American Pain Society
ASA – American Society of Anaesthesiologists
AST – Aspartate Aminotransferase
AUC – Area Under Curve
BP – Blood Pressure
CBV – Cerebral Blood Volume
CN – Cranial Nerve
CNS – Central Nervous Systems
COX – Cyclooxygenase
DSMB – Data Safety and Monitoring Board
ERAS – Enhanced Recovery After Surgery
FRS – Facial Rating Scale
HADS – Hospital Anxiety and Depression Scale
HR – Heart Rate
IASP – International Association for the Study of Pain
ICH - International Headache Society
ICP – Intracranial Pressure
ICU – Intensive Care Unit
IEC – Institutional Ethics Committee
IM – Intramuscular
IPI – Integrated Pulmonary Index
IRB – Independent Review Board
IV – Intravenous
MAP – Mean Arterial Pressure
MeSH – Medical Subject Headings
MMT – Multimodal Therapeutics
NRS – Numerical Rating Scale
NSAID – Non-steroidal Anti-Inflammatory Drugs
NT – Neurotransmitter
OIH – Opiate Induced Hyperalgesia
PACU – Post Anaesthetic Care Unit
PC – Pain Catastrophizing
PCA – Patient Controlled Analgesia
PCH – Post-craniotomy Headache
PNS – Peripheral Nervous System
PONV – Postoperative Nausea and Vomiting
PRN – Pro Re Nata (as needed)
PROSPECT – Procedure-Specific Postoperative Pain Management
PROMIS - Patient-Reported Outcomes Measurement Information System
RCT – Randomized Controlled Trial
SA GCP – South African Good Clinical Practice
SAHPRA – South African Health Products Regulatory Authority
TENS – transcutaneous electrical nerve stimulation
THA – Total Hip Arthroplasty
TKA – Total Knee Arthroplasty
UCT HREC – University of Cape Town Human Research Ethics Committee
VAS – Visual Analogue Scale
VGCC – Voltage Gated Calcium Channels
VRS – Verbal Rating Scale

List of figures

List of tables

Chapter 1:
Literature Review

1.1. Introduction

Acute postoperative pain is a symptom frequently reported by patients who have undergone major surgery, and has been shown to negatively influence the rate of recovery and quality of life of a patient by inflicting emotional and physical distress [1]. Various interventions are widely available in the perioperative setting to reduce and manage postoperative pain. These include the administration of opioid and other analgesic agents, local anaesthetic infiltration techniques and patient-controlled analgesia (PCA). However, evidence suggests that postoperative pain remains inadequately treated [1–3]. Moreover, poorly managed postoperative pain is associated with an increased risk of pulmonary, cardiovascular and gastrointestinal complications, as well as the development of chronic pain syndromes that may be associated with prolonged opioid use and dependency [2,3].

In 2016, the American Pain Society (APS), in collaboration with the American Society of Anaesthesiologists (ASA), published evidence-based clinical practice guidelines on the management of postoperative pain [1]. These guidelines aim to provide safer and more effective management of postoperative pain by including strategies such as perioperative pain management education and planning, the use of multimodal analgesia, and smoothing of the transition to outpatient care. The use of multimodal analgesia is also supported by other emerging guidelines such as the Enhanced Recovery After Surgery (ERAS) [4] and Procedure-Specific Postoperative Pain Management (PROSPECT) [5] . These two guidelines emphasize the benefit of multimodal analgesia for a number of surgical procedures which include; total knee or hip arthroplasty, laparoscopic cholecystectomy, thoracotomy, hemorrhoid surgery and more [6]. Notably, no such guideline yet exists for craniotomy and other neurosurgical procedures, and literature on the use of multimodal analgesia in neurosurgery is scant.

Inadequate management of post-craniotomy headache (PCH) primarily stems from the misconception that there is little need for pain relief due to the absence of pain receptors within the brain parenchyma [7,8]. In contrast, the meninges, periosteum and extracranial muscles are richly innervated with pain receptors [8,9]. Furthermore, the paucity of appropriate pain assessment tools and lack of standardized treatment protocols, as well the variation in analgesia preferences of attending anaesthetists, surgeons and physicians, may all contribute to an underestimation of the severity of postoperative pain associated with craniotomy [2,10]. It is essential to manage PCH effectively in the immediate postoperative period to prevent patient agitation, vomiting, hypertension and any other factors that can cause increased intracranial pressure (ICP) or cerebral edema which, in turn, may be associated with serious complications and poor outcomes [11,12]. Gold standard pain management techniques such as PCA and opioid treatment, are typically associated with miosis (excessive constriction of the pupil) and

sedation, which can interfere with the accuracy of postoperative neurological assessments in patients, who have undergone craniotomy [7,11,13]. Given the unique, numerous and multifactorial mechanisms underlying PCH, which include meningeal irritation, surgery-related soft tissue trauma, activation of inflammatory/nociceptive mediators, nerve injury,[7,9] and psychogenic factors, a multimodal approach to analgesia may be more effective in this type of surgery.

This study aims to investigate the efficacy of a novel multimodal analgesic regime within the neurosurgical setting. To provide an appropriate literature review in support of the aims of this study, various topics will be reviewed. These include the incidence and pathophysiology of PCH, and the current approaches to the management of PCH. In addition, the evidence supporting the use of multimodal analgesia in the management of postoperative pain proposed by the APS and ASA, as well as the rationale for conducting clinical trials to test the effectiveness of new treatment regimens.

1.2. Post-craniotomy headache

Incidence

PCH is defined by the International Headache Society (ICH) as a secondary headache that develops within 7 days of a craniotomy [14]. Despite its recognition as a specific headache disorder, the incidence and severity of PCH is often underestimated and its treatment remains inadequate [7].

Little information was available regarding pain experienced by patients undergoing neurosurgery until 1996. In that year, De Benedittis *et al.* published a pilot study that investigated the incidence, severity and duration of pain experienced by patients undergoing various neurosurgical procedures. They reported that 60% of individuals had moderate to severe pain after neurosurgery, which was superficial in nature and of a somatic origin [15]. By 'somatic in origin' De Benedittis *et al.* implied that this pain arose from the musculature surrounding the skull, the meninges and the scalp, rather than from the brain tissue itself (i.e. from a visceral origin). The findings of De Benedittis *et al.'s* seminal 1996 study remain widely cited by researchers in the field of PCH.

The results of studies on the incidence of PCH vary widely from 15% to 95% [9,16,17]. The widely cited studies by Mordhorst *et al.* (2010) and Suksongpong *et al.* (2016) report incidences of PCH in 87% and 75% of patients, respectively, within the first 24 hours after surgery [18,19]. A literature review by Molnar *et al.* (2014) concluded that the high incidence of PCH reported in the De Benedittis study was supported by the findings of subsequent studies with between 69-76% of patients experiencing PCH [20]. Although these studies all conclude that there is a

high and significant incidence of PCH, they fail to report the incidence of pain experienced by patients prior to surgery, and any effect this may have had postoperatively. Preoperative pain is considered to be a predictor of moderate to severe postoperative pain [21] and it is clearly important to differentiate pain related to a pre-existing or underlying disorder from pain of new onset relating to a neurosurgical procedure. In 2003, Gee *et al.* conducted a retrospective study investigating the prevalence of PCH in 107 neurosurgical patients [22]. The cohort included surgeries such as tumor resection, hemorrhage and intractable epilepsy. Due to the underlying pathology and indications for neurosurgery, 41% of their patients had headache prior to surgery. Of this group, 63% continued to experience pain postoperatively. Of those patients who had no pain prior to surgery, only 19% experienced postoperative pain. Interestingly, 72% of the latter were patients who underwent craniotomy for intractable epilepsy, a disorder that is not commonly associated with chronic headache symptoms. In most patients with epilepsy, headaches are typically post-ictal and limited to the period immediately following a seizure [23]. The results of Gee *et al.'s* study suggest that the underlying pathologies requiring neurosurgical intervention can have a significant influence on the patients' perioperative pain experience, with the surgical procedure either exacerbating the pain level or providing relief. It is also possible that the type of headache experienced preoperatively may differ from that experienced postoperatively. For example, surgery may result in relief from chronic headaches, while at the same time causing a new onset of superficial, localized PCH. Either way, the presence of preoperative pain may play a significant role in the management of PCH.

Pathophysiology

In most medical conditions, a thorough understanding of the underlying pathophysiology is helpful in order to select an appropriate treatment plan. Unfortunately, the pathophysiology of PCH remains poorly understood.

Pain is defined by the International Association for the Study of Pain (IASP) as "the unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [24]. Tissue damage activates a sensory process of nociception, whereby a noxious stimulus signals neural pathways from the peripheral nervous system (PNS) to the central nervous system (CNS) for the processing of pain perception [25]. The activation of nociceptive receptors results in the release of various neurotransmitters and inflammatory mediators, all of which play a key role in the process of nociception. The absence of nociceptive receptors within the brain parenchyma has been used to support the mistaken belief that craniotomy does not cause severe or even moderate pain [7,9,13]. However, the ICH classification of PCH as a secondary headache [14], along with reports of PCH being

experienced as “superficial”, “pulsating and pounding”, and “tension type” headaches by patients [26,27] may shed light on possible underlying pathophysiological mechanisms.

PCH is somatic in origin and nociceptive in nature, and believed to be caused by the surgical stress inflicted on the soft tissue structures, musculature and meninges surrounding the brain parenchyma [17,26]. The calvarium, also termed the cranium, is the part of the skull covering the intracranial cavity that houses the brain. Surrounding the cranium are two muscles in particular that play an important role in PCH, the occipitofrontalis and temporoparietalis (**Figure 1A** [28]**).** The galea aponeurotica is a fibromuscular sheet that covers these two muscles, as well as the entire cranium. Depending on the neurosurgical procedure concerned, supratentorial or infratentorial approaches may be adopted, both of which require the incision and reflection of musculature that is strongly adherent to the skull. A supratentorial approach is typically associated with less pain when compared to the infratentorial approach. This is due to less muscle mass in the supratentorial region [13,27].

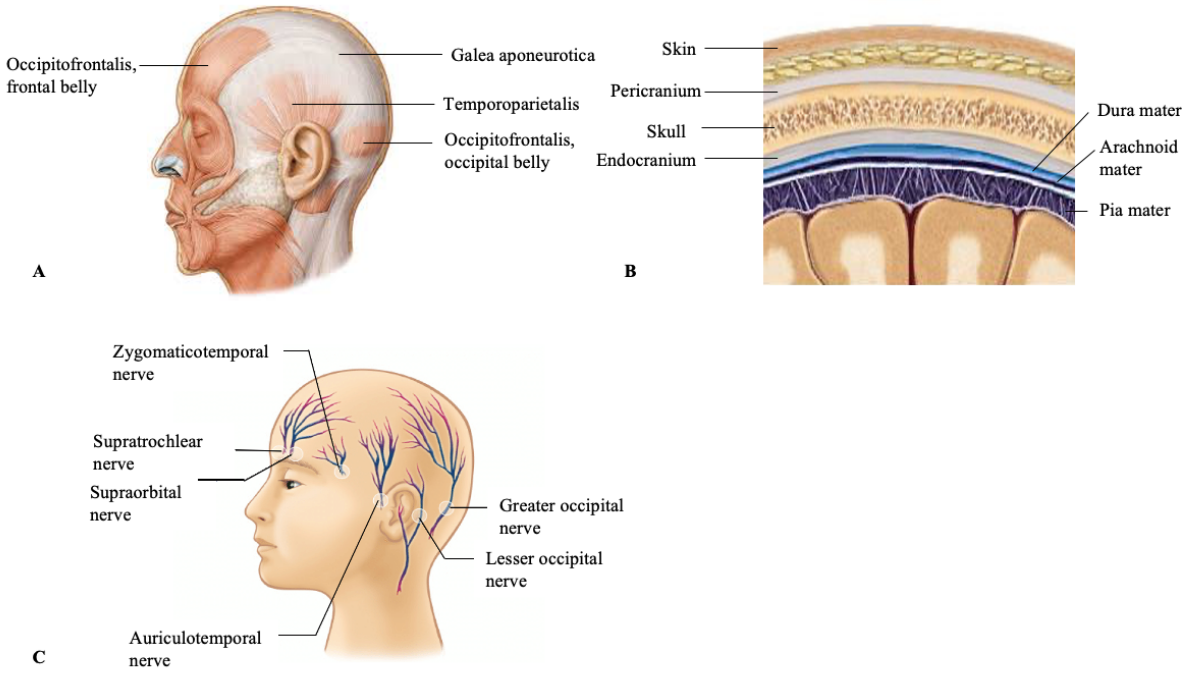

Figure 1: Structures of the scalp

A Musculature of epicranium[28], **B** Cross section of the head[29], and **C** Innervation of the head[30]

An inner layer of fibrous tissue called the endocranium lines the cranium; this layer becomes continuous with the pericranium, an outer layer of connective tissue. Deep to the endocranial layer are the meninges, which enclose the brain. The dura mater is the outermost layer, the arachnoid mater is the middle layer, and the pia mater makes up the innermost layer. The pia

mater is adherent to the brain parenchyma **(Figure 1B** [29]**)**. Cutaneous innervation of the anterior scalp consists of branches originating from the trigeminal nerves (CN V) including the supratrochlear and supraorbital nerves originating from the ophthalmic divisions (V_1), the zygomaticotemporal nerves originating from the maxillary divisions (V_2), and the auriculotemporal nerves originating from the posterior trunk of the mandibular divisions (V_3). In addition, innervation from the greater and lesser occipital nerves originate from the second cervical nerve roots. **(Figure 1C** [30]**)**. The dura mater is innervated by nerve branches that originate from the cervical plexus and accompany the meningeal arteries. Nociceptors in the free endings of these nerves fibers are activated by the noxious stimuli induced by surgical trauma which, in turn, activate the nociceptive pathways resulting in pain perception in the somatosensory cortex. [13,17,26]

The nociceptive pathway of the head and facial region involves the trigeminothalamic tract (**Figure 2** [31]**)**, which differs from the rest of the body that utilizes the spinothalamic tracts.

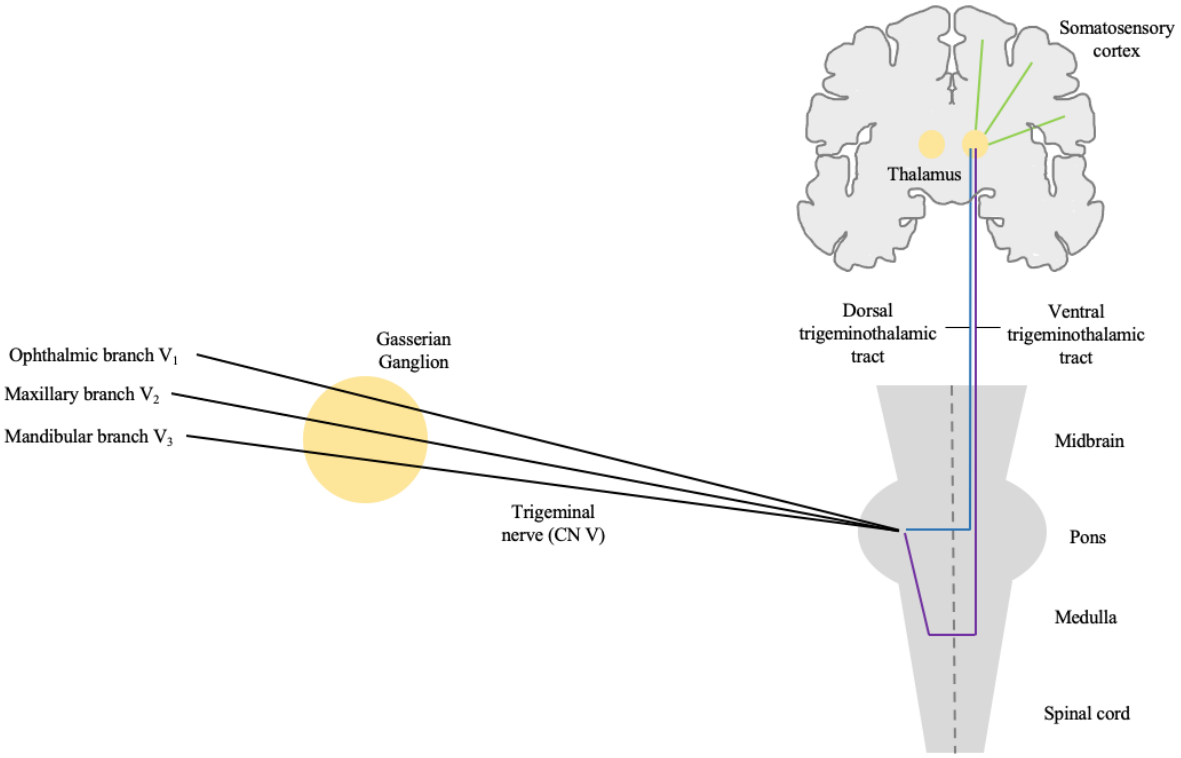

Figure 2: Trigeminothalamic tract

Adapted from Singh *et al*. (2019) [31]

Primary afferent sensory neurons project from the trigeminal root ganglion (also known as Gasserian ganglion) to the periphery and terminate as free nerve endings rich in nociceptive receptors. At the trigeminal root ganglion, they synapse with second-order neurons that project to the CNS, entering at the pons. From the pons the nerve fibers of the ventral

trigeminothalamic tract descend to the medulla to innervate a subdivision of the trigeminal nuclear complex, then cross over the neural midline to ascend to the thalamus. The dorsal trigeminothalamic tract crosses over the neural midline at the level of the pons and ascends to the thalamus. From the thalamus, both dorsal and ventral tracts synapse with third-order neurons, which relay information to the somatosensory cortex [32].

Apart from this structural difference in the nociceptive pathways between the head/facial region and the rest of the body, the process of nociception is largely uniform throughout the body. It is complex in nature but, put simply, the nociceptors are located on the peripheral free nerve endings of two main types of fibers. C-fibers are unmyelinated with a slow conduction that transmit delayed dull pain, and Aδ-fibers are myelinated with fast conduction that transmit sharp pain [33]. Following tissue and cellular damage, numerous and varied chemical mediators and enzymes, such as bradykinin, histamine, prostaglandins, and substance P, etc., are released from the surrounding cells which stimulate nearby nociceptors [11,32]. These noxious stimuli cause depolarizing action potentials to be transmitted along the primary afferent nerve fibers to the presynaptic nerve terminals which synapse with second-order neurons in the ipsilateral trigeminal nucleus. Electrical impulses in the second-order neurons cross the midline and are transmitted to the contralateral thalami where they synapse with third-order neurons which, in turn, project to the somatosensory cortex neurons for processing of pain perception [11,33,34]. Appropriate pharmacological interventions that target a specific enzyme or neurotransmitter can interrupt the nociceptive pathway and modulate pain perception. The action of chemical modulators, enzymes and neurotransmitters will be described later in this review when considering possible pharmacological interventions.

Beyond the nociceptive nature of PCH, other factors such as sensitization and wind-up, inflammation, and nerve damage contribute towards the complex pathophysiology of PCH. Sensitization occurs due to chemical changes in the dorsal horn of the spinal cord or, in the case of PCH, the trigeminal nucleus. Sensitization describes a decrease in the stimulation threshold of nociceptors due to repetitive stimulation and increased firing rate [35]. This causes the nerve cell to experience stimuli with greater intensity and thus become more sensitive to activation [8,34]. Similarly, wind-up, which is thought to induce and maintain sensitization [35], is due to the repetitive activation of nociceptors and associated C-fibers causing prolonged amplification of dorsal horn (or trigeminal nucleus) responses [36]. Sensitization and wind-up can result in secondary hyperalgesia, which is the heightened perception of pain at the site of injury, and allodynia, which is the sensation of pain induced by normally non-painful stimuli such as light touch [34]. These two phenomena, amongst others, contribute to the intensity of a patient's pain experience after a neurosurgical procedure. For example, neuromas may occasionally arise in nerve fibers damaged during surgery, which results in abnormal tissue

growth and axonal sprouting. These damaged axons are believed to have abnormal voltage-gated Na^+ channels resulting in a state of increased axonal hyper-excitability, thus increasing the firing rate to the second- and third-order neurons which, in turn, increase nociceptive perception [37].

An additional factor to consider in the pathophysiology of PCH is the insertion of fixating pins into the skull in order to stabilize the head during surgery. This procedure may induce noxious stimuli and result in changes in haemodynamic responses that influence blood pressure, heart rate and ICP [38–40].

1.3. Current approaches to the management and treatment of PCH

It is established that there is a high incidence of moderate to severe pain following craniotomy and the adequate treatment thereof is vital. Numerous pharmacological interventions are available for effective treatment of general postoperative pain, but in general, current management of PCH in the neurosurgical setting remains inadequate.

A search was conducted on Pubmed.gov to identify the available literature on the current analgesic management and treatment of PCH. Although not a formal systematic review, the search, using terms such as 'postoperative pain', 'craniotomy', 'analgesia', 'pain measurement', and 'pain management', with alternative spellings or combinations, and including medical subject heading (MeSH) terms, yielded 168 results. Thirty-six studies involving pediatric populations, animal studies, alternative non-pharmacological therapies, and those considered irrelevant to the PCH context were excluded from this review. Fifty publications consisted of systematic and narrative reviews on the management of PCH, highlighting the various therapeutic options available and providing commentary on the interventions explored to date. There is general and recurring consensus in this literature that although numerous pharmacological interventions are available for the management of PCH, clinical evidence is lacking as to which interventions are most effective. This conclusion is supported by the limited number of randomized controlled trials (RCT) and investigational publications identified in the search results. A 2019 Cochrane review identified 42 RCTs evaluating pharmacological interventions for acute PCH management, which included a study dating back to 1998 [41]. Tsaousi *et al.* (2017) identified only 19 RCTs conducted between 2011 and 2016 [42]. These numbers reflect the scarcity of evidence-based literature available on the subject of PCH management, which may explain the absence of standardized treatment regimes.

In addition to pain relief, goals of analgesic management in PCH include maintaining haemodynamic stability and neurocognitive functioning. It is important to adequately treat moderate to severe pain to avoid patient agitation, hypertension, vomiting or similar events

that can, in turn, lead to increased intracranial pressure, cerebral edema or intracranial haemorrhage [11,12]. At the same time, it is important to maintain a level of neurocognitive awareness in patients who have undergone neurosurgery during the immediate postoperative period so that the medical team is able to accurately assess them for any complications or neurological deterioration [7]. Opioids are widely prescribed for the management of moderate to severe pain because of their superiority in efficacy over most other analgesics. However, side effects of opioid use, such as sedation, miosis and respiratory depression, can interfere with standard postoperative neurological assessments. It is for this reason that there is a general reluctance to use opioids in the neurosurgical setting [43].

Parenteral opioids target mu (μ), kappa (κ) and delta (δ) opioid receptors, located both centrally and peripherally, to inhibit voltage gated Ca^{2+} channels and reduce neuronal excitability. This decrease in neuronal excitability prevents the transmission of painful stimuli from the primary afferent neurons to second-order neurons, thus inhibiting the cascade of events in the nociceptive pathway described earlier [11]. The most commonly used opioids in the neurosurgical setting are codeine phosphate, tramadol and morphine. Although morphine provides the strongest analgesic effect, being 10 times more potent than codeine phosphate, a survey based in the UK reported that 70% of neurosurgical units prefer to use intramuscular codeine phosphate as the first-line opioid, with only 30% using morphine first-line [44]. These figures are similar to those reported in a survey of Canadian neurosurgeons [45]. Interestingly, the use of second-line potent opioids was found to be higher in those who utilized codeine phosphate as first-line analgesic, compared to those utilizing morphine [45]. Codeine phosphate is a pro-drug with only 5-15% of the dose being metabolized into morphine. Due to individual differences in the expression of Cytochrome P-450 2D6, the enzyme which is required for the demethylation of codeine phosphate into morphine, the analgesic effect of codeine phosphate varies significantly between patients [44,46]. Tramadol is another weak μ-opioid receptor agonist that is associated with little respiratory depression due to its lower affinity for μ-receptors [47]. Unfortunately, the relatively high incidence of nausea and vomiting after tramadol administration remains a concern in neurosurgical patients [46]. Tramadol is also known to decrease seizure threshold and should be avoided in patients with epilepsy or who have a lowered seizure threshold [44].

Despite the recognized side effects of opioids and concern that they may mask early signs of neurological deterioration, the limited literature available seems to support the overall safety and efficacy of opioid use in PCH treatment. A study by Morad *et al.* (2009) randomized patients into either a PRN group (n=35), receiving 25-50μg IV fentanyl every 30 minutes as needed, or to a PCA group (n=29) receiving 0.5μg/kg fentanyl with a lockout time of 15min and a maximum of 4 doses per hour. Results showed that, within the first 16 postoperative

hours, patients in the PCA group had significantly lower pain scores and higher overall fentanyl dosage when compared to the PRN group. Despite the higher fentanyl use in the PCA group, there were no significant differences in the prevalence of nausea and vomiting or other adverse events/side effects between groups [48]. Similarly, Na *et al.* (2011) reported that patients (n=53) receiving IV-PCA with 0.2μg/kg/hr fentanyl and 0.3mg/kg/hr ketorolac had significantly lower pain scores 4 hours and 24 hours after surgery, compared to patients (n=53) receiving fentanyl and ketorolac on an as needed basis. Additionally, IV-PCA did not result in respiratory depression or miosis [49]. Jellish *et al.* (2006) investigated whether or not the addition of anti-emetic, ondansetron, decreases the incidence of postoperative nausea or vomiting. Patients scheduled for craniotomy with tumor resection were randomized into one of three groups, PCA placebo (PPCA) (n=40), PCA with morphine (MPCA) (n=40) and PCA morphine and ondansetron (OMPCA) (n=40). Not only were pain scores higher in the PPCA group compared to the other groups, but also the average rescue analgesia dose in this group was twice that required in the MPCA and OPCA group. This result is unsurprising, as it affirms a high incidence of moderate to severe pain in neurosurgical patients requiring effective pain relief. Furthermore, the addition of ondansetron in this study did not significantly reduce the incidence or severity of nausea and vomiting [50]. Although not their primary objective, the findings of a study by Dilmen *et al.* (2016), supported the use of PCA morphine. They reported that it prevented moderate to severe pain following supratentorial craniotomies and that its use was not associated with severe opioid-related side effects [43]. In a follow-up study, Akcil & Dilmen *et al.* (2018) demonstrated that PCA with 0.5mg morphine, lockout time of 10 minutes and maximum dose of 10mg for 4 hours was safe to use for effective PCH management, and that opiate-induced respiratory depression could be monitored using the non-invasive Integrated Pulmonary Index (IPI) [51]. In 2004, Roberts *et al.* commented that the justification for limited morphine use after craniotomy is based largely on anecdotal evidence but that there is no inherent risk of its use under close supervision [46]. This statement seems to be supported by the more recent literature presented above. However, additional methodological studies are required to produce evidence-based guidelines for opioid use in neurosurgery.

Intraoperatively, the administration of opioids such as remifentanil and sufentanil, which are μ-opioid receptor agonists that act on the spinothalamic tract, is often currently used in the neurosurgical setting [52]. Remifentanil is rapidly metabolized into inactive metabolites with a half-life as short as 3-10 minutes. This fast elimination of the drug means that continuous intraoperative administration of the drug is necessary to achieve and maintain optimal opioid effects. The very short half-life of remifentanil also means that little if any opioid effect remains once emergence from general anaesthesia occurs and that the patient is likely to request postoperative analgesia at a much earlier stage. Also, the large doses of remifentanil

required intraoperatively result in a phenomenon known as 'opioid-induced hyperalgesia' (OIH) [8,12] in which painful noxious stimuli produce exaggerated responses. It has been shown that the concurrent use of non-opioid analgesia can alleviate this hyperalgesia response [53]. In comparison, sufentanil is a highly lipophilic opioid with a long half-life of 164 minutes. Literature suggests that patients receiving sufentanil experience superior pain relief postoperatively compared to remifentanil. However, due to its longer half-life, sufentanil results in a longer time to wake-up from general anaesthesia and extubation. For this reason, remifentanil is preferred when rapid recovery for neurological examination is required [52,54].

Paracetamol (IV acetaminophen, a non-opioid) is widely used in the neurosurgical setting due to its excellent tolerability, high bioavailability, long half-life and cost-effectiveness, but it has proven inadequate as a stand-alone treatment [11,55,56]. Paracetamol shares the same analgesic effect as non-steroidal anti-inflammatory drugs (NSAIDs) by inhibiting cyclooxygenase (COX) enzymes, in turn preventing the synthesis of prostaglandins. However, it is a much weaker analgesic compared to many other NSAIDs. Paracetamol treatment is often paired with opioids to achieve optimal pain relief. A 2002 study by Verchére *et al.* demonstrated the inefficacy of paracetamol treatment alone by comparing the analgesic efficacy of paracetamol alone (P), paracetamol combined with tramadol (PT), and paracetamol combined with nalbuphine (PN). Inclusion into the P treatment group was terminated prematurely, after only 8 participants had been recruited into this arm of the study, due inefficient pain relief. In contrast, pain relief was effective in the PT (n=27) and PN group (n=29), with the PT group requiring more rescue analgesia than PN group [57]. Although paracetamol is ineffective as a stand-alone treatment, it has been suggested to provide opioid-sparing effects and an increased patient comfort level. The opioid-sparing effects of paracetamol was investigated in a RCT by Greenberg *et al.* (2017) comparing IV paracetamol (n=66) to placebo (n=65). Within the first 24 postoperative hours, 15.2% of the paracetamol group and 6.2% in the placebo group remained opioid-free. Although this shows a trend of reduced opioid use with paracetamol administration, the difference did not reach statistical significance [58]. It is also noteworthy that more than 80% of the study population required additional opioids for adequate pain relief, reiterating the inefficacy of paracetamol use alone. Ineffective opioid-sparing effects were reported in two other RCTs comparing paracetamol versus normal saline placebo. Sivakumar *et al.* (2019) found no significant difference in narcotic consumption between groups receiving paracetamol (n=102) versus placebo (n=102) over a 48-hour period. Patients receiving paracetamol did, however, report significantly lower postoperative pain scores than those who received placebo [59]. Similarly, Artime *et al.* (2018) reported no difference in opioid consumption or pain scores between patients receiving 24-hour paracetamol (n=45) vs placebo

(n=41) although there was a higher satisfaction in overall pain management in patients receiving paracetamol [60].

Lastly, scalp block and wound infiltration are other techniques commonly used in the management of PCH. Scalp blockade is the process whereby a local anaesthetic is injected into the nerves that provide innervation to the scalp. It is often performed prior to cranial pin insertion to anaesthetize the superficial and deep layers of the scalp [61]. This method, however, does not provide any analgesic effects to the dural layers [62]. Scalp/wound infiltration involves local anaesthetics being injected into the scalp surrounding the surgical incision site, either prior to incision, after surgical closure, or both. Blockade of the scalp region pre-incision can blunt noxious stimuli induced by cranial pin insertions, scalp incision and muscle separation, which helps to stabilize hemodynamic responses during surgery [63]. Pinosky *et al.* (1996) [63], was the first to demonstrate the effect of using a 0.5% bupivacaine scalp block on the autonomic response to cranial head pinning. Twenty-one participants were randomly allocated to one of two treatment groups receiving either 0.5% bupivacaine or normal saline solution. Solutions were injected into respective regions blocking the supraorbital, supratrochlear, auriculotemporal, postauricular branches of the greater auricular and the greater, lesser and third occipital nerves, five minutes before head pinning procedures. Hemodynamic responses were monitored at various time points. Results confirmed that 0.5% bupivacaine reduces haemodynamic responses such as hypertension and tachycardia during head pinning procedures, thus limiting anaesthetic requirements during this period. Studies comparing scalp block, local infiltration and routine analgesia demonstrate that scalp block is often superior in providing haemodynamic stability during cranial pin insertion with no increases in mean arterial pressure (MAP), heart rate (HR) or blood pressure (BP) [64–66]. Both scalp block and local infiltration provide stable haemodynamic responses to skin incision compared to a remifentanil-based anaesthetic alone [65].

It has also been suggested that scalp blockade and infiltration have little effect on patient motor or sensory functions thus providing favorable conditions for immediate postoperative neurological assessments and a safe option for PCH treatment [11]. However, the analgesic efficacy of these methods in PCH treatment, and any opioid sparing effects they may have, remain unclear due to the low-quality evidence and the methodological weakness of available studies [67,68]. Small sample sizes and the fact that RCTs investigating scalp block/infiltration predominantly focus on haemodynamic responses as the primary outcome, with pain intensity typically being regarded as a secondary outcome, add to this low-quality evidence. The study by Song *et al.* (2015) suggests that the preemptive use of scalp infiltration prior to surgical trauma blocks peripheral noxious stimuli, lowers the use of intraoperative analgesics (such as remifentanil), prevents central hypersensitization and possibly also lowers opioid-induced

hyperalgesia. This preemptive infiltration resulted in lower mean pain scores within the first 6 hours post-surgery and statistically delayed the mean time to first postoperative analgesic dose, compared to infiltration at skin closure [69]. A significantly delayed time to first dose of rescue analgesic was also reported by Zhou *et al.* (2016) in patients receiving preemptive scalp infiltration with 0.5% ropivacaine compared to placebo. In addition, morphine consumption in the first 24 hours was significantly higher in the placebo group, indicating beneficial opioid sparing effects [70]. Similar results are also seen with scalp nerve block using 0.75% [66]. The duration of the analgesic effect provided by scalp infiltration or scalp block appears to be relatively short. Yang *et al.* (2020) found that a 0.5% ropivacaine scalp block provided pain relief for up to 4 hours after craniotomy, while lower doses of 0.2% and 0.33% provided pain relief for up to 2 hours [71]. Nevertheless, it seems that scalp block or infiltration provide a suitable analgesic option with respect to haemodynamic stability intraoperatively, and limited pain relief postoperatively.

The literature summarized above confirms that various analgesic interventions are commonly used for treatment of PCH but that their efficacy is likely sub-optimal. This may be due to insufficient dosage because of concern about potential associated side effects, weak analgesic properties, brevity of action and other factors. Moreover, because of the low-quality of available evidence, there is currently no standardized treatment guideline for the management of PCH. Consequently, alternative medications, such as dexmedetomidine, gabapentinoids and NSAIDs, are now being investigated for their potential utility, safety and efficacy in the neurosurgical setting, and these will be discussed in the next section.

1.4. Guidelines on the management of postoperative pain recommended by the APS and ASA

In 2016, the American Pain Society (APS), in collaboration with the American Society of Anaesthesiologists (ASA), published clinical practice guidelines on the management of postoperative pain [1]. These guidelines aim to provide safer and more effective management of postoperative pain by including strategies such as perioperative pain management education and planning, the use of multimodal pharmacological modalities, and smoothing the transition to outpatient care.

The APS/ASA clinical practice guideline consist of 32 recommendations divided into 10 categories. With the current study's aims in mind, three relevant categories will be discussed with special reference to recommendations, supporting evidence and relevance to the neurosurgical setting.

1.4.1. Preoperative evaluation

> "*The panel recommends that clinicians conduct a preoperative evaluation including assessment of medical and psychiatric comorbidities, concomitant medications, history of chronic pain, substance abuse, and previous postoperative treatment regimens and responses, to guide the perioperative pain management plan (strong recommendation, low-quality evidence).*" [1]

It is recommended that patients' medical and psychiatric comorbidities, history of previous postoperative pain experiences and/or chronic pain, concomitant medications and other factors are carefully evaluated preoperatively [1]. This information may assist in the identification of predictive factors for postoperative pain and result in earlier intervention and improved peri-surgical management [72]. Common predictive factors such as age, gender, anxiety, pre-existing pain and perception of pain experience have been correlated to both pain intensity and the use of analgesia after surgery [72,73]. Studies report younger patients are more at risk for experiencing PCH, and that the probability of suffering from PCH decreases by 3% for every additional year of life [18]. This may be due to reduced sensory perception in older populations [18], or due to altered pharmacodynamic and pharmacokinetic profiles in different age groups resulting in differing analgesic requirements [21]. Similarly, higher pain scores in the early postoperative period are reported in female patients compared to males [74]. Studies investigating total knee arthroplasty (TKA) and total hip arthroplasty (THA) have also identified younger age and female gender to be predictive factors of postoperative pain. In addition, severity of preoperative pain at the surgical site has been found to be a risk factor for moderate to severe pain experience [75]. Sommer *et al.* (2010) reported that patients, who suffered pain prior to surgery, had a greater risk of experiencing moderate to severe pain postoperatively compared to those who did not [21]. A possible hypothesis for this is the phenomenon of central sensitization, discussed in section 1.2, in which chronic noxious stimuli can result in neuroplastic changes in the spinal cord, causing exaggerated responses to mild stimuli.

Pain is a subjective sensory and emotional experience. Therefore, it is unsurprising that psychological factors such as anxiety, depression and pain catastrophizing (PC) may predict postsurgical pain. PC refers to the anticipation of an exaggerated negative consequence or outcome from a specific situation. It has been associated with heightened levels of postoperative pain because patients focus excessive attention on their pain experience and awareness of their bodily sensations [21,76]. It is also often closely associated with a high anxiety trait. Individuals who generally respond anxiously to threats in the environment are regarded as hypersensitive and more psychologically responsive to stimuli [73]. Therefore, in order to reduce postoperative pain, reassurance, good communication and, if indicated, preoperative

anxiolytics are advised for patients experiencing high levels of preoperative anxiety or surgical fear.

The benefit of identifying predictive factors in the preoperative evaluation is that the treating physicians can be alerted to the individual analgesic requirements of patients and, in this way, improve the speed of recovery and prevent the development of chronic pain.

1.4.2. Use of a validated pain assessment tool

> *"The panel recommends that clinicians use a validated pain assessment tool to track responses to postoperative pain treatments and adjust treatment plans accordingly (strong recommendation, low-quality evidence)."* [1]

A key factor in successful management of postoperative pain is the accurate measurement of pain intensity levels in order to adjust treatments accordingly [1]. The APS/ASA guideline recommends four validated pain intensity assessment scales and several studies have compared these with the aim of determining which is the most reliable. The Visual Analogue Scale (VAS) consists of a 100mm horizontal line, the two extremities of which are respectively labeled as "no pain" and "worst possible pain". Patients are asked to identify a point on the line which best represents the intensity of pain they are experiencing. In contrast, the Numerical Rating Scale (NRS) is an eleven-point rating scale from 0–10 in which the lower (0) and upper (10) limits respectively represent "no pain" and "worst possible pain". The Verbal Rating Scale (VRS) is a five-point scale consisting of a list of phrases that describe the intensity of pain. Lastly, the Face-Rating Scale (FRS) is a six-point scale consisting of images of facial expressions representing increasing levels of pain [77]. Ferreira-Valente *et al.* (2011) compared the validity of these four scales in quantifying pain responses to stimulation at four different temperatures. This study concluded that NRS was superior followed by the VAS, VRS and FRS. The NRS was preferred over the VAS by patients and clinicians due to the simplicity and ease of its administration [77]. A systematic literature review by Hjermstad *et al.* (2011) concluded that the VAS and NRS are equally effective in assessing pain intensity but that the VAS may be associated with the lower levels of patient compliance and greater risk of discrimination [78].

1.4.3. Use of multimodal therapies

> *" The panel recommends that clinicians offer multimodal analgesia, or the use of a variety of analgesic medications and techniques combined with nonpharmacological interventions, for the treatment of postoperative pain in children and adults (strong recommendation, high-quality evidence)."* [1]

Accumulating evidence suggests that simultaneous use of multiple analgesic agents, each targeting different pain-related pathways or receptors, may act synergistically to result in superior pain relief [1,4,5,53]. Multimodal therapeutics (MMT) includes the simultaneous use of both opioid and non-opioid analgesics, which are occasionally administered with non-pharmacological therapeutic modalities such as transcutaneous electrical nerve stimulation (TENS). Currently, there is insufficient evidence to support or discourage the use of non-pharmacological modalities such as acupuncture or massage in MMT. However, the APS/ASA guidelines recommend that effective, non-opioid analgesics be routinely used in MMT protocols, as systemic opioids may not be required in all patients. The goal of MMT is to utilize these non-opioid analgesics to reduce the requirement for opioid analgesic use, and to limit undesirable opiate-related side effects [1].

The following section focuses on the guideline recommendations and supporting evidence for the use of two non-opioid analgesics that are central to our study.

Non-Steroidal Anti-Inflammatory Drugs

> *"The panel recommends that clinicians provide adults and children with acetaminophen and/or nonsteroidal anti-inflammatory drugs (NSAIDs) as part of multimodal analgesia for management of postoperative pain in patients without contraindications (strong recommendation, high-quality evidence)."* [1]

As discussed previously, surgical trauma to soft tissue structures results in the release of chemical mediators and enzymes which, in turn, bathe nociceptors to result in a noxious stimulus [32]. Prostaglandin, an active lipid compound synthesized through the oxygenation of unsaturated fatty acid arachidonic acid by COX enzymes, is of particular interest. Two types of COX enzymes are known. COX-1 is considered a 'housekeeping' enzyme that maintains baseline levels of prostaglandins for healthy cellular functioning, such as platelet aggregation and gastroprotection. In contrast, COX-2 enzymes are activated in cellular/tissue damage and produce prostaglandins that mediate and facilitate the inflammatory response [79,80]. Prostaglandin levels are typically increased in inflamed and damaged tissue, and contribute to signs of inflammation such as pain, swelling, redness, and increased temperature, and can influence the release of adrenergic neurotransmitters [79]. **(Figure 3** [81]**)**

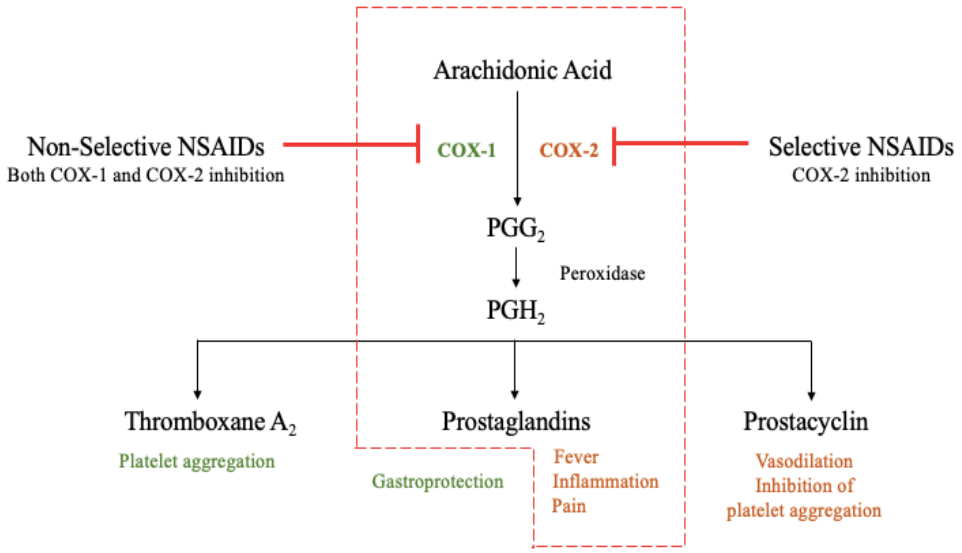

Figure 3: NSAIDs pharmacological action

Cyclooxygenase enzymes are responsible for the biosynthesis of prostaglandins from arachidonic acid. Red dotted line indicating desired pharmacological target of non-selective and selective NSAIDs which target COX enzymes to inhibit the synthesis of prostaglandins, in turn providing analgesic, anti-inflammatory and anti-pyretic effects.

Adapted from Day *et al.* (2013) [81]

Abv: PGG_2 – Prostaglandin G2, PGH_2 – Prostaglandin H2

Two key drug classes target COX enzymes by inhibiting the synthesis of prostaglandins, in this way modulating inflammatory responses to provide analgesic effects. The first of these, as recommended by the APS/ASA panel, is paracetamol (acetaminophen), which is a non-NSAID that has anti-pyretic and analgesic properties [80]. The use of paracetamol is widely encouraged and utilized in the neurosurgical setting despite its being ineffective as a stand-alone treatment [11,55]. The second drug class recommended by the panel is NSAIDs. Two types of NSAIDs are available. Non-selective NSAIDs, such as ibuprofen, diclofenac, and ketorolac, etc., which inhibit both COX-1 and COX-2 enzymes. Selective NSAIDs, such as celecoxib and parecoxib, inhibit only COX-2 enzymes. Because of its housekeeping role, the inhibition of COX-1 enzyme can result in the loss of gastroprotective and platelet aggregation mechanisms resulting in undesirable adverse events such as gastric ulcers, an increased bleeding tendency, and renal damage [82]. These side effects raise the question as to whether or not NSAID use is appropriate in the neurosurgical setting, especially as these may increase the risk of intraoperative bleeding and subsequent postoperative intracranial hemorrhage. However, evidence suggests that, because the COX-2 enzyme has little, if any, anti-platelet activity, selectively inhibiting its action

should not materially increase the risk of intraoperative or postoperative bleeding. Consequently, the use of selective COX-2 inhibitors in single doses or short courses is regarded as acceptable in patients undergoing neurosurgery [83–85].

Only two RCTs have investigated the use of selective-NSAIDs in the neurosurgical setting. Jones *et al.* (2009) reported that participants randomized to an experimental group (n=41) who received a single dose of intravenous (IV) 40mg parecoxib at dural closure exhibited significantly reduced VAS pain scores at 6 hours postoperatively compared to those in the saline placebo control group (n=39). There were, however, no significant differences in nurse-administered intramuscular (IM) morphine prn dosages between these groups in the Post Anaesthetic Care Unit (PACU). Furthermore, there was only minimal, and insignificant reduction in IM morphine use in the experimental group at the 6hr and 12hr time points post-surgery [83]. Similarly, Williams *et al.* (2011) found no difference in PCA morphine consumption or pain scores during the first 24 hours post-surgery in patients undergoing supratentorial craniotomies between groups receiving IV 40mg parecoxib (n=47) or saline placebo (n=49) at the time of dural closure [84]. This limited literature suggests that single dose parecoxib offers little opioid sparing effects. It is noteworthy that these studies investigated the use of parecoxib in isolation and not as a non-opioid analgesic component of MMT. Studies investigating the concomitant use of selective NSAIDs together with other recommended non-opioid analgesics may identify clinical benefit.

Gabapentinoids

> *"The panel recommends that clinicians consider use of gabapentin or pregabalin as a component of multimodal analgesia (strong recommendation, moderate-quality evidence)."* [1]

Gabapentin and pregabalin are gabapentinoids that regulate the alpha-2 delta-1 (α2-δ1) subunit of voltage-gated calcium channels (VGCC) in presynaptic neurons [86]. As discussed above, noxious stimuli induced by tissue damage initiate a process of neuronal transduction. When an action potential is transmitted along the primary afferent nerve fibers to the pre-synaptic nerve terminal, it opens the VGCC which results in a Ca^{2+} influx into the neuron. The increase in intracellular Ca^{2+} triggers neurotransmitter (NT) vesicle exocytosis and the release of excitatory NTs, such as glutamate, substance P, noradrenaline, dopamine, and serotonin etc., into the synaptic cleft. Here, the NTs bind to receptors on the post-synaptic nerve terminal and trigger an electrical impulse which travels along the second- and third-order neurons to higher cortical structures for pain perception [87]. Gabapentin and pregabalin do not inhibit

these VGCC but rather down-regulate VGCC in hyperexcitable neurons, such as those associated with epilepsy or central sensitization. In this way, the influx of Ca^{2+} into the presynaptic cell is reduced. This, in turn, reduces the release of excitatory NTs into the synaptic cleft, thus modulating the hyperexcitability induced by noxious stimuli [88]. **(Figure 4.)**

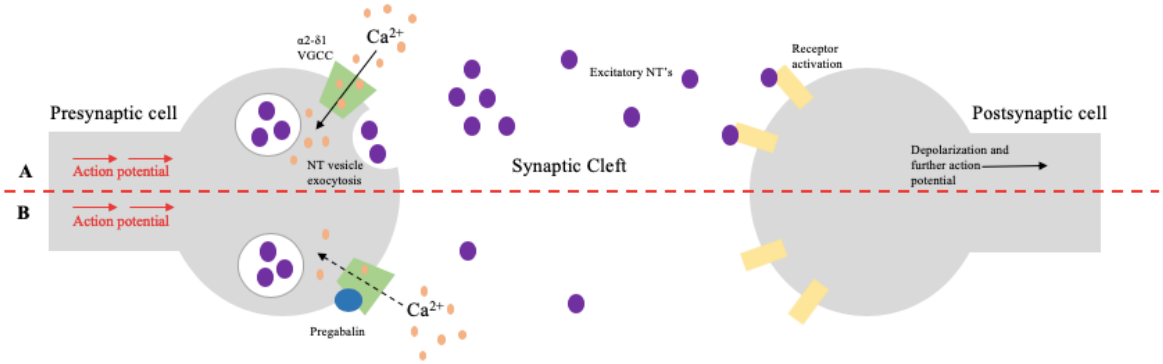

Figure 4: Gabapentinoids pharmacological action

A The arrival of an action potential at the presynaptic cell opens VGCC. The influx of CA^{2+} results in neurotransmitter (NT) vesicle exocytosis and the release of excitatory NT's into the synaptic cleft. NT's attach to receptors on the postsynaptic cell causing subsequent depolarization and further action potential. **B** Pregabalin regulates α2-δ1 VGCC to decrease the influx of Ca^{2+} and limiting the release of excitatory neurotransmitters (NT) into the synaptic cleft.

Due to the role of central sensitization in PCH, the use of gabapentinoids in the neurosurgical setting may be beneficial. The panel found that these drugs are effective when administered 1-to-2 hours preoperatively in the following doses: gabapentin, 600mg or 1200mg, and pregabalin, 150mg or 300mg [1]. Some trials have also utilized postoperative single or multiple doses. Currently, insufficient literature is available to confirm an optimal dosage regime. Pregabalin is more potent than gabapentin and has greater biological activity. The use of gabapentinoids has been associated with reduced postoperative pain scores and opioid sparing effects in various surgical settings. For example, a mixed surgical cohort RCT by Hah *et al.* (2018) investigated the effect of 1200mg preoperative gabapentin, followed by 600mg three times a day for 72 hours (n=208), versus placebo (n=202), on the rate of pain and opioid use cessation postoperatively. The study found that the gabapentin group had a 24% increase in opioid cessation, although there was no difference in average time to pain

relief between groups [89]. Various meta-analyses of mixed surgical cohorts report that both pregabalin and gabapentin significantly reduce pain scores and opioid consumption within the first 24-hour postoperative period compared to placebo. However, these findings included studies utilizing both single and multiple doses in the perioperative setting emphasizing, once again, that optimal dosing regimens have yet to be established. It is also worth noting that there is an increased incidence of sedation and visual disturbances associated with gabapentinoid use compared to placebo [90–93].

To date, four RCTs have explored gabapentinoid use within the neurosurgical setting. Shimony *et al.* (2016) investigated a treatment regime consisting of 150mg pregabalin administered the night prior to surgery, 1.5 hours before surgery and then twice daily for 72 hours postoperatively, compared to a placebo. The authors found that the pregabalin group (n=50) had significantly lower pain scores and analgesic consumption on postoperative day 0 to 2 compared to placebo (n=50). Furthermore, they found that the rate of postoperative nausea and vomiting (PONV) and request for anti-emetics was lower in the pregabalin group [94]. Lamsal *et al.* (2019) found no difference in median postoperative VAS scores between groups receiving either single dose 75mg pregabalin (n=20), 150mg pregabalin (n=20) or placebo (n=20) before anaesthesia induction, although, postoperative fentanyl consumption was lower in the 150mg pregabalin group indicating possible opioid sparing effects [95]. These two studies utilized substantially different dosage regimes and, consequently, delivered different results regarding analgesic efficacy. Lamsal *et al*. (2019) argues that prolonged dosage regimes of pregabalin increase the risk of sedation, dizziness and visual disturbances, which may be particularly undesirable in neurosurgical patients. In contrast, Shimony *et al.* (2016) report that no severe adverse events were attributed to their specified pregabalin dosage regime. Zeng *et al.* (2019) reported increased sedation at 2 hours postoperatively in patients receiving 600mg gabapentin the night before surgery, and another 600mg gabapentin two hours before anaesthesia induction (n=52) when compared to placebo (n=50). Despite this sedation, postoperative pain scores were significantly reduced in the first 24 hours, as were vomiting and anti-emetic use in the gabapentin group [96]. Similar analgesic efficacy was not achieved with a single dose of 600mg gabapentin administered 2 hours prior to anaesthesia induction, although this did provide a reduction in the incidence of nausea [97]. Larger trials are required to investigate optimal dosages and durations of gabapentinoid use for analgesia in neurosurgical patients and its potential role in MMT.

It is surprising that MMT has not been investigated more widely in the neurosurgical setting to develop validated treatment regimes. Programs such as PROSPECT and ERAS, which emphasize the use of MMT, have developed a variety of standardized treatment plans for a number of other surgical interventions including caesarian section, colonic resection, hemorrhoid surgery, herniorrhaphy, thoracotomy, total hip arthroplasty and total knee arthroplasty amongst others [4–6]. However, no standardized drug treatment plan has been developed for neurosurgery despite a clear need for this. A study by Johnson *et al.* (2019) identified domains of recovery that should be better managed and considered when identifying which interventions should be included in an ERAS protocol for elective intracranial surgery. Using the Quality of Recovery-15 (QoR-15) score, a quantitative assessment that allows investigators to determine the effect of interventions on recovery as experienced by the patient, authors identified postoperative analgesia and PONV as the lowest scoring domains [98]. In 2018, Wang *et al.* designed and implemented a novel neurosurgical ERAS protocol for elective craniotomy to investigate its safety and efficacy at a tertiary medical center in China. This protocol utilized an array of physical therapeutic modalities with limited emphasis on pharmacological interventions. Pharmacological intervention was limited to the addition of acetaminophen/NSAIDs in the ERAS group. Patients in this group received acetaminophen/NSAIDs if postoperative VAS score was >5 and central analgesics, such as morphine or equivalent, if postoperative VAS was >7, compared to the control group, who received only the latter. The authors found that the ERAS protocol reduced the duration of postoperative hospital admission, as well as the duration of post-operative pain [99]. Similarly, Titsworth *et al.* (2016) showed that the implementation of a literature-based standardized analgesia protocol led to improvements in the use of multimodal analgesics and responses to pain after spinal surgery. Implementation of this protocol resulted in a 32% reduction in surgery-related pain [10]. This underscores the benefit that may be provided through an evidence based standardized MMT treatment regime for craniotomy patients. However, the lack of convincing evidence from RCTs on MMT protocols for neurosurgery limits the development and widespread implementation of such a protocol [100].

1.5. Clinical trial fundamentals

> "*A properly planned and executed clinical trial is the best experimental technique for assessing the effectiveness of an intervention. It also contributes to the identification of possible harms."* – Friedman *et al.* (2015) [101]

The World Health Organization (WHO) defines a clinical trial as "a type of research that studies new tests and treatments, and evaluates their effects on human health outcomes" [102]. Clinical trials provide a bridge between the scientific discoveries made in the laboratory and

meaningful health outcomes that can be implemented at the patients' bedside. This research methodology is used to investigate a range of new therapeutic drugs, biologicals, devices, diagnostic testing, regimens, and various other surgical/educational/implementation techniques [102]. To limit bias, the effect of an intervention of interest is typically compared to a control group. The control groups may utilize a placebo to mimic the appearance of the new intervention, the current best standard intervention, or both.

It is vital to ensure that there is sufficient equipoise to motivate undertaking a clinical trial; in other words, there must be a significant gap in knowledge regarding the effectiveness, safety, benefits and risks of a new intervention compared to current standard treatments [103]. Furthermore, the ethical regulation of interventional clinical trials by Institutional Review Boards (IRBs) or Independent Ethics Committees (IECs) is essential to protect the safety and rights of human subjects, which is the first priority. Prospective, randomized, double-blinded clinical trials are the most dependable and unbiased way to investigate whether or not a proposed treatment regimen produces significant clinical benefits with minimal risk to the patient.

Clinical Trial Phases

Clinical trials investigating the beneficial and adverse effects of new or existing pharmacological agents in human subjects are categorized into phases I to IV. These phases

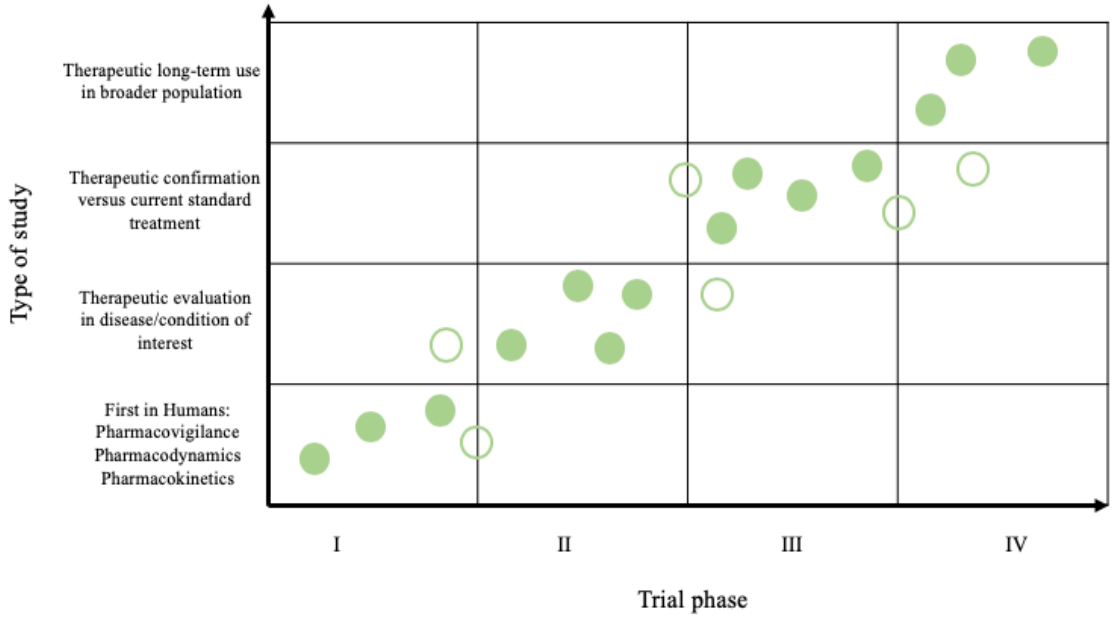

Figure 5: Clinical trial phases

Correlation between study phase and type of study for pharmacological agents in humans. Dots represent individual studies. Each individual study has an objective, design, conduct, analysis and report. The outlined dots are representative of studies which overlap 'type of study' and 'trial phase'.

Adapted from Friedman *et al.* (2015) [101]

may overlap depending on the aim of the study. **Figure 5** [101] illustrates the correlation between trial phases and types of studies.

Phase I trials are the first stage, after animal testing, during which a new pharmacological intervention is tested in healthy human subjects. In this phase the pharmacovigilance, pharmacodynamics and the pharmacokinetics are investigated in order to establish safety for use in humans, and to identify and define any associated adverse effects or events. Phase II trials are considered 'proof of concept studies' to confirm efficacy of a drug or intervention in managing a pathological condition, and to establish optimal doses of the drug in human subjects. Strict inclusion and exclusion criteria are followed in this phase to ensure that participants have no other diseases, comorbidities or complications apart from those of interest. Phase III trials investigate how effective the new/experimental drug is in a broad spectrum of the diseased population compared to current standard practice and/or placebo. This is where the risks and benefits of the intervention versus current standard practice are weighed to determine if it is clinically beneficial. Lastly, Phase IV trials are considered as 'post-marketing surveillance' studies. After an intervention or drug is registered and becomes widely available to the public, Phase IV studies investigate their long-term benefits and risks in a larger population. Safety monitoring is crucial throughout all trial phases. [103]

Randomization

In phase III trials, where a new intervention (experimental cohort) is compared to current standard practice (control cohort), participants must be allocated to a treatment or placebo group without bias. This is typically achieved through the process of randomization, during which participants are randomly allocated to experimental and control intervention groups on a 1 to 1 basis. This is not only essential in producing a reliable experimental design by eliminating selection, systematic and other bias, randomization also reduces the variability of known and unknown confounding factors by resulting in comparable groups with regards to characteristics such as age and sex etc. [104]. Various methods of randomization are available, including allocation by a random number list, blocked randomization, stratified randomization by predefined variables or cluster randomization by groups of participants, and so on. The ultimate goal of randomization is to conceal intervention allocation so that investigators are unable to predict the next allocation. [103]

Blinding

In RCTs, blinding procedures are utilized in an attempt to further eliminate bias during study procedures and are considered an indispensable feature of good trial design. Single-blinding is when one group of individuals is blinded to their treatment allocation; examples include the

investigators conducting assessments or the participants receiving treatment versus placebo. Double-blinding refers to the situation where both investigators and participants are unaware of the treatment allocation. Double-blinding also involves blinding of clinicians (nursing staff, surgeons, physicians, and allied medical practitioners, etc.), data collectors and analysts, as well as outcome adjudicators such as the data safety and monitoring boards (DSMBs) and monitors [105]. In this way, double-blinding prevents investigators and participants from being physically or psychologically influenced by their knowledge of the treatment allocation [106]. Blinding procedures also minimize selection bias, help to reduce assessment bias and increase retention and compliance of trial participants thus adding significant value to the quality of the study. Although effective blinding is vital, it is also necessary for an independent external monitor to be available, who is able to break the blinding should this become necessary. An example would be if a participant develops serious symptoms and signs which may represent a severe adverse reaction to the treatment.

1.6. Concluding remarks

The published clinical practice guidelines on postoperative pain management produced by the APS and ASA aim to provide safer and more effective management of postoperative pain by including strategies such as perioperative pain management education and planning, the use of multimodal analgesia, and smoothing the transition to outpatient care [1]. Given what appears to be a high incidence of inadequate treatment of PCH, implementation of such guidelines may be beneficial in the neurosurgical setting to improve patient care and recovery.

Chou *et al.* (2016) have noted that selection of an appropriate MMT regime for specific surgical procedures is challenging due to the wide range of possible combinations available, in terms of drug classes and dosage regimes, and also the limited evaluation of these in rigorous clinical trials [1]. And yet, such clinical trials are essential to demonstrate evidence-based clinical effectiveness and identify the potential benefit of such MMT protocols [107].

After reviewing the recommendations and guidelines on postoperative pain management produced by the APS and ASA, as well as other available literature on the subject as summarized above, we believe that a MMT regime including NSAIDs and gabapentinoids may be beneficial in the neurosurgical setting for pain relief. We propose that, by means of a randomized clinical trial, we may be able to show whether or not such a MMT regime provides clinical benefit by reducing postsurgical patient-reported pain intensity and opioid consumption.

Chapter 2:
Methods

2.1. Rationale

It is established in the literature that the incidence and severity of PCH is often underestimated and that its treatment is inadequate [7]. This is largely due to the cautious use of opioids in order to avoid adverse side effects that may interfere with routine postoperative neurological assessments [43]. Current approaches to PCH management, such paracetamol and codeine phosphate, provide inadequate analgesic effects.

The published guidelines on management of postoperative pain by the APS and ASA strongly recommend the use of MMT [1]. Although published guidelines such as ERAS and PROSPECT support MMT for a wide variety of surgical settings, no such protocol yet exists for neurosurgery [4,5]. In the APS/ASA guideline, the evidence for including NSAIDs and gabapentinoids in multimodal perioperative analgesic regimes has been rated as 'high-quality' and 'moderate-quality' respectively [1]. However, this evidence stems largely from general, orthopedic and cardiothoracic surgical settings. The use of gabapentinoids in neurosurgery has only been investigated in four RCTs to date. At the time of initiating this study, there had been no studies which investigated the combined use of gabapentinoids and NSAIDs for neurosurgical analgesia.

This study therefore aims to assess the efficacy of a multimodal analgesic regime including gabapentinoids and NSAIDs on postoperative pain intensity in patients undergoing craniotomy. This data will contribute toward the existing body of literature available on the management of PCH and, if found to be effective, may aid in the development and implementation of an evidence-based approach to the treatment of PCH.

2.2. Aims and Objectives

The aim of this study is to determine whether or not a novel multimodal therapeutic regime comprising of a one-hour preoperative dose of oral 150mg pregabalin (Lyrica®), a dose of IV 40mg parecoxib (Rayzon®) at surgical closure and a two-hour postoperative dose of oral 150mg pregabalin (Lyrica®), has an effect on patient reported post-neurosurgical pain scores when compared to placebo and the current postoperative analgesic regime utilized at a local South African hospital.

To address this aim, the following objectives were defined:

1) To undertake a randomized, double-blinded, placebo-controlled trial which will investigate whether or not a novel, multimodal analgesic regime significantly reduces patient reported postoperative pain intensity scores, in patients undergoing elective epilepsy-related craniotomies.

2) To determine whether or not this proposed novel multimodal analgesic regime provides reduced postoperative opioid analgesic consumption in patients undergoing elective epilepsy-related craniotomies compared with current postoperative analgesic practice.
3) To develop an improved standardized analgesia protocol for neurosurgical patients during the perioperative period.

2.3. Study Outcomes

The primary and secondary outcomes of the study were defined as follows:

The primary outcome of the study was the difference in patient-reported pain intensity scores between experimental and control groups postoperatively, using repeated measures of the validated Numerical Rating Scale (NRS) over the first 24 postoperative hours.

Secondary outcomes of the study included: (1) patient-reported pain intensity scores postoperatively, using repeated measures of the validated Visual Analogue Scale (VAS) over the first 24 postoperative hours, (2) patient-reported pain intensity scores at 48 and 72 postoperative hours, (3) patient-reported Postoperative Nausea and Vomiting (PONV) intensity scores, (4) prevalence of patient-reported side effects of their medication based on a predefined checklist and (5) total consumption of postoperative opioid and non-opioid analgesic agents.

The null hypothesis of the study stated that there is no difference in patient-reported pain intensity scores between experimental and control groups over the first 24 postoperative hours.

2.4. A randomized, double-blinded, placebo controlled clinical trial

2.4.1. Ethical and regulatory approval

The investigational products, pregabalin and parecoxib, are not experimental drugs and are registered with the South African Health Products Regulatory Authority (SAHPRA):

- Pregabalin 150mg (Lyrica®): registration number A39/2.5/0268
- Parecoxib 40mg (Rayzon®): registration number 36/2.9/0120

The following regulatory authorities approved the conduct of this study (appendix A1):

- UCT Human Research Ethics Committee (HREC) with approval number 222/2018
- SAHPRA Clinical Trials Unit with approval number 20180809
- Mediclinic Clinical Research Committee

This trial has been registered on the South African National Clinical Trials Register (SANCTR) with DOH number DOH-27-0119-6056 (http://www.sanctr.gov.za).

2.4.2. Sample size calculation

Calculations for sample size are shown in **Table 1** below. To consider an interim analysis at 50% recruitment the sample size was inflated by 1.01%. Furthermore, taking in consideration a 5% dropout rate the desired sample size was increased to n=54 participants.

Table 1: Sample size calculation

Test Significance Level, α	0.050
Number of Levels, M	4
Variance in Means, Between Groups	0.076
Variance in Means, Between Levels	0.971
Variance in Means, Levels by Groups	1.321
Between-Groups Error Term	1.334
Within-Group Error Term	0.861
Measure of Sphericity, ε	0.990
Bias Term Multiplier, g_1	-3.208
Power, Between Groups (%)	81.53%
Power, Between Levels (%)	100%
Power, Levels by Groups (%)	100%
Sample Size per Group, n	25

Appendix A2 details the choice of study site and sample population, as well as the investigators involved.

2.4.3. Participant inclusion and exclusion criteria

Inclusion criteria:

- Male and female patients, over the age of 18 years, with a diagnosis of epilepsy and who were admitted to Constantiaberg Hospital for elective neurosurgical procedures including craniotomy for cortical resection or lobectomy for management of their epilepsy.
- Patients under ASA Physical Status Classification I and II.
- Patients who fully understood the implications of the study protocol, including the principle of control and randomization, and who had provided signed informed consent to participate in the study protocol.
- Patients who understood the VAS, NRS and PONV intensity scale assessments.

Exclusion criteria:

- Patients under 18 years of age.

- Patients who were admitted to Constantiaberg Hospital for other neurosurgical procedures.
- Subjects who were unwilling or unable to provide informed consent.
- Patients under ASA Physical Status Classification III and IV.
- Subjects who presented with contraindications to the use of parecoxib or pregabalin as defined on the latest South African package inserts, including:
    - Hypersensitivity to any active substance or excipients of either Lyrica® or Rayzon®.
    - History of hypersensitivity to sulphonamides.
    - Patients who had experienced bronchospasm, acute rhinitis, nasal polyps, angioedema, urticaria or allergy-type reactions after taking NSAIDs.
    - Severe impairment of hepatic function as indicated by serum Aspartate Aminotransferase [AST] and Alanine transaminase [ALT] levels at the discretion of JB.
    - Severe renal impairment as indicated by serum urea and creatinine levels at the discretion of JB
    - Post- and pre-operative analgesia in the setting of coronary artery bypass surgery (CABG).
    - Established ischaemic heart disease and/or cerebrovascular disease (stoke) and peripheral arterial disease.
    - Pregnancy and lactation.
- A history of rheumatologic, fibromyalgia, causalgia, or any other chronic pain syndromes in the year immediately preceding the elective neurosurgery.
- Cognitive impairment as indicated by a score of 0-23, measured using the Folstein Mini-Mental State Exam.
- Psychosocial comorbidities, including anxiety, depression and pain behaviour were noted, but did not necessarily result in exclusion.
- Perception of pain between individuals of varied age and gender were noted but did not result in exclusion.

2.4.4. Recruitment and informed consent procedures

Patients, who were identified as eligible for inclusion in the study were informed of the study procedures via a verbal explanation of the study protocol, randomization principles and the known side effects of the study medication. Patients were provided with an explanatory document detailing the study protocol and implication of their participation in paper format to peruse in their own time. Patients were given 24 hours to consider participation in the study

and study investigators were available to address any questions or uncertainties during this time.

If the patient agreed to partake in the study, all informed consent documentation (Appendix A3) was presented to the patient for completion. At this time the patient was reminded of the risks and benefits associated with the study, and that they were able to withdraw from the study at any given time point. After the informed consent forms were signed by the participant, the investigator and a witness, the patient was enrolled into the study and randomized into a blinded treatment group.

2.4.5. Randomization and blinding procedures

Randomization was performed using a block design on a 1:1 ratio. This ensured that participants enrolled into the two groups would be similar with regards to parameters such as age and sex, etc., and that an interim analyses would be possible at certain time-points during the course of the study [101]. A block size of four was utilized which produced six possible combinations of group assignments: (1) AABB, (2) BBAA, (3) ABAB, (4) BABA, (5) BAAB, (6) ABBA. Block arrangements were then selected at random using a list of random numbers generated using the RANDBETWEEN (1;6) function on Excel. CL performed all randomization procedures for the study by generating the master list of randomized numbers and subsequent treatment allocations. This information was passed on to the study pharmacist, who remained unblinded throughout the course of the study, and who conducted all treatment allocation procedures. All investigators, attending neurologists, anaesthetists and nurses, as well as participants remained blinded to the treatment allocation.

Following patient enrolment, each participant was allocated a unique enrolment code to ensure anonymity during data capturing procedures. This information was used by the study pharmacist who allocated all treatments according to the master randomization list. Treatment allocation was designated as 'treatment A' or 'treatment B', with the respective treatment known only to the study pharmacist. Importantly, the study pharmacist was unblinded during all stages of the study to ensure participant safety. Where unblinding was appropriate, 'treatment A' was revealed to be the control group, and 'treatment B' to be the experimental group.

This study was double-blinded and involved the use of a placebo in order to make the interventions within the control and experimental groups appear indistinguishable to participants and investigators. Placebo for pregabalin (Lyrica®) was in the form of a ProbiFlora™ Adult Everyday Flora Balance 2 strain probiotic capsule, and placebo for parecoxib (Rayzon®) was in the form of 2ml Sabax Sodium Chloride 0.9% solution in a sterile syringe prepared by the study pharmacist.

2.4.6. Treatment regime

The multimodal analgesic regime investigated in this study was as follows:

- Oral 150mg pregabalin (Lyrica®) *OR* placebo one hour before surgery
- IV 40mg parecoxib (Rayzon®) *OR* placebo at surgical closure
- Oral 150mg pregabalin (Lyrica®) *OR* placebo two hours after surgery, or as close as possible to this timepoint, depending on the state of responsiveness of the participant

The second dose of pregabalin (Lyrica®) or matching placebo was omitted in certain instances in which participant drowsiness was sufficiently severe to prevent oral consumption of medication. This decision was made at the discretion of JB and was not considered as a participant dropout, as randomization likely would ensure that this occurred equally frequently in the two arms of the study.

All study medication was packaged and prepared by the study pharmacist according to packaging instructions. Sealed packages containing either the placebo or active study medication were labeled according to the requirements set out by the South African Good Clinical Practice (SA-GCP) guidelines. This included the name, address and telephone number of investigators, the dosage, route of administration, quantity, batch number, trial reference number, participant enrolment code, directions for use and storage conditions, as well as wording clearly stating, 'For clinical trial use only'.

The standard of care received by both experimental and control groups consisted of:

- IV Paraspen® (1g paracetamol) 6-hourly repeats for the first 24 postoperative hours
- Opioid analgesics:
  - IM or oral DF118 Forte® (25 – 75mg dihydrocodeine) as needed (prn)
  - Oral Ultram® (50mg tramadol) as needed (prn)
  - IV Oxynorm® (10mg/ml oxycodone) as needed (prn)
  - IV Demerol® (50mg/ml pethidine) as needed (prn)
- Non-opioid analgesics:
  - Oral Celebrex® (100mg celecoxib) as needed (prn)
  - Oral Mybulen® (200mg ibuprofen, 350mg acetaminophen, 10mg codeine phosphate), Napacod® (450mg acetaminophen, 10mg codeine phosphate), Gen-payne® (200mg ibuprofen, 250mg acetaminophen, 10mg codeine phosphate) or Stilpane® (320mg acetaminophen, 8mg codeine phosphate) as needed (prn)
  - Oral Prolief® (500mg paracetamol) as needed (prn)

- Anti-emetics:
    - IV Emistop® or oral Zofer® (4mg ondansetron) as needed (prn)
    - IV or oral Kyrtil® (3mg granisetron) as needed (prn)
    - IV Stemitil® (12.5mg prochlorperazine) as needed (prn)

The above standard of care was tailored to each participant as done in everyday practice. Medication was administered according to individualized prescriptions at the discretion of JB and the attending anaesthesiologist. All postoperative medications, as defined by the standard care, were prepared and dispensed by the hospital pharmacy as per standard daily practice.

2.4.7. Assessments

2.4.7.1. Preoperative procedures

Prior to surgery the participants were asked to complete a series of questionnaires in order to identify poor baseline cognitive impairment and any additional confounding factors such as anxiety, depression and pain behavior which might represent exclusion criteria. These questionnaires included the Folstein Mini-Mental State Exam, Hospital Anxiety and Depression Scale (HADS) assessment, and Patient Reported Outcomes Measurement Information System (PROMIS) questionnaires on pain behaviour. Participants were instructed in the use of the VAS and NRS assessments, as well as the PONV intensity scale assessments. (Appendix A4)

The VAS assessment required participants to identify a point on the given 100mm horizontal line that they felt best described the average pain experienced from the time of the operation or the last assessment. The VAS scores were then determined using a ruler to measure the distance in millimetres between the left ‘no pain’ anchor and the point marked by the participant along the line. This provided a score between 0 – 100 with the following recommended cut off points: no pain (0–40 mm), mild pain (40-44 mm), moderate pain (45–74 mm), and severe pain (75–100 mm) [108].

The NRS assessment required participants to indicate the numeric value on the 11-point scale that they felt best described the maximum pain experienced since the operation or since the last assessment. Three descriptive points are marked on the scale with 0 indicative of ‘no pain’, a scores of 5 indicative of ‘moderate pain’ and a score of 10 representing the ‘worst possible pain’.

The PONV intensity scale required participants to answer a short series of multiple-choice questions to best describe the intensity of nausea and vomiting experienced after surgery. A total score of ≥50 is defined as clinically important PONV [109].

The participants' preoperative pain intensity scores were recorded one hour before surgery. The preoperative questionnaire evaluations and pain score assessments all took place at the participants' bedside and were limited to a maximum duration of 15 minutes in order to minimize the burden on the participants and nurses. AN, who was blinded to the treatment allocation, conducted all preoperative questionnaire evaluations, pain score assessments and data capturing onto a REDCap database during this phase.

2.4.7.2. Postoperative data collection

Postoperative data was collected once the participant had been transferred from the post-anaesthetic care unit (PACU) to the intensive care unit (ICU). The first measure of post-surgical pain intensity was taken 1-hour after surgical closure using both the VAS and NRS. Pain intensity was measured again 8, 24, 48 and 72 hours following the initial pain assessment. AN conducted all pain assessments under the supervision of an ICU or ward nurse on duty, and pain scores were captured onto a REDCap database.

In addition to the pain intensity assessment at the prescribed time points, participants were asked to indicate whether or not they had experienced any side effects to their medications using a predefined checklist. Participants were also asked to rate their postoperative nausea and vomiting (PONV) intensity using the PONV intensity scale at 6-, 24- and 72-hours post-surgery. Lastly, each participant's use of postoperative opioid and non-opioid analgesics was recorded and the data was captured onto the REDCap database.

Time point assessments were flexible to some degree, depending on the mental responsiveness of the participant and the time of day/night. However, all assessments were made as close as possible to the prescribed time schedule. Once the participant had completed all study-related assessments and been discharged from the hospital, appropriate exit procedures took place, which defined the study endpoint. An outline of the planned perioperative research procedures are shown in **Figure 6.**

2.5. Data analysis

All statistical analyses were performed on STATA and R software by an external biostatistician. An interim analysis took take place at the 50% recruitment target mark. The purpose of the mid-study interval analysis was to evaluate whether or not there was sufficient evidence of efficacy to justify early termination of the trial (measured by the significance of the preliminary data).

Descriptive statistics were used to summarize the demographic and covariate characteristics of the study population. A measure of standardized differences was utilized to determine any imbalances in baseline characteristics between groups. Quantile regression was employed to

adjust for baseline imbalances in analyzing the difference in patient-reported pain scores between experimental and control groups over a 24-hour period, which served as the primary outcome of the study. Furthermore, exploratory data analysis was performed using individual and mean profile plots. Since our data was longitudinal in nature, a mixed model analysis using area under the curve was used to investigate intervention effects. Comparative statistics was used to analyze the following variables: (1) Association of PONV intensity scores and treatment, (2) Difference in number of patient-reported adverse events between experimental and control groups and (3) Difference in means of total consumption of postoperative NSAIDs, opioids and non-opioid analgesics between experimental and control groups.

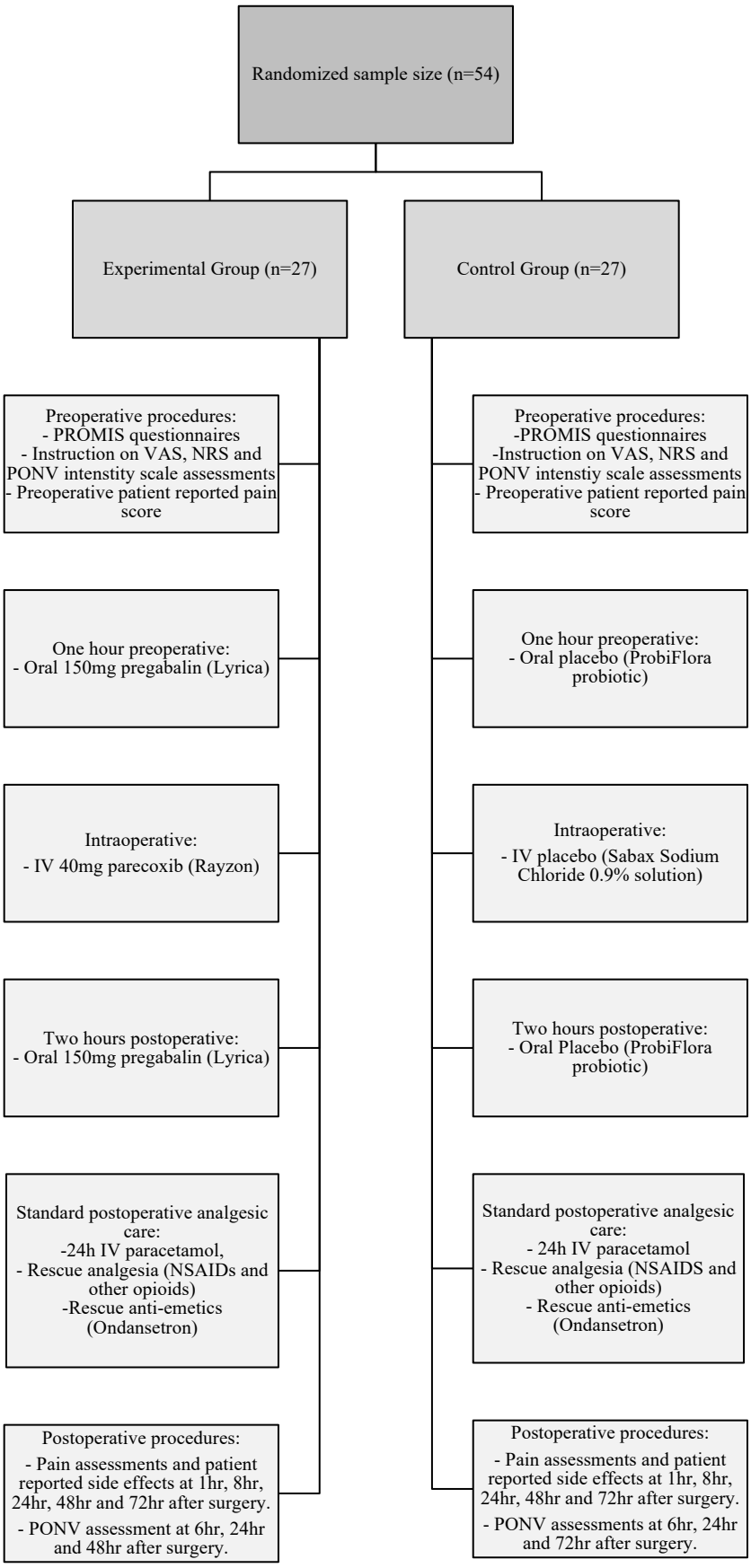

Figure 6: Planned research procedures for experimental and control groups

Chapter 3:
Results

3.1. Participant recruitment

Participant screening and recruitment commenced in July 2019 and ceased in August 2020. A total of 34 patients were screened for eligibility, six of whom declined participation and were excluded. Twenty-eight participants were enrolled in the study for blinded randomization into one of two treatment groups. Treatment Arm A was a control group in which participants received a placebo, and treatment Arm B was the experimental group in which participants received the active medication as defined in **Table 2** below. One participant was withdrawn from the study due to postoperative aphasia - no postoperative data was collected from this participant. **(Figure 7)**

Table 2: Medication allocated to treatment arms

Treatment Arm A **Control Group**	**Treatment Arm B** **Experimental group**
ProbiFlora™ Adult Everyday Flora Balance 2 strain probiotic capsule	150mg Pregabalin (Lyrica®)
2ml Sabax Sodium Chloride 0,9% solution	40mg Parecoxib (Rayzon®)

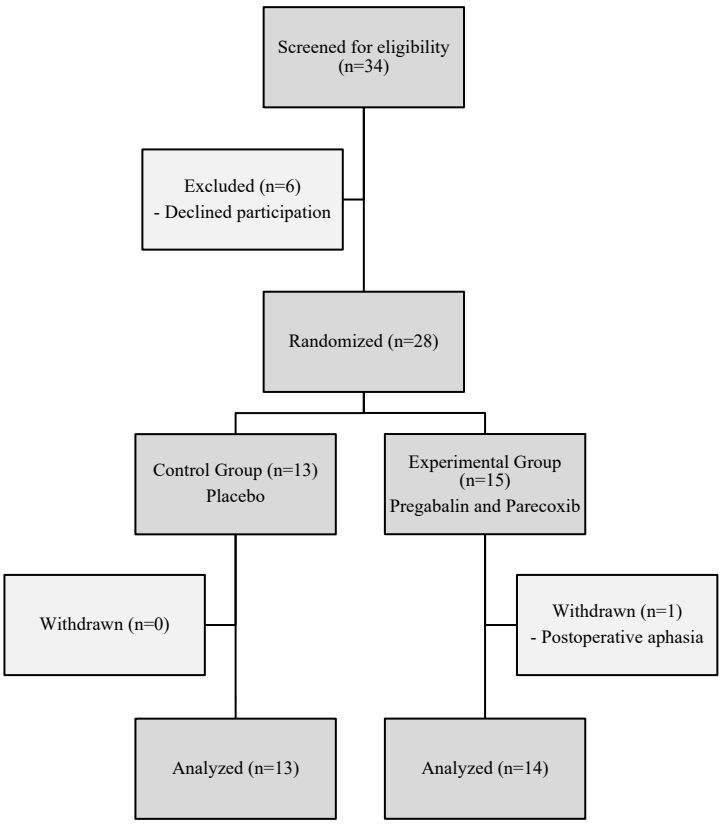

Figure 7: CONSORT diagram

The interim analysis, which was originally scheduled to take place once 50% of the recruitment target was met, was conducted earlier, at 44% recruitment, because of circumstances relating to the COVID-19 pandemic. Due to the nationwide lockdown, limitations were placed on elective surgeries which, in turn, resulted in a suboptimal rate of recruitment into the study between March and June of 2020. The interim analysis showed no evidence for efficacy to justify early termination of the study. However, the study was later terminated after the enrolment of 28 participants for ethical reasons, after the publication in August 2020 of a meta-analysis with unambiguous results (Verret *et al*. 2020 [110]), and, consequently, the study did not reach the desired sample size of 54 participants. The decision to stop the study early was guided by the study monitor.

3.2. Baseline characteristics

A cumulative total of 27 out of the 28 enrolled participants completed the study. Data analysis revealed that there were no significant imbalances with regards to the distribution of sex, Folstein mini-mental exam scores, HADS anxiety class scores or pain behaviour scores between groups. In addition, there was no difference in the mean duration of surgery between groups. **(Table 3)**

However, several baseline characteristics differed between groups, where the degree of difference is indicated by a standardized difference > 0.1. There was a significant difference in mean age (stddiff = 0.60) and the HADS depression class scores (stddiff = 0.19) between groups. A significant difference was also found between the groups in the number of participants in whom sub-dural electrode EEG monitoring had been performed prior to definitive surgery (stddiff = 0.25). This was reflected in a marked difference in the preoperative pain intensity scores between groups (NRS: stddiff = 0.47, VAS: stddiff = 0.45). These differences between groups indicate that our randomization procedures did not achieve their purpose due to the early termination of the study. Had the study reached its full sample size of 54 participants, randomization would likely have eliminated these imbalances.

Table 3: Demographic and baseline characteristics

Variable	Control group Placebo	Experimental group Pregabalin/Parecoxib	stddiff
Number of participants	13	14	
Age in years	45.9 ± 12.7	38.3 ± 12.8	0.60*
Women	7 (54%)	7 (50%)	0.07
MMSE	27.2 ± 2.2	27.9 ± 2.1	-0.16
HADS anxiety class			-0.39
Normal	9 (69%)	7 (50%)	
Borderline abnormal	2 (16%)	3 (21%)	
Abnormal	2 (15%)	4 (29%)	
HADS depression class			0.19*
Normal	12 (92%)	13 (93%)	
Borderline abnormal	0 (0%)	1 (7%)	
Abnormal	1 (8%)	0 (0%)	
PROMIS pain behaviour score	26 [21-28]	25 [21-28]	-0.16
Sub-dural electrodes prior to definitive surgery	6 (46%)	5 (33%)	0.28*
Preoperative NRS	1 [0-4]	0 [0-1]	0.47*
Preoperative VAS	2 [0-47]	0 [0-7]	0.45*
Surgery duration in minutes	180 [135-212]	165 [160-210]	0.19

Data is given as frequency (%)[a], mean ± SD for parametric, or median [IQR] for non-parametric as indicated
[a] Percentage rounded off to nearest whole number
stddiff = standard difference, *significant stddiff>0.1
MMSE = Mini-mental state exam score
HADS = hospital anxiety and depression
NRS = 0 – 10-point numerical rating scale
VAS = 100mm visual analogue scale

3.3. Pain parameters

Pain intensity was measured at 1-, 8-, 24-, 48-and 72-hour time points postoperatively using the NRS and VAS. Participant compliance was higher using the NRS assessments compared to the VAS assessment. The NRS assessments were completed at all time points by all participants. However, some participants were unable or unwilling to complete the VAS assessment at the 1-hour (48% of participants) and 8-hour (22% of participants) time points. Descriptive statistics of NRS and VAS scores by treatment are shown in **Table 4 and Table 5** below.

Table 4: Descriptive statistics of NRS scores by treatment

Treatment	Time point	n	Mean	SD	p25	p50	p75	Min	Max
Control group Placebo	Preop	13	2.0	2.4	0	1	4	0	6
	1hr	13	5.9	2.3	5	5	8	1	9
	8hr	13	4.4	2.7	3	4	5	0	9
	24hr	13	5.4	3.3	4	5	8	0	10
	48hr	12	5.8	3.0	4	5.5	8.5	1	10
	72hr	12	4.3	2.9	2.5	4	7	0	8
Experimental group Pregabalin/Parecoxib	Preop	14	0.9	2.2	0	0	1	0	8
	1hr	13	4.5	2.8	2	5	7	0	9
	8hr	14	3.4	2.7	0	3	6	0	7
	24hr	14	4.3	2.1	3	4	6	1	8
	48hr	14	3.6	2.3	2	3	6	0	7
	72hr	14	4.4	2.4	2	5	6	1	8

p = percentile
NRS = 0 – 10-point numerical rating scale

Table 5: Descriptive statistics of VAS scores by treatment

Treatment	Time point	n	Mean	SD	p25	p50	p75	Min	Max
Control group Placebo	Preop	13	19.5	24.1	0	2	47	0	60
	1hr	6	35.5	19.8	23	34	46	9	67
	8hr	9	44.8	31.4	25	41	55	0	94
	24hr	11	47.4	33.4	23	48	81	0	100
	48hr	10	49.8	29.0	32	36.5	76	12	93
	72hr	11	38.9	30.5	11	38	70	0	84
Experimental group Pregabalin/Parecoxib	Preop	14	9.2	21.5	0	0	7	0	75
	1hr	8	45.3	35.3	15	46.5	76.5	0	86
	8hr	12	33.5	27.5	11	26.5	53	0	84
	24hr	13	38.8	25.0	16	50	59	0	69
	48hr	12	32.3	24.0	13.5	23.5	56	0	68
	72hr	12	41.3	27.4	13	46	61.5	7	84

p = percentile

VAS = 100mm visual analogue scale

The mean profile plots of NRS score by treatment illustrate that, on average, the control group appears to have higher NRS mean pain profiles than the experimental group over the entire study duration **(Figure 8)**. The mean NRS score decreased for both the control and experimental groups from the 1st hour to the 8th hour after surgery. Thereafter, both groups had increased mean NRS scores from the 8th hour to 24th hour. The control group displayed a sharper increase in mean NRS pain scores compared to the experimental group.

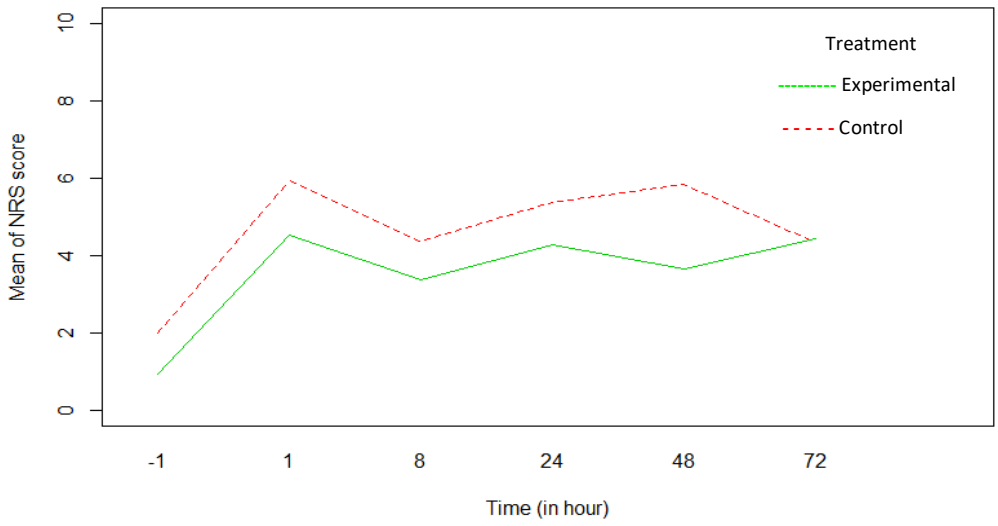

Figure 8: Mean profile plot of NRS score by treatment

Differing mean profile plots were observed for the mean VAS scores **(Figure 9).** The control group displayed increased mean VAS scores from the 1st hour to 8th hour, whereas the experimental group had decreased mean VAS scores during this period.

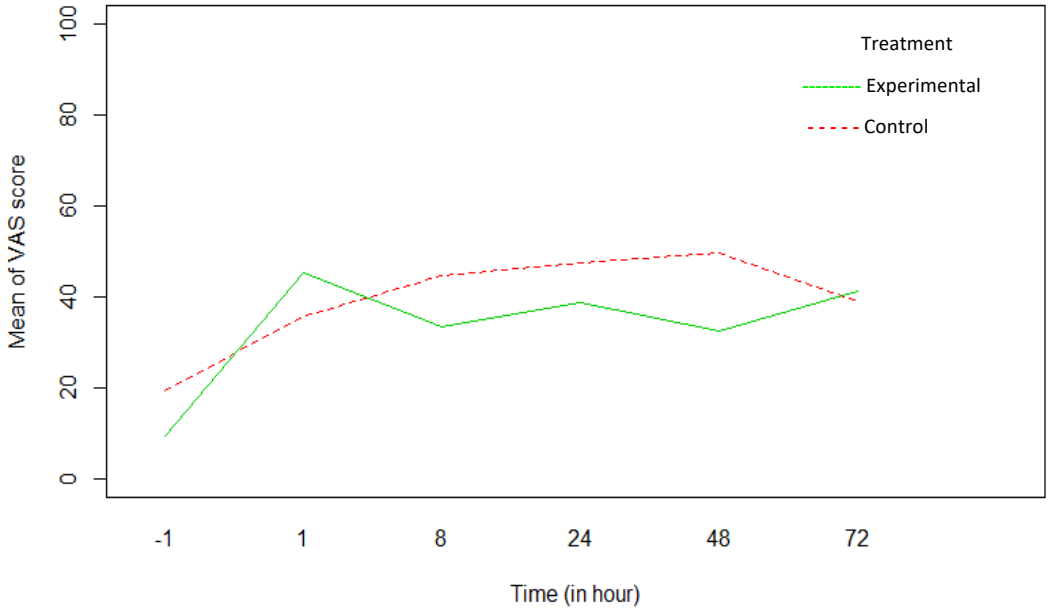

Figure 9: Mean profile plot of VAS score by treatment

In respect of the primary outcome, the study showed no significant difference. The means of maximum NRS and VAS scores, respectively reported by patients within the first 24 postoperative hours, and over the entire 72-hour period, were evaluated for differences between groups. No statistically significant differences were found between groups in the mean of maximum NRS pain scores in the first 24 postoperative hours ($p = 0.218$) or for the entire 72 hours ($p = 0.293$) **(Table 6)**. The same was true for the mean maximum VAS pain scores over these time periods. The 95% confidence interval show that in the first 24 hours after surgery, a difference greater than 29 points on the VAS scale (from 0-100) in favour of the active treatment arm has been excluded with confidence. This study therefore does not exclude a clinically significant difference in outcomes, given the findings of a systematic review of minimum clinically important differences in patient scores [111].

Table 6: Mean maximum pain scores by treatment

Time point	Maximum score	Control group Placebo	Experimental group Pregabalin/Parecoxib	95% CI	p-Value
First 24 hours	NRS	7.0 ± 2.3	5.9 ± 2.3	-0.72, 3.00	0.218
	VAS	48.5 ± 32.4	53.4 ± 27.6	-28.72, 18.93	0.676
Entire 72 hours	NRS	7.4 ± 2.2	6.6 ± 1.7	-0.75, 2.37	0.293
	VAS	58.1 ± 27.0	59.9 ± 25.1	-22.49, 18.79	0.855

Data is given as mean ± SD
NRS = 0 – 10-point numerical rating scale
VAS = 100mm visual analogue scale
95% CI mean difference between treatments

The areas under the response curves (AUCs) were respectively calculated for NRS from 0-to-24 hours, and for 0-to-72 hours using the trapezoidal rule. The AUC represents the cumulative NRS scores experienced over the exposure time period. There was no statistically significant intervention effect seen when comparing the mean difference in AUC24 (p = 0.1667) and AUC72 (p = 0.1082). **(Figure 10)**

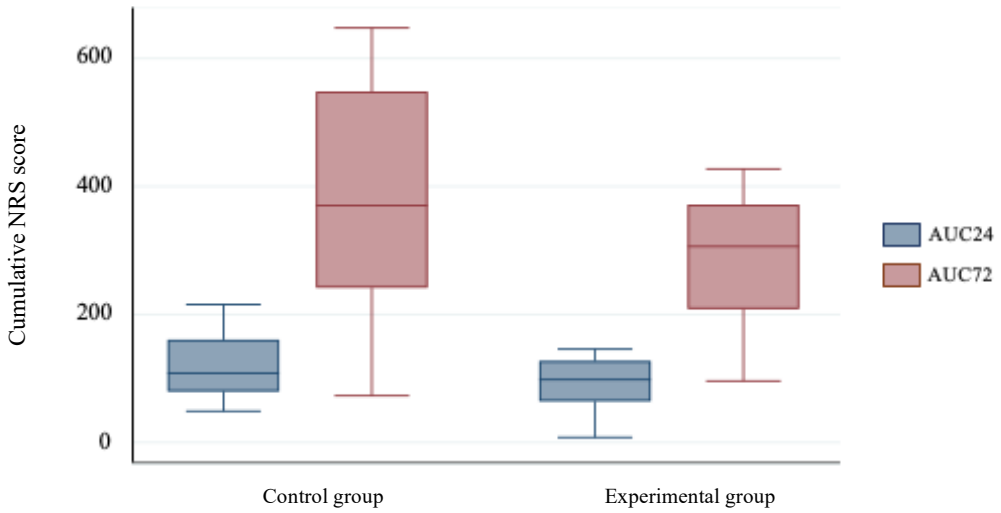

Figure 10: Box and Whisker Plot of area under the NRS response curve

3.4. Postoperative nausea and vomiting (PONV)

Intensity of PONV was assessed at 6-, 24- and 72-hours. A score >50 indicated clinically significant PONV. Only one participant who was in the control group presented with a score >50 and this occurred at the 6-hour assessment. Using the Wilcoxon rank sum test, there was no statistically significant association between PONV intensity scores and the treatment group at 6- (p = 0.257), 24- (p = 0.787) or 72-hour (p = 0.682) time points.

3.5. Adverse events

The control group reported an average of 2.15 side effects per participant and the experimental group an average of 5.14 side effects per participant. Blurred vision was prevalent in participants receiving pregabalin and parecoxib with a frequency of 71%, compared to only 8% in those receiving placebo. Further analysis using the Pearson Chi-squared test of association found that there was a significant association between the treatment group and blurred vision (p = 0.001). Dizziness and fatigue were also prevalent in the experimental group. A total of 64% of participants receiving pregabalin and parecoxib reported dizziness compared to 31% of participants, who received the placebo. Compared with 50% of participants in the experimental group, only 23% of participants in the control group reported fatigue. No significant association was found between the experimental group and dizziness (p = 0.082) or fatigue (p = 0.236).

3.6. Analgesia use

Additional opioid and non-opioid analgesia use in the first 24 postoperative hours was compared between groups to identify any opioid sparing effects of pregabalin and parecoxib use. Patients in the experimental group consumed statistically significantly less dihydrocodeine (mean = 107.5mg) than those who received placebo (mean = 173.8mg) (p = 0.029). No significant difference was seen in codeine, ibuprofen or paracetamol use between the groups **(Table 7)**. Furthermore, there was no statistically significant association between total additional opioid and non-opioid analgesia use and the experimental group **(Table 8)**. Given these findings, we believe that there is insufficient evidence, at 5% level of significance, to indicate a difference in total postoperative analgesia use between groups in the first 24 postoperative hours.

Table 7: Difference in total additional opioid and non-opioid analgesia (mg) by treatment

Variable		Control group Placebo	Experimental group Pregabalin/Parecoxib	Coeff (95% CI)	p-Value*
Additional opioid analgesia	Codeine	22.5 ± 25.4	13.7 ± 15.7	-8.7 (-25.4, 7.9)	0.288
	Dihydrocodeine	173.8 ± 72.8	107.5 ± 75.3	-66.3 (-125.2, -7.5)	0.029
Additional non-opioid analgesia	Ibuprofen	215.4 ± 310.5	200 ± 341.9	-15.4 (-275.0, 244.2)	0.904
	Paracetamol	5355.5 ± 1856.6	5206.7 ± 852.7	-129.1 (-1260.1, 1001.8)	0.816

Data is given as mean ± SD
*Simple linear regression, ref: arm A. Data satisfied normality.

Table 8: Number of total additional opioid and non-opioid analgesia by treatment

Variable	Categories	Control group Placebo	Experimental group Pregabalin/Parecoxib	p-Value*
Additional opioid analgesia	Meperidine			0.222
	No	11	14	
	Yes	2	0	
	Morphine			0.678
	No	9	11	
	Yes	4	3	
	Oxycodone			0.9999
	No	9	9	
	Yes	4	5	
	Tramadol			0.9999
	No	12	12	
	Yes	1	2	
Additional non-opioid analgesia	Celecoxib			0.9999
	No	11	11	
	Yes	2	3	
	Parecoxib			0.9999
	No	12	13	
	Yes	1	1	

Data is given as frequency
* Wilcoxon rank sum test. Non-parametric data.

Chapter 4:
Discussion

This randomized, double-blinded, placebo-controlled clinical trial investigated the effect of a multimodal analgesic regimen consisting of pregabalin and parecoxib compared to placebo treatment in craniotomy patients. Comparisons were made using patient-reported post-neurosurgical pain scores according to NRS and VAS assessments. To our knowledge, this is the first study to investigate the combined use of gabapentinoids and NSAIDs in the neurosurgical setting. This study shows that, in patients undergoing elective craniotomy for the treatment of their epilepsy, the administration of oral 150mg pregabalin one hour before surgery, IV 40mg parecoxib at surgical closure and oral 150mg pregabalin two hours after surgery provided no superior analgesic effect when added to a standard postoperative analgesic regime and compared to placebo. Because the study was terminated early and therefore underpowered, a difference cannot be excluded. However, patients in the treatment arm used significantly less dihydrocodeine in the first 24 hours after surgery than patients in the placebo arm. This is noteworthy as this is the principal medication used for treatment of severe postoperative pain at the study site. The study medications were associated with an increased rate of adverse events, notably blurred vision and dizziness, likely attributable to the use of pregabalin. Because of premature termination of the trial for ethical reasons, the results provide insufficient evidence to reject our null hypothesis, which states that there is no difference in patient-reported pain intensity scores between experimental and control groups in the first 24 postoperative hours.

There is a long-standing, generally held and non-evidence-based belief that, because nociceptors are absent within the brain parenchyma, patients undergoing craniotomy may experience less pain than those undergoing other surgical procedures [7,8]. For this reason, it is argued that less analgesia is required following craniotomy and that low-dose, weak opioids may provide sufficient post-surgical pain relief in this setting [112]. In recent years, this has been challenged with reports providing evidence that up to two thirds of craniotomy patients experience PCH, and that currently administered analgesic regimens provide insufficient pain relief [9,113]. In this study, 63% of patients experienced moderate to severe pain (indicated by an NRS score ≥ 5) at the time of their first postoperative pain assessment 1 hour after surgical closure. Furthermore, this persisted until 24 hours after surgery, with 53% of patients reporting moderate to severe pain intensity at the latter time point. These study results support recent findings in the literature which report a similar high incidence of postoperative pain following craniotomy [15,18,19]. Despite these reports of high PCH prevalence and the importance of adequate pain relief to prevent patient agitation and associated complications, the established narrative and reluctance to use opioids in the setting of craniotomy continues to result in the under-treatment of PCH. Health professionals should be encouraged to use scientific, evidence-based principles to guide their treatment of PCH rather than personal or local

preference. That said, there is only limited evidence-based clinical information available in the literature to guide such use of analgesia [9]. Nevertheless, the development of an effective, standardized and evidence-based analgesic protocol remains crucial to provide improved patient care and better outcomes after craniotomy [55,114].

The use of gabapentinoids within a multimodal analgesic regimen has been increasingly investigated in various surgical settings, where it is suggested to reduce opioid requirements, and lower postoperative pain scores [90–93]. The APS and ASA guideline on the management of postoperative pain management suggests that the inclusion of a preoperative gabapentinoid is effective in improving analgesia after surgery. However, because of limited supporting evidence-based literature, no authoritative guidelines are available regarding optimal dosage regimens, whether or not single or multiple doses are appropriate, and the time points at which this drug should be administered [1]. A meta-analysis published in 2015 concluded that there was no difference in 24-hour postoperative pain scores in RCTs utilizing single preoperative gabapentinoid dosing regimens versus those with multiple dosing regimens in a variety of surgical procedures [93]. In patients undergoing laparoscopic cholecystectomy, a single preoperative dose of 150mg pregabalin administered one hour before surgery significantly reduced postoperative pain and fentanyl consumption over the first 24 hours after surgery [115]. Similarly, a reduction in pain intensity was reported in patients undergoing coronary artery bypass surgery who received a single dose of 600mg gabapentin two hours before surgery [116]. These findings were not reflected in neurosurgical settings. Lamsal *et al.* (2020) and Misra *et al.* (2013) demonstrated that single preoperative doses of 150mg pregabalin and 600mg gabapentin, respectively, were ineffective in reducing postoperative pain scores after craniotomy [95,97]. In contrast, 75mg pregabalin administered twice daily (with the first dose one hour before surgery and the second 12 hours later) was found to be effective in reducing pain for patients undergoing mastectomy [117]. Although the same dosage regime (75mg twice daily) did not result in reduced PCA consumption over the first 24 hours post spinal fusion surgery, a higher dose of 150mg pregabalin given at the same time points significantly reduced PCA consumption [118]. This suggests that multiple doses of pregabalin may be required for effective analgesia in the neurosurgical setting. Shimony *et al.* (2016) demonstrated that the prolonged use of 150mg pregabalin over 72 hours did provided superior analgesic effects or reduced postoperative pain scores in neurosurgical patients [94]. There is concern regarding the side effects of sedation, dizziness and visual disturbances associated with prolonged pregabalin use, especially in neurosurgical patients. Although the study by Shimony *et al.* reported that none of these side effects were attributable to their respective dosing regimen, and that the prolonged use of pregabalin was safe to use in neurosurgical patients [94], meta-analyses report contradictory results. In almost all the surgical categories included in a meta-analysis

performed by Lam *et al.* (2015), increased incidences of sedation, visual disturbances and dizziness were associated with pregabalin use [93]. Similarly, in their systematic review, Mishriky *et al.* (2015) reported that side effects were commonly associated with pregabalin in the 55 studies they analyzed [91].

Based on this information, we reasoned that multiple doses of pregabalin would be required to improve post-surgical pain relief in neurosurgical patients but that, in order to limit the adverse drug effects, its administration should not be continued beyond 24 hours post-surgery. Pregabalin reaches its peak plasma concentration within one hour of oral administration, has a mean elimination half-life of 6.3 hours, and achieves a steady state at around 24 hours with 12-hourly dosing [119]. Buvanendran *et al.* (2010) reports that a single dose of 300mg pregabalin reaches sufficient levels of bioavailability in the central nervous system 6 hours after oral administration in order to have therapeutic effects in the form of reduced neuronal hypersensitivity [120]. Therefore, our study team reasoned that a one-hour, preoperative dose of oral 150mg pregabalin would allow for sufficient plasma concentrations around the time of surgical head-pinning procedures, surgical opening and reflection of the surrounding musculature, periosteum and dura; all procedures which are associated with nociceptive responses in neurosurgery. Furthermore, that a second two-hour postoperative oral dose of 150mg pregabalin should allow for additional analgesic effects in the immediate postoperative period up to 24 hours after surgery. The addition of IV 40mg parecoxib at the time of surgical closure, which reaches its peak plasma concentration within 30 minutes and has a mean elimination half-life of 8 hours [121], would suppress inflammatory responses to surgically damaged tissue and, in this way, reduce noxious stimuli when the patients wake up from surgery. In addition, the parecoxib would provide synergistic analgesic effects when prescribed together with the pregabalin. The combined use of gabapentinoids and NSAIDs has been investigated in only two studies to date, both of which are in the setting of Total Knee Arthroplasty. Lee *et al.* (2015) demonstrated that a single preoperative dose of 150mg pregabalin combined with 400mg celecoxib lowered pain scores at 6- and 12-postoperative hours in comparison to celecoxib administration alone [122]. The second study by Lubis *et al.* (2018) found a significant reduction in postoperative morphine consumption in patients receiving combined use of pregabalin and celecoxib compared to placebo [123]. Interestingly, dosing regimens of (1) a single dose 150mg pregabalin with 400mg celecoxib, and (2) 75mg pregabalin dose twice daily for 3 preoperative days with 200mg celecoxib, did not show any significant differences in postoperative morphine consumption. Authors did, however, report side effects in the group with prolonged pregabalin use [123]. Based on the dosing regimen proposed in the current study, we anticipated that we would observe the optimal analgesic

effects, reflected as lower pain scores and decreased opioid use, within the first 8 hours of surgery, and that these may persist to 24 hours.

We found that the use of preoperative oral 150mg pregabalin, intraoperative IV 40mg parecoxib and postoperative oral 150mg pregabalin in patients undergoing craniotomy for epilepsy treatment did not result in significantly lower mean maximum pain intensity scores over the first 24 postoperative hours compared to a placebo. Additionally, an exploratory mixed model analysis using area under the NRS response curve revealed no intervention effect. Area under the curve analysis calculates the cumulative NRS scores experienced over the exposure time period. When dividing by the exposure time, the average NRS score during exposure can be calculated. No significant difference was found between groups when comparing AUC score units. Despite not reaching statistical significance, the mean profile plots of NRS and VAS scores show that patients who received placebo treatment had, on average, higher NRS and VAS mean scores compared to patients who received the multimodal regime. Using the NRS scores, it is seen that both groups show a decrease in pain from the 1st hour to 8th hour, followed by an increase to the 24th hour. The control group had a higher rate of increase compared to the experimental group. Interestingly, the VAS scores revealed a different pattern between groups from the 1st hour to 8th hour compared to the NRS scores. The mean VAS scores increased from the 1st hour to 8th hour in the control group, whereas it decreased for the experimental group during this period. The pattern revealed by the mean pain profiles of the VAS score is one we would expect to observe given our dosing regimen, as the pregabalin and parecoxib work synergistically to provide analgesic effects within the first 8 hours after surgery. The reasons for the difference in mean profile plots seen between NRS and VAS scores are unclear as both assessments measure the same outcome. It is possible that this difference is due to the large amount of missing data for VAS scores, a consequence of participants inability or unwillingness to complete this assessment after surgery. This observation supports the superiority of the NRS assessment over the VAS assessment due to its simplicity and ease of administration [77]. Furthermore, it supports the conclusion made by Hjermstad *et al.* (2011) which stated that the VAS assessment is associated with lower levels of patient compliance and greater risk of discrimination [78].

In this study, we found that the use of pregabalin and parecoxib in the neurosurgical setting does not result in a statistically significant reduction in postoperative pain scores compared to placebo, a conclusion which is in line with the presented literature [39,84,95]. However, these RCTs investigated isolated single dosing of either pregabalin or parecoxib rather than a combined multiple dosing regimen, as investigated in our study. Caution must be exercised in making the inference that non-significance implies that an intervention is not effective. Gates *et al*. (2019) raised the concern that use of significance thresholds create a binary classification

of results as either 'effective' or 'ineffective' when, in fact, this is not always clear-cut [124]. The authors suggest that the use of statistical significance to conclude the clinical effectiveness of a treatment is not justifiable because common issues such low recruitment numbers, poor compliance, high drop-out rates, co-interventions and increased variability can reduce the power of a study. As is standard practice in science, the possibility of a false negative outcome must always be considered. Therefore, more research is required to definitively separate non-significant results that derive by chance from those that derive from a true lack of treatment benefit.

A possible reason, which may have influenced the lack of statistical significance in this study, is small sample size. The originally proposed sample size to detect differences at 5% significance level in this study was estimated at 54 participants. However, before premature termination, we had only recruited 27 participants. Participant recruitment into the trial was slowed considerably due to the circumstances surrounding the COVID-19 pandemic. More particularly, the increased diversion of hospital beds and resources to the management of COVID-19 patients resulted in restrictions being placed on elective surgery. This, in turn, resulted in suboptimal participant recruitment. A limitation worth noting is the fact that some patients were excluded at the discretion of JB which may have resulted in some inclusion bias. Only participants who, at the discretion of the attending neurologist, had cognitive impairments that would prevent them from providing adequate informed consent were not invited to take part in this study. All patients meeting inclusion and exclusion criteria were invited to take part in this trial. Furthermore, the review and findings of a meta-analysis by Verret *et al.* (2020) [110], which was published in August 2020 after recruitment into our study was well established, resulted in a decision to terminate the study early. Verret *et al.* (2020) conducted a meta-analysis to determine whether or not any clinically significant analgesic effects had been found in postoperative pain management with the use of gabapentinoids. A search of 281 studies (which notably includes only two studies from the neurosurgical setting) concluded that gabapentinoids were associated with lower pain intensities at 6-hours, 12-hours, 24-hours and 48-hours but that these lower pain intensities did not reach clinical significance defined as a minimal clinically important difference of 10/100 points. Furthermore, there was an increase in prevalence of dizziness and visual disturbances associated with gabapentinoid use. The authors concluded that the results do not support routine use of gabapentinoids in management of postoperative pain and that the probability of achieving a clinically meaningful postoperative analgesic effect was, at best, negligible. Given these convincing results, we considered that continued recruitment of participants to the treatment group of our study was unlikely to demonstrate any clinically significant benefit, whereas it was likely to increase the risk of visual disturbances and/or dizziness. This being

the case, we regarded it as unethical, in accordance with the SA-GCP guidelines, to continue with the study.

In our study, total use of additional opioids in the first 24 postoperative hours acted as a secondary outcome to investigate opioid-sparing effects of our multimodal regime. All participants enrolled into the trial, regardless of treatment group, received the current standard of care at the study site. This consisted of IV paracetamol in the first 24 postoperative hours and administration of additional opioid and non-opioid analgesics as needed at the discretion of the attending physician. This is in line with current management of PCH reported in literature, as discussed in section 1.3. Since standard of care is typically individualized to each patient, and based on their immediate analgesic requirements, we found that the use of varied opioid and non-opioid analgesics did not provide a uniform platform for fair comparison of analgesic consumption. For example, drugs such as morphine and oxycodone were utilized by 26% and 33% of patients, respectively, resulting in non-parametric data distribution and median scores of zero, whereas drugs such as dihydrocodeine, codeine, ibuprofen and paracetamol were used by all patients and were therefore the only drugs that allowed for accurate comparison. It is also worthwhile noting that the study design initially included the use of PCA morphine for the first 24 postoperative hours as standard of care for all participants. This was done in an attempt to standardize postoperative pain treatment, in order to allow for sufficient pain relief, and for the easier monitoring and data capture of additional analgesia use, as well as to mirror similar study designs in the literature. Following an adverse event involving miosis in an enrolled participant, the attending anesthesiologist and nursing staff recommended the discontinuation of PCA morphine as it compromised neurological monitoring of patients. Consequently, standard analgesic care was re-instated in place of PCA morphine on grounds of patient safety.

The findings of this study provide limited evidence on the opioid-sparing effects of concurrent pregabalin and parecoxib use in craniotomy. Patients in the experimental group used significantly less dihydrocodeine than patients who received placebo ($p = 0.029$). The finding of reduced dihydrocodeine use in the experimental group is noteworthy as administration of this medication represents the principal treatment of refractory, severe PCH at this hospital. These results are similar to those reported in the Lubis *et al.* (2018) study, where authors demonstrated that the use of pregabalin and celecoxib significantly reduced postoperative morphine consumption in total knee arthroplasty [123]. However, the total consumption of additional codeine, ibuprofen and paracetamol were not significantly different between groups. Since these are combined first-line therapies for PCH, the lack of a significant difference in their use is perhaps unsurprising, given that all patients require analgesia. The frequency of other additional opioid and non-opioid analgesics was not significantly different

between groups. Within the neurosurgical setting, the evidence for opioid-sparing effects of pregabalin and parecoxib remains contradictory. Misra *et al.* (2013), Zeng *et al.* (2018) and Williams *et al.* (2011) found no significant differences in postoperative opioid consumption between placebo and gabapentin or parecoxib use [84,96,97]. In contrast, Shimony *et al.* (2016), Lamsal et al. (2020) and Jones et al. (2020) reported significant reductions in opioid consumption between placebo and pregabalin or parecoxib use [83,94,95].

Lastly, our study found that the use of pregabalin and parecoxib resulted in an increased incidence of blurred vision, dizziness and fatigue compared to placebo. It is noteworthy that blurred vision was common and reported by 71% of patients in the experimental group but in only 8% of patients in the control group. Visual disturbances and sedation are well recognized adverse events associated with pregabalin use [119]. Our findings showed that a twice daily dose of pregabalin resulted in increased frequency of blurred vision, which differs from the results of Shimony *et al.* (2020) who reported that prolonged pregabalin use over 72 hours was associated with no adverse events [94].

In conclusion, multimodal therapeutics has been suggested by the APS and ASA for the management of postoperative pain and publications such as ERAS and PROSPECT increasingly support this. However, the use of gabapentinoids and NSAIDs as components of a multimodal analgesic regime for neurosurgical patients has yet to be extensively investigated, and there is currently only limited literature available with regards to optimal doses. This randomized clinical trial does not provide sufficient evidence to demonstrate that the use of one-hour preoperative 150mg pregabalin, intraoperative 40mg parecoxib and two-hour postoperative 150mg pregabalin provides superior analgesic effects to a current standard analgesic regime. In addition, the increased incidence of visual disturbances associated with pregabalin use is undesirable for neurosurgical patients. Our study does not support the combined use of gabapentinoids and NSAIDs within a multimodal regime for neurosurgical patients. The secondary outcome finding of this study, demonstrating reduced dihydrocodeine use, strongly merits further study comparing intraoperative parecoxib with placebo as this may reduce post-operative opiate use, while avoiding the confounding side-effects shown in this study.

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Appendices

A1: Ethical and Regulatory approvals

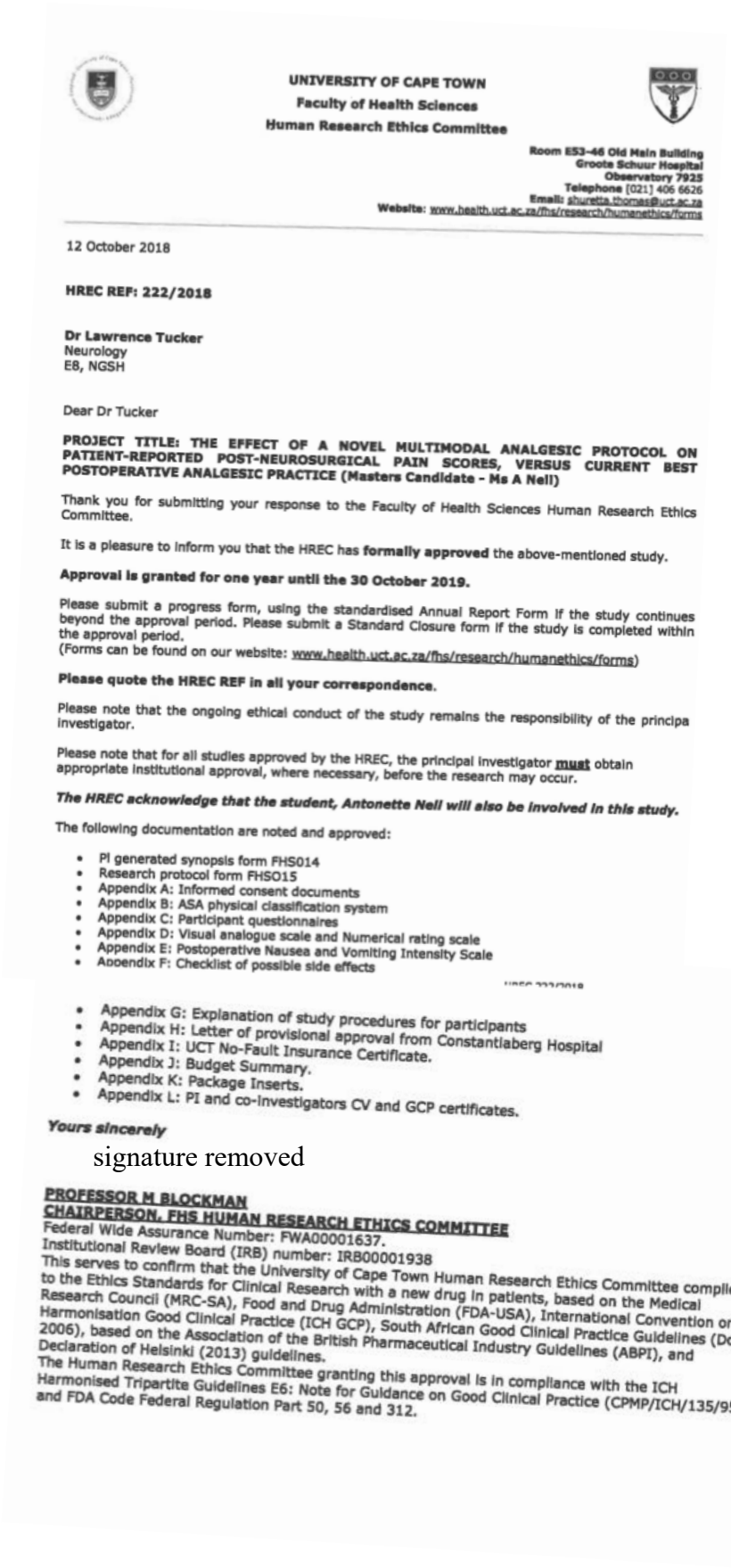
A2: Study site, sample population and investigators

A3: Informed consent form

A4: Participant assessments

A5: TurnItIn: Similarity Index Report

A1: Ethical and Regulatory Approval



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
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Website: www.health.uct.ac.za/fhs/research/humanethics/forms

12 October 2018

HREC REF: 222/2018

Dr Lawrence Tucker
Neurology
E8, NGSH

Dear Dr Tucker

PROJECT TITLE: THE EFFECT OF A NOVEL MULTIMODAL ANALGESIC PROTOCOL ON PATIENT-REPORTED POST-NEUROSURGICAL PAIN SCORES, VERSUS CURRENT BEST POSTOPERATIVE ANALGESIC PRACTICE (Masters Candidate - Ms A Neil)

Thank you for submitting your response to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 October 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principa investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student, Antonette Neil will also be involved in this study.

The following documentation are noted and approved:

- PI generated synopsis form FHS014
- Research protocol form FHSO15
- Appendix A: Informed consent documents
- Appendix B: ASA physical classification system
- Appendix C: Participant questionnaires
- Appendix D: Visual analogue scale and Numerical rating scale
- Appendix E: Postoperative Nausea and Vomiting Intensity Scale
- Appendix F: Checklist of possible side effects

- Appendix G: Explanation of study procedures for participants
- Appendix H: Letter of provisional approval from Constantiaberg Hospital
- Appendix I: UCT No-Fault Insurance Certificate.
- Appendix J: Budget Summary.
- Appendix K: Package Inserts.
- Appendix L: PI and co-investigators CV and GCP certificates.

Yours sincerely

signature removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

UNIVERSITY OF CAPE TOWN

HUMAN RESEARCH ETHICS COMMITTEE
01 OCT 2019
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.10.2020
☐ Not approved	See attached comments		
Signature Chairperson of the HREC	Signature Removed	Date Signed	1/10/2019

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	01 October 2019		
HREC REF Number	222/2018	Current Ethics Approval was granted until	30 October 2019
Protocol title	The effect of a novel multimodal analgesic protocol on patient-reported post-neurosurgical pain scores, versus current best postoperative analgesic practice.		
Protocol number (if applicable)	MMTv1.0		
Are there any sub-studies linked to this study?	☐ Yes ☑ No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Dr Eddy Lee Pan		
Department / Office Internal Mail Address	E8 Division of Neurology, Groote Schuur Hospital, Observatory.		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

SAHPRA
SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

Private Bag X828, PRETORIA, 0001
Tel 012 395 8000
Tel:
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Fax 012 395 9201
Enquiries:
Reference:

EMAILED

MS KEDIBONE MALATJI

Datum * Date **15 January 2019**

Tel: 012 395 8729
Fax: 012 395 8129

Ms A Nell
Division of Neurology
E8, Groote Schuur Hospital
Anzio Road
Observatory, Cape Town
7925
Fax: 0214066251

Dear Ms Nell,

AUTHORISATION FOR THE IMPORTATION OF UNREGISTERED MEDICINE IN TERMS OF SECTION 21 OF THE MEDICINES AND RELATED SUBSTANCES CONTROL ACT, 1965 (ACT 101 OF 1965)

PRODUCT: PREGABALIN (TEVA®)

Your application letter dated **22 June 2018** refers

1. **RESOLUTION AND APPROVAL**
It was recently resolved by the South African Health Products Regulatory Authority (SAHPRA) that; the clinical trial application according to the following
Protocol be approved:-
MMTv1.0 version 1.0 dated 2018
The effect of a novel multimodal therapeutic protocol on patient-reported post-neurosurgical pain scores, versus current best postoperative analgesic practice

1.1 **BEFORE COMMENCEMENT OF TRIAL**
Please Note: Copies of written Ethics Committee approval/(s) to be submitted to SAHPRA before the study commences.

2. **AUTHORISATION**
Authorisation is hereby granted for the importation and administration of a sufficient quantity, for the duration of the trial, of the unregistered medicine:
PREGABALIN (TEVA®)
solely for the purpose of a clinical trial to be conducted by:

Dr EL Pan	Dr Butler's Private Practice, Epilepsy Unit, Constantiaberg Mediclinic Hospital	Principal Investigator
Dr J Butler	Dr Butler's Private Practice, Epilepsy Unit, Constantiaberg Mediclinic Hospital	
Dr LTucker	Dr Butler's Private Practice, Epilepsy Unit, Constantiaberg Mediclinic Hospital	

3. **PLEASE FORWARD**
It is a requirement that a copy of this letter be forwarded to all the relevant Trialist/(s), including the approving Ethics Committee(s).

4. **THIS AUTHORISATION IS SUBJECT TO THE FOLLOWING PROVISOS:**
(a) SAHPRA shall be informed immediately of any toxic effects or death, which may occur during the Clinical Trial and of any data received which, might cast doubt on the validity of the continuation of the Clinical Trial.
(b) SAHPRA shall be notified of any decision to discontinue the Clinical Trial. The reason for such cancellation shall be stated.
(c) The Clinical Trial shall be conducted in accordance with the Protocol submitted to SAHPRA. Any Amendment/(s) to the Protocol shall first be submitted to SAHPRA for approval. All Clinical Trials be conducted in accordance with ICH GCP Guidelines, and the South African Clinical Trials Guidelines.
(d) The medicine shall be administered by or under the direction of the authorised Trialist. In the case where the Trialist permits another Medical Practitioner to administer a medicine, which is exempted from the registration for the purpose of the Trial, the Trialist shall remain responsible for any eventuality arising from such usage.
(e) Where a Trialist who is not authorised in the initial Authorisation, is requested to participate in the Clinical Trial, SAHPRA requests that the relevant SAHPRA Curriculum Vitae Format be completed detailing their Full Names, Address and Qualifications of the proposed Trialist (Practitioner) concerned, and be submitted to the Council for Approval.
(f) In the event of the authorised Trialist ceasing to participate in the Clinical Trial, SAHPRA shall be informed and the reason for such cessation shall be given.

5. **PROGRESS REPORTS**
SAHPRA must be furnished with signed six-monthly Progress Report from each Trialist including a report of the Final Results.

6. **INFORMED CONSENT**
It is a SAHPRA Council requirement that in all Clinical Trials the 'Principles of Informed Consent' should be adhered to. This applies to Trial Volunteers, as well as Participants (Patients). (Reference: Section 4.8 of ICH GCP Guidelines and Section 3.5 of SACT Guidelines).

Note: Dr Tucker has been redesigned as a Sub-I due to limited experience in the conduct of clinical trial. Dr Eddy Lee Pan is appointed as the PI for this study.

No exemption of study material required for this study. Medicines will be sourced locally.

Yours faithfully,

Signature Removed

MS KEDIBONE MALATJI

FOR AND ON BEHALF OF THE ACTING CHIEF EXECUTIVE OFFICER

TRIAL REFERENCE NO: 20180809

MEDICLINIC

MEDICLINIC CORPORATE OFFICE
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02 February 2019

Ms A Nell
Mediclinic Constantiaberg
Burnham Road
Plumstead
8001

nllant002@myuct.ac.za

Dear Ms Nell

PERMISSION TO CONDUCT RESEARCH AT MEDICLINIC CONSTANTIABERG

Your research proposal entitled "The effect of multimodal therapeutic protocol on patient-reported post-neurosurgical pain scored versus the current postoperative analgesic practice, employed at local South African Hospital" – Protocol MMTv1.0 refers.

It is in order for you to conduct your research at Mediclinic Constantiaberg, and I wish you success with this project.

Yours sincerely

Signature Removed

Dr Chris du Plessis
General Manager Clinical Services
MEDICLINIC SOUTHERN AFRICA

A2: Study site, sample population and investigators:

This study was established and conducted at JB Private Epilepsy Practice at Constantiaberg Mediclinic Hospital. JB practice specializes in the diagnosis and treatment of epilepsy, including surgical interventions for the management of intractable epilepsy. For this study, patients who are scheduled for elective neurosurgery, involving epilepsy-related craniotomies with either cortical resection or lobectomy for the management of their epilepsy, were recruited, randomized and enrolled into the study continuously over the course of two years. This hospital in the private healthcare sector allowed for a homogenous study population for this study, as it has a long-established epilepsy unit and standardized treatment methodology for the management of epilepsy, which does not yet exist at Groote Schuur Hospital or elsewhere in the South African public health care sector. Additionally, the neurologist, neurosurgeon, anaesthetist and nursing staff remained constant throughout the study, thus reducing potentially confounding variables. **Table A1** outlines the respective roles and responsibility of key researchers and staff involved in the study. Further justification for the conduct of this clinical trial in the private sector is due to the fact that we can be certain that the headache or pain experienced after an elective epilepsy-related craniotomy will be largely attributed to the tissue trauma induced by the surgical procedure, i.e., the underlying disorder of epilepsy is not a confounding factor to headaches. Whereas other neurosurgical procedures, such as subdural hemorrhage, tumor resection etc., which are routinely performed in the public healthcare sector such as Groote Schuur Hospital, the headache or pain experienced after surgery may be confounded by the underlying disorder and associated chronic headaches.

Table A1: Researchers role and responsibilities involved in the study

Name and qualifications:	Role:	Responsibilities:
AN BSc, BMedSci Hons, MSc candidate	Student Researcher	Patient recruitment and enrolment, administration of preoperative questionnaires, instruction of VAS and NRS to participants, blinded administration of VAS and NRS pain assessments, blinded administration of PONV assessments, data capturing and database management.
ELP MBChB, MMed	Principal investigator	Oversee study procedures and protocols, and regular review of progress of the study
LT MBChB, MSc, FCP(SA), PhD	Sub-investigator Primary supervisor.	Oversee study procedures and protocols, and regular review of progress of the study.
JB MBChB, FCP(SA)	Neurologist Sub-investigator Secondary supervisor	Acting neurologist. Attend to clinical pre- and post-operative day-to-day care of participants, including prescription of medication and daily evaluation of clinical progress post-surgery. Oversee study procedures and progress.
RM MBChB, FCS(SA)	Neurosurgeon	Acting neurosurgeon.
RE MBChB, MRCP, FRCP	Monitor	Oversee study procedures and protocols. Ensure study compliance with Good Clinical Practice.
NS BPharm	Pharmacist (2019)	Randomization and participant treatment allocation to study/ control groups. Blinding. Study and placebo medication preparation and dispensing.
NF BPhram, PharmD	Pharmacist (2020)	
CL PhD Statistics AY MSc Statistics	Biostatistician	Data analysis.

A3: Informed consent document

Informed consent document

Study title: The effect of a novel multimodal therapeutic protocol on patient-reported post-neurosurgical pain scores, versus the current postoperative analgesic practice employed at a local South African Hospital.

Project Leader: Antonette Nell

Investigators: Dr James Butler, Dr Eddy Lee Pan and Dr Lawrence Tucker

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Because you live with epilepsy and have been scheduled for an elective neurosurgical operation which is indicated for the management of your epilepsy, we have asked you to consider taking part in this research study.

Please take time to read the following information carefully regarding the study procedures and do not hesitate to contact the investigators to ask any questions that may arise. It is important for you to fully understand why the research is being done and what is required of you should you decide to partake in the study.

Why is the study being done?

Patients undergoing neurosurgical operations frequently experience high levels of pain after surgery. This study aims to investigate whether or not a new approach to pain relief can reduce pain levels in patients who have had neurosurgery compared with the standard anti-pain medication that is used at present.

What is 'Multimodal Therapeutics'?

Multimodal therapeutics involves the use of a number of pain relief medications which respectively target different pain pathways and which, when used together, are expected to provide superior pain relief. In this study, two pain medications; pregabalin (Lyrica®) which is also used to treat epilepsy, and parecoxib (Rayzon®), which is an anti-inflammatory drug, will be prescribed in addition to other standard pain relief medications. Lyrica® and Rayzon® are not experimental drugs, as they are registered with the South African Health Products Regulatory Authority (SAHPRA) and are already widely prescribed to control non-surgery related pain. There is no known adverse interaction between Lyrica® and Rayzon®, or between these two medications and other standard medications usually prescribed for surgery-related pain.

How the study works: Randomization, Study Group and Control Group

If you agree to participate in this study, you will be randomly allocated to either an experimental group (in which case you will receive Lyrica® and Rayzon®, in addition to standard medications which are usually prescribed to control surgery-related pain), or a control group (in which case you will receive a placebo along with the standard medications which are usually prescribed to control surgery-related pain). Before, during and after surgery your doctors will administer doses of either the active medications (i.e. Lyrica® and Rayzon®) or a placebo (a non-active agent such as a probiotic or saline). You, your doctors and your nurses will not know whether you have been prescribed the active medication or the placebo, only the pharmacist who is allocated on this study will know the treatment group. Because the active medication appears slightly different in looks to the placebo, you will be asked by the pharmacist to please close your eyes while the medication is administered so that you remain unaware of your treatment group. All patients participating in this study, whether they are allocated to the experimental or control groups, will also receive the current standard best analgesia practice at Constantiaberg Hospital, in the form of intravenous paracetamol (Perfalgan®) and additional opioids or pain relief medication as needed, to the discretion of the anaesthetist and Dr Butler.

Why have I been chosen to partake in this study?

You have been identified as an eligible participant for this study because you live with epilepsy and have been scheduled to have neurosurgical operation performed for the management of your epilepsy.

What is required of me if I agree to partake in the study?

It is important for you to be aware that taking part in this study will in no way alter the outcome of your epilepsy-related surgery or the standard of care you receive while you are in hospital. As outlined above, if you agree to participate you will be allocated to one of two treatment groups. The control group will receive the current best pain management practice and the study group will receive Lyrica® and Rayzon® in addition to current best pain management practice. Your allocation to one of these groups will take place at random and you will not know to which group you have been allocated.

Prior to surgery you will be asked to complete a series of questionnaires to assess any pain behaviour, anxiety and depression you might have experienced in the past. You will also be instructed on how to rate your pain using two different pain assessment methods called the Visual Analogue Scale and the Numerical Rating Scale. Once you have regained awareness after your operation and have been at bed rest for at least 20 minutes you will be asked to estimate how severe your pain is using the same two pain assessment methods. You will also be asked to report on any side effects that you may be experiencing using a checklist. These procedures will be

repeated 8 hours, 24 hours, 48 hours and 72 hours after your operation. In addition, you will be asked to estimate the level of nausea and vomiting you are experiencing at 6 hours and 24 hours after your operation. All assessments will take place at your bedside and not last longer than 15 minutes.

What are the risks and discomforts associated with the study?

Any risks associated with your epilepsy-related neurosurgery will be unaffected by this study. Administration of the study drugs (Lyrica® and Rayzon®) and other standard pain medication present minimal physical risk, which is limited to the possible side effects of the medications. Although side effects are unlikely, occurring in 1% of individuals, these may include: abnormal co-ordination, back pain, blurred vision, confusion, constipation, dizziness, dry mouth, erectile dysfunction, euphoric mood, fatigue, flatulence, fluid retention, increased appetite, increased sweating, indigestion, insomnia, irritability, itching of skin, low blood pressure, memory impairment, numbness, sore throat, tremor, trouble breathing, vertigo and weight gain. Other uncommon side effects occurring in 0.1% of individuals include bruising, decreased urinary output, depression, dry eyes, earache, hallucination, hot flushes, joint pain, lack of energy, mood swings, muscle twitching, palpitations, rash, strokes, and wound infection. All your side effects, as well as your kidney and liver function will be monitored closely during the study to determine any serious negative effects due to the medication.

How will I benefit from the study?

The benefits of the study are unknown; however, it is important to stress that if you choose not to participate in the study, this will in no way negatively affect the care you receive in hospital and your pain management will be according to the best current standard practice for pain relief.

Will I be reimbursed for my participation in the study?

If you choose to participate in the study, you will receive a reimbursement of R300 cash upon the completion of the study. This will be to compensate for any inconveniences caused during the time taken to complete the study assessments.

Will my personal information be kept confidential?

Yes. If you choose to participate in the study, all your data will be anonymized and allocated a unique code. This unique code will be used in all data capturing procedures and all communication with third parties (e.g. biostatistician). Your anonymized data will be stored in a password-protected database in a secure location.

What if I change my mind about participation after I have already signed the informed consent?

You are able to withdraw from the study at any time and for any reason.

What happens if I get hurt taking part in this study?

This research study is covered by an insurance policy taken out by the University of Cape Town if you suffer a bodily injury because you are taking part in the study.

The insurer will pay for all reasonable medical costs required to treat your bodily injury, according to the SA Good Clinical Practice Guidelines 2006 (or latest version), which are based on the Association of the British Pharmaceutical Industry Guidelines. The insurer will pay without you having to prove that the research was responsible for your bodily injury. You may ask the study doctor for a copy of these guidelines.

The insurer will not pay for harm if, during the study, you:

- Use medicines or other substances that are not allowed
- Do not follow the study doctor's instructions
- Do not tell the study doctor that you have a bad side effect from the study medicine
- Do not take reasonable care of yourself and your study medicine

If you are harmed and the insurer pays for the necessary medical costs, usually you will be asked to accept that insurance payment as full settlement of the claim for medical costs. However, accepting this offer of insurance cover does not mean you give up your right to make a separate claim for other losses based on negligence, in a South African court.

It is important to follow the study doctor's instructions and to report straightaway if you have a side effect from the study medicine.

Who can I contact to find out more?

If you and your family have any additional questions, please do not hesitate to contact:

Name: Antonette Nell

Telephone number: 079 881 3522

Email: nllant002@myuct.ac.za

Who can I contact to report any complaints?

The UCT's Faculty of Health Sciences Human Research Ethics Committee can be contacted on 021 406 6338 in case you have any ethical concerns or questions about your rights or welfare as a participant on this research study.

	Protocol MMTv1.0. The effect of a novel multimodal therapeutic protocol on patient-reported post-neurosurgical pain scores, versus the current postoperative analgesic practice, employed at a local South African Hospital.
	Investigators: PI: Dr Eddy Lee Pan Sub-investigator: Dr Lawrence M Tucker and Dr James Butler Student researcher: Ms. Antonette Nell
	Informed consent form

This consent form asks for:

1. Permission to be allocated to one of two postoperative pain treatment groups.
2. Permission to conduct questionnaire evaluations and pain assessments at various time points.
3. Analysis and use of this information in a scientific study
4. Use of this information in the publication of an article in a scientific journal

I confirm that I have been fully informed regarding all procedures, risks and other aspects of this study and that I understand what is required of me as a participant of this study. I further confirm that I have voluntarily agreed to partake in this study.

Printed name of participant: _____

Signature of participant: _____

Date: _____

Printed name of person obtaining consent:_____

Signature of person obtaining consent:_____

Date: _____

Printed name of witness: _____

Signature of witness: _____

Date: _____

For any questions regarding this document, please contact Antonette Nell on 079 881 3522 or email nllant002@myuct.ac.za

A4: Participant assessments

Folstein Mini-Mental State Exam:

I. Orientation (Ask the following questions; correct = □	Participants' Answer	(Maximum Score = 10)
What is today's date?		1 ☐
What is today's year?		1 ☐
What is the month?		1 ☐
What day is today?		1 ☐
Can you also tell me what season it is?		1 ☐
Can you also tell me the name of this hospital?		1 ☐
What floor are we on?		1 ☐
What city are we in?		1 ☐
What country are we in?		1 ☐
What province are we in?		1 ☐
II. Immediate recall	Participants' Answer	(Maximum score = 3)
Ask the subject if you may test his/her memory. Say "ball", "flag", "tree" clearly and slowly, about a second for each. Then ask the subjects to repeat them. Check the box at right for each correct response. The first repetition determines the score. If he/she does not repeat all three correctly, keep saying them up to six tries until he/she can repeat them.	Ball ☐ Flag ☐ Tree ☐	1 ☐ 1 ☐ 1 ☐ Number of trials: _____
III. Attention and calculation	Participants' Answer	(Maximum score = 5)
A. Counting Backwards Test		
Ask the subject to begin with 100 and count backwards by 7. Record each response. Check one box at right for each correct response. Any responses 7 or less that the previous response is correct subtractions. 93, 86, 80, 72, 65 is a score of 4; 93, 86, 78, 70, 62 is 2; 92, 87, 78, 70, 65 is 0.	93 ☐ 86 ☐ 79 ☐ 72 ☐ 65 ☐	1 ☐ 1 ☐ 1 ☐ 1 ☐ 1 ☐

B. Spelling Backwards Test		
Ask the subject to spell the word "WORLD" backwards. Record each response. Check one box at right for each correct response.	D ☐ L ☐ R ☐ O ☐ W ☐	1 ☐ 1 ☐ 1 ☐ 1 ☐ 1 ☐
C. Final Score:		
Compare the scores of A and B. Write the greater of the two scores at right, and use it in deriving the TOTAL SCORE		
IV. Recall	Participants' Answer	(Maximum score = 3)
Ask the subject to recall the three words you previously asked him/her to remember. Check the boxes at right for each correct response.	Ball ☐ Flag ☐ Tree ☐	1 ☐ 1 ☐ 1 ☐ Number of trials: _____
V. Language	Participants' Answer	(Maximum score = 9)
Naming: Show the subject a wristwatch and ask him/her what it is. Repeat for a pencil.	Watch ☐ Pencil ☐	1 ☐ 1 ☐
Repetition: Ask the subject to repeat "No, ifs, ands or buts"		1 ☐
Three Stage Command: Establish the subject's dominant hand. Give the subject a sheet of blank paper and say "Take the paper in your right/left hand, fold it in half and put it on the floor"	Takes paper in dominant hand ☐ Folds paper in half ☐ Puts paper on the floor ☐	1 ☐ 1 ☐ 1 ☐
Reading: Hold up the card that reads, "close your eyes." So the subject can see it clearly. Ask him/her to read it and do what it says. Check the box at right only if he/she actually closes his/her eyes.		1 ☐

Writing: Give the subject a sheet of blank paper and ask him/her to write a sentence. It is to be written spontaneously. If the sentence contains a subject and a verb, and is sensible, check the box at right.		1 ☐
Copying: Show the subject the drawing of intersecting pentagons. Ask him/her to draw the pentagons (about one inch each side) on the paper provided. If ten angles are present and two intersect, check the at right.		
DERIVING THE TOTAL SCORE		
Add the number of correct responses. The maximum is 30.	**Total score**_____	
23-30 = Normal / 19-23 = Borderline / <19 = Impaired		

Hospital Anxiety and Depression Scale:

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

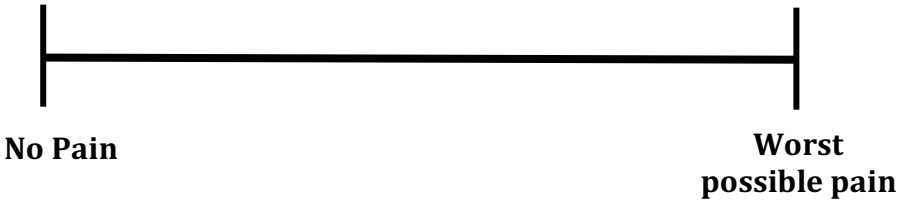
PROMIS Pain behavior questionnaire:

Please respond to each item by marking one box per row.

	In the past 7 days....	**Had no pain**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
PAINBE2	When I was in pain I became irritable.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
PAINBE3	When I was in pain I grimaced.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
PAINBE8	When I was in pain I moved extremely slowly……..……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
PAINBE24	When I was in pain I moved stiffly ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
PAINBE25	When I was in pain I called out for someone to help me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
PAINBE37	When I was in pain I isolated myself from others.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
PAINBE45	When I was in pain I thrashed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

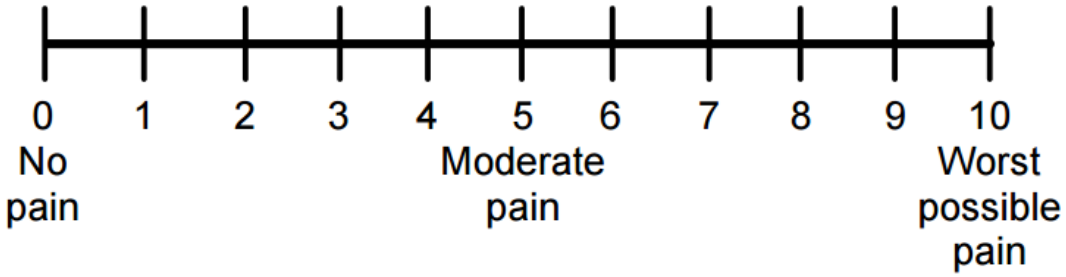
Visual analogue scale (VAS):

Please mark on the below line where you feel best describes your current pain intensity:



Numerical rating scale (NRS):

Please indicate a numeric value on the below line that you feel best describes your current pain intensity:



Postoperative Nausea and Vomiting:

PONV Assessment	Score
A: At 6 / 24 / 72 hours after surgery	
Q1: Have you vomited or had any dry retching*? a) No b) Once or Twice c) Three or more times	 0 2 50
Q2: Have you experienced a feeling of nausea (*an unsettled feeling in the stomach and slight urge to vomit). If yes, has your feeling of nausea interfered with activities of daily living, such as being able to get out of bed, being able to move about freely in bed, being able to walk normally or eating and drinking? a) No b) Sometimes c) Often or most of the time d) All of the time	 0 1 2 25
Q3: Has your nausea been mostly: a) Varying *("comes and goes")?* b) Constant *("is nearly or almost always present")?*	 1 2
Q4: What was the duration of your feeling of nausea (in hours [whole or fraction])?	_____._____h
For part A, if answer to Q1 = c), score A = 50; otherwise, select the highest score of Q1 or Q2, then multiply x Q3 x Q4	PONV intensity score (0-6h) A=

* Count distinct episodes: several vomits or retching events occurring over a short time frame, say 5 min, should be counted as one vomiting/dry-retching episode; multiple episodes require distinct time periods without vomiting/dry-retching

Side effect checklist:

Please tick below if you are experiencing any of the following side effects:

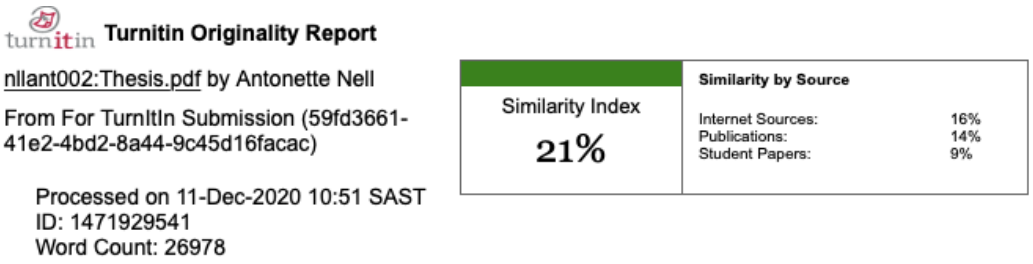
Common:

- ☐ Abnormal co-ordination
- ☐ Back pain
- ☐ Blurred vision
- ☐ Confusion
- ☐ Constipation
- ☐ Dizziness
- ☐ Dry mouth
- ☐ Erectile dysfunction
- ☐ Euphoric mood
- ☐ Fatigue
- ☐ Flatulence
- ☐ Fluid retention
- ☐ Increased appetite
- ☐ Increased sweating
- ☐ Indigestion
- ☐ Insomnia
- ☐ Irritability
- ☐ Itching of skin
- ☐ Low blood pressure
- ☐ Memory impairment
- ☐ Numbness
- ☐ Sore Throat
- ☐ Tremor
- ☐ Trouble Breathing
- ☐ Vertigo
- ☐ Weight gain

Uncommon:

- ☐ Bruising
- ☐ Decreased urinary output
- ☐ Depression
- ☐ Dry eyes
- ☐ Earache
- ☐ Hallucination
- ☐ Hot flushes
- ☐ Joint pain
- ☐ Lack of energy
- ☐ Mood swings
- ☐ Muscle twitching
- ☐ Palpitations
- ☐ Rash
- ☐ Strokes
- ☐ Wound infection
- ☐ Bradycardia (to be reported by nurses)
- ☐ Hyperglycemia (to be reported by nurses)
- ☐ Tachycardia (to be reported by nurses)
- ☐ Thrombocytopenia (to be reported by nurses)

A5: TurnItIn: Similarly Index Report



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