An-Najah National University

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A Comparison of Pre-Emptive Effect of Oral Pregabalin and Gabapentin on Acute Postoperative Pain in Patients Undergoing Lumber Spine Surgeries

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Dedication

At first, I dedicate this work to Almighty ALLAH, without his mercy and sympathy I would not be able to accomplish this work, and my great teacher and messenger, Mohammed (May Allah bless and grant him). I would like to express the deepest gratitude to my family, who have supported me at every step of this journey and aspired me to work hard to achieve my dreams. Thanks for listening to my problems and providing perspective. I would not be who am I today without you all. My husband, who has been a constant source of support and encouragement during the challenges of graduate. To all my friends who encourage and support me, all the people in my life who touch my heart, I dedicate this research.

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الإقرار

أنا الموقع أدناه مقدم الرسالة التي تحمل العنوان:

A comparison of pre-emptive effect of oral Pregabalin and gabapentin on acute postoperative pain in patients undergoing lumber spine surgeries

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Declaration

The work provided in this thesis, unless otherwise referenced, is the researcher's own work and has not been submitted elsewhere for any other degree or qualification.

Student's Name: **اسم الطالب:**

Signature: **التوقيع :**

Date: **التاريخ :**

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Table of Abbreviations

ASA	American Society of Anesthesiologists
BMI	Body Mass Index
CNS	Central Nervous System
CO2	Carbon Dioxide
CSF	Cerebrospinal fluid
GA	General Anesthesia
Hrs.	Hours
IV	Intravenous
Kg	Kilogram(s)
O2	Oxygen
PACU	Post Anesthetic Care Unit
PONV	Postoperative Nausea and Vomiting
VAS	Visual Analog Scale
COX-2	cyclooxygenase-2
GABA	Gamma amino butyric acid
C max	Maximal plasma concentrations
AUC	Area under the curve
t 1/2	Elimination half-life
PO	Postoperative

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Abstract

Introduction: Postoperative pain is a constant complication after lumber spine surgeries, which causes delayed discharge of patients and decreased patient functioning. Pregabalin and Gabapentin have been well-known for their neuropathic pain relief, and pre-emptive Gabapentinoids have been claimed to reduce post-operative pain.

Study method: This study is a true experimental randomized, double-blind, placebo controlled, prospective study, conducted Rafedia Government Surgical Hospital in Nablus, Palestine. The study is done on 60 male and female patients undergoing elective lumber spine surgeries under department of neurology. American Society of Anesthesiologists (ASA) physical status I and II patients, Age ranging from 18 to 70 years. Sample is divided into three groups (20 patient each): Pregabalin 150 mg group, gabapentin group and placebo group. Drugs were administered one hour preoperatively and assessed periodically after surgery for visual analogue scale, Ramsey sedation score, first time of rescue analgesia, total

amount of rescue analgesia and the incidence of nausea and vomiting to compare the efficacy of the drugs on postoperative pain and there side effects on the patients.

Study result: In this study, pain scores were significantly lower in both the Pregabalin and gabapentin groups than in the placebo group. The results of our study revealed that the Pregabalin group had significantly lower scores for a longer interval (up to 6 hours after surgery) than the gabapentin group and compared to the placebo group. Significant prolongation in pain relief in the Pregabalin and Gabapentin groups compared to the placebo group and significant longer pain relief in Pregabalin when compared with Gabapentin alone. The highest amount of analgesic Paracetamol given was in the placebo group compared to the Pregabalin and Gabapentin groups. And the lowest amount of Paracetamol given was in the Pregabalin group. The incidence of nausea and vomiting among participants in the placebo group was higher compared to participants in the gabapentin group (80% versus 40%) and the Pregabalin group (80% versus 35%). Sedation scores were higher in the first 6 hours after surgery in the Pregabalin and Gabapentin groups compared to the placebo group.

Conclusion: Preemptive Pregabalin (150 mg) is established to be more effective than Gabapentin (300 mg), in prolongation of postoperative analgesia with reduced rescue analgesic requirements**.**

Keywords: Pregabalin, Gabapentin, Preemptive analgesia, lumber spine surgeries

Chapter One

Introduction

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage(1).

Post-operative pain is caused by the surgical trauma and the inflammation resulting from tissue trauma, tissue injury or direct nerve injury, which is accompanied by local chemical releases and systemic changes such as tachycardia, hypertension and increased blood glucose. Surgical trauma induces acute post-operative pain and hyperalgesia which could lead to chronic pain in the post-operative period if left untreated, and there is a relationship between acute postoperative pain and the development of psychological morbidities such as post-operative depression and anxiety(2).

In most cases, patients under go lumber spine surgeries to get rid of lower back pain. Nevertheless, the tissue damage during surgery is a cause of development of postsurgical pain. Poorly controlled acute postoperative pain is a predictor of chronic postsurgical pain development(3). Short-term postoperative pain management and its outcome on pain intensity is a reliable predictor of the long-term outcome of chronic postsurgical pain in disc surgery patients; therefore, a multimodal treatment setting including a cooperating interdisciplinary team and multimodal analgesia seems necessary to achieve substantial pain relief, which in turn may lead to a faster recovery and improved long-term outcomes(4).

Preoperative administration of Paracetamol, COX-2-specific inhibitors and Gabapentinoids (i.e. gabapentin and Pregabalin), in addition to regional/ local anesthetic techniques are critical components of an optimal multimodal analgesic approach minimizing the dose of medication, to lessen the side effects and provide adequate analgesia.

Gabapentinoids, as a part of multimodal analgesia, are commonly administered preoperatively, as they have shown to reduce postoperative opioid consumption and pain scores, mainly for surgical procedures with a high tendency of tenacious postoperative pain(5).

Problem statement and significance of the study

Lower back pain is a main reason for lumber spine surgeries, therefor patients undergo this procedure for the expected pain relief. Neverthless, tissue damage during surgery is the chief cause for development of chronic postsurgical pain, and as pain becomes chronic,fundamental changes to neuronal phenotypes and brain circuits occur. These changes can alter sensory, emotional, and motivational centres of the brain and interfere with the action of traditional analgesic medications. It has been stated by Kurd et al (6) that tissue damage causes the pain during spine surgery and sufficient post-operative pain control enhances mobility and boosts rehabilitation and patient satisfaction. Poorly controlled acute postoperative pain is a predictor of chronic postsurgical pain development(3). It was shown that Short-term postoperative pain management and its outcome on pain

intinsity had a reliable predictor of the long term outcome of chronic postsurgical pain in disc surgery patients(4).

Postoperative pain has been described as one of the main four causes for delayed discharge from the hospital after day surgery among post-operative nausea and vomiting, going late to theatre and social factors. Therefor, adequate post-operative pain relief and multimodal analgesic regimen must be an integral part of administration of anesthesia. Drugs currently available to treat acute pain are mostly ineffective at preventing it and opioids are too often overused in the post-discharge period(3), causing multible complications such as postoperative nausea and vomiting, dizziness and respiratory depression(5, 7). A multimodal treatment setting including a cooperating interdisciplinary team is necessary to achieve substantial and long-lasting pain relief, which in turn may lead to a faster recovery and improved long-term outcomes(4).

Pre-emptive analgesia is a new model of analgesia to be introduced and studied in our territory hospitals. Moreover, there is not any published studies covering pre-emptive oral Gabapentinoids in Palestine hospitals.

Aim of the study

Based on the knowledge presented concerning the management of post-operative pain, this study is intended to compare the pre-emptive analgesic effectiveness of oral gabapentin versus oral Pregabalin in patients undergoing lumber spine surgeries under general anesthesia.

Research objectives

1. Assess if pre-emptive Pregabalin will reduce acute postoperative pain in patients undergoing lumber spine surgeries under general anesthesia?
2. Assess if pre-emptive gabapentin will reduce acute postoperative pain in patients undergoing lumber spine surgeries under general anesthesia?
3. Assess which drug causes more post-operative pain reduction.

Research questions

1. Does pre-emptive Pregabalin reduce acute postoperative pain in patients undergoing lumber spine surgeries under general anesthesia?
2. Does pre-emptive gabapentin reduce acute postoperative pain in patients undergoing lumber spine surgeries under general anesthesia?
3. Which drug does cause more acute postoperative pain reduction?

Research hypothesis

Pregabalin and Gabapentin are effective in reducing acute postoperative pain in patients undergoing lumber spine surgeries under general anesthesia.

Background

Definition of pain: Pain is defined as an unpleasant sensory and emotional experience related to actual or potential tissue damage or described in terms of such damage(1).

Surgical trauma induces hyperalgesia which could lead to chronic pain in the post-operative period if left untreated. Post-operative pain could be

attributed to inflammation resulting from tissue trauma, tissue injury or direct nerve injury. Nociceptor sensitization can be contributed to pro-inflammatory mediators released as a result of tissue injury such as prostaglandins, interleukins, cytokines and neurotrophins. Also, peripheral sensitization and spontaneous pain behavior following an incision caused by the reduction in tissue pH and oxygen tension, and increased lactate concentration which may be persistent at the surgical site for several days(8). Pain also has endocrine-metabolic responses, which result from the stress-response which is mainly released through afferent neurogenic stimuli from the surgical area. Neuroendocrine response is mainly characterized by amplified adrenergic activity by increased cortisol observed as systemic such as tachycardia, hypertension, and increased blood glucose. Also, substrate mobilization and increased energy and oxygen consumption. Neurogenic blockade and analgesia with local anesthetics can prevent a major part of the stress-response to surgery(9).There is a relationship between acute postoperative pain and psychological morbidity such as post-operative depression and anxiety. Pain has been shown to cause altered synaptic connectivity and altered dopamine signaling. These changes have been known to trigger negative symptoms of depression and may form the link between pain and depression and anxiety(2).

Physiology of pain: Nociception encompasses the regular functioning of physiologic structures, which includes four stages: transduction, transmission, perception and modulation.

- **Transduction**

Nociceptors are stimulated by a noxious stimulus, causing ion channel (sodium, potassium, calcium) on the nociceptors to open, generating electrical impulses that transport through axons of two main types of nociceptors that are transmitted to the spinal cord, brainstem, thalamus, and cortex. There are two chief types of nociceptors: A delta fibers and C fibers.

- **Transmission**

Transmission refers to the passing action potential from the peripheral terminal through axons to the central terminal of nociceptors in the central nervous system. It is throughout this time that pain control can take place. Opioids block the release of neurotransmitters.

- **Perception**

Perception refers to the conscious awareness of pain. Interpretation of pain can be influenced by various factors, including genetics, life experience, gender roles, cultural preferences, past pain experiences, and level of health.

- **Modulation**

Modulation refers to the alteration (increase or decrease) of sensory input, by either inhibition or enhancement through supraspinal stimuli arising from the pons, medulla, and midbrain. An examples of pain modulation is when an individual experiences a painful stimuli but does not feel any pain,

the reverse effect is when somebody has a paper cut and experiences extreme pain(10).

Multimodal analgesia

Multimodal pain therapy or balanced analgesia was first introduced in 1993, as a way to manage postoperative pain. It was introduced to improve analgesic effectiveness and decrease adverse effects by implying a combination of different classes of analgesics as well as use of different sites of administration of the analgesics and by that; improving pain management and relief(11, 12).

Pre-emptive analgesia

The concept of preemptive analgesia was found in 1913 by Crile by the use of regional blocks in addition to general anesthesia and as a result, preventing intraoperative nociception and the formation of painful scars caused by the changes in the central nervous system intraoperatively(13).

Preemptive analgesia is defined as treatment that starts preoperatively, prevents central sensitization caused by incisional injury occurring intraoperatively only, and prevents the establishment of central sensitization which is caused by incisional and inflammatory injuries that occurs intraoperatively and the initial postoperative period. Requirements for adequate preemptive treatment include a confirmation of the efficacy of the direct pharmacologic treatment and an extension of the antinociceptive treatment into the initial postoperative period(14).

Gabapentin

Gabapentin, a second generation anticonvulsant drug which was presented in 1993 for treating refractory partial seizures. Far ahead it was found to have an efficacy in treating chronic pain caused by conditions as inflammatory pain and malignant pain, post herpetic neuralgia, diabetic neuropathy, HIV- related neuropathy, trigeminal neuralgia, complex regional pain syndromes. Lately its use has been extended to treat postoperative pain(15).

Chemistry: Gabapentin,- 1-(amino methyl) cyclohexane acetic acid is a structural analogue of Gamma amino butyric acid (GABA), an inhibitory neurotransmitter. It is a white crystalline solid, highly charged at physiological pH and is freely soluble in water(15).

Oral bioavailability: Absorption of gabapentin is not dose dependant, because of a saturable L-amino acid transport mechanism in the intestine. Hence oral bioavailability varies inversely with dosage. After a single dose of 300 and 600mg, bioavailability was found to be 60% and 40% respectively and decreased to 35% at steady state with a dose of 1600 mg three times a day(15).

Distribution: Widely distributed in human tissues and fluid after administration. Volume of distribution is 0.6-0.8l/Kg. Concentration in adipose tissue is low because it is highly ionized at physiological pH. Less than 30% is bound to plasma proteins. Concentration in cerebrospinal fluid is 5-35% of those in plasma and in brain tissue it is 80% of those in plasma.

Peak plasma level of gabapentin of 2.7-2.99 was found to be achieved after 3- 3.2 h of ingesting single dose 300 mg capsule(15).

Metabolism: Gabapentin is not metabolized in the human body. It does not induce hepatic microsomal enzymes(15).

Elimination: Gabapentin is eliminated unchanged in urine. The unabsorbed drug is excreted in faeces. Renal clearance is related in a linear manner to creatinine clearance. Elimination half-life is 5-7 hours in patients with normal renal function and is unchanged by dose. It can be removed by hemodialysis(15).

Drug interactions: Cimetidine, a H2 receptor blocker decreases renal clearance when given alongside gabapentin. It was founf that antacids decrease gabapentin bioavailability when given concurrently(15).

Special conditions:

- Renal insufficiency: half life of gabapentin is increased in patients with decreased creatinine clearance. Which makes dose adjustment necessary.
- Hemodialysis: half life of gabapentin is decreased.
- Age: With increasing age, renal clearance decreases. Which makes the reduction of dose required in patients who have age linked decline in renal function.
- Gender: Pharmacokinetic parameters for male and female are alike and which means no significant gender differences.

- Pregnancy and lactation: pregnancy category C. Animal studies have discovered fetal toxicity including late ossification of several bones. There is no controlled data in human pregnancy. Gabapentin is secreted into human milk. Gabapentin should be given only when benefit outweighs risk(15).

Mechanisim of anti- nociception: The precise mechanism is not fully elucidated but its hypothized that the anti nociceptive target of gabapentin is the voltage gated calcium channels which are upregulated in the dorsal root ganglia and spinal cord after surgical trauma. Gabapentin selectively binds to α2δ subunit of voltage gated calcium channels and inhibits calcium entry through these channels by this means inhibiting the release of excitatory neurotransmitters (glutamate, aspartate, substance P, calcitonin gene related peptide) from the main afferent nerve fibres in the pain pathway. Gabapentin does not affect the nociceptive threshold but has antiallodynic and anti-hyperalgesic properties. Gabapentin activates the 21 descending nor adrenergic system and produces spinal nor epinephrine release, which acts on spinal α2 adrenoreceptor to produce analgesia(15).

Perioperative benefits: Gabapentin has "off label" perioperative uses and applications such as perioperative anxiolysis, post operative analgesia, reduction of haemodynamic response to laryngoscopy and intubation and the prevention of chronic post surgical pain, postoperative nausea, vomiting and delirium(15)..

Advers effects: Most commonly, Sedation and dizziness, followed by asthesia, headache, nausea, ataxia, weight gain and amblyopia(15).

Pregabalin

Pregabalin, olso named S-(+)-3-isobutylgaba, is a formed lipophilic analogue of GABA substituted at the 3-position to ease diffusion across the blood–brain barrier.

Pregabalin occurs in isomeric forms, with pregabalin being the pharmacologically active enantiomer. Even though pregabalin is structurally interrelated to GABA, it is inactive at GABA receptors and does not seem to mimic GABA physiologically. Furthermore, pregabalin does not have the affinity for receptor sites or alter responses accompanying the action of numerous common drugs for treating seizures or pain, which suggests that its mechanism of action is novel (16).

Pregabalin pharmacological effects are a consequence from its action as a ligand at the alpha-2- delta binding site, which is associated with voltage-gated calcium channels in the central nervous system (CNS). Pregabalin shows effective anticonvulsant, analgesic, and anxiolytic activity in numerous animal models (16).

Absorption: Pregabalin is quickly and widely absorbed after oral dosing in the fasting state, with maximal plasma concentrations occurring ∼1 h after single or multiple doses, and steady state being achieved within 24–48 h after repetitive administration. Maximal plasma pregabalin concentrations (C max) and total exposures (AUC) are relative to dose after either single

or multiple dosing . Oral bioavailability is high at ≥90% and is independent of dose. Mean elimination t1/2 of pregabalin is 6.3 hours and is also independent of dose and repeated drug administration . These findings of constant dose-proportional pharmacokinetics, validate confidence in the estimate of dose–response relationships in clinical practice**.** The concentration–time profiles of pregabalin are comparable after two- or three-times daily administration, which reflects the clinical findings that pregabalin administered via either dosing regimen resulted in similar efficacy. The administration of pregabalin with food has no clinically related effect on the amount of pregabalin absorbed ,consequently providing a dosing regimen that is uncomplicated by meals (16).

Distreputionː Pregabalin is a substrate of the system L transporter, which is responsible for the transport of large amino acids across the brain and gut. As a consequence, pregabalin has been shown to quickly penetrate the blood–brain barrier in preclinical studies conducted in mice, rats, and monkeys. This is of apparent importance for a drug that influences CNS activity (16).

Metabolisimː Pregabalin undergoes negligible metabolism in

Humans (16).

Eleminationː Pregabalin is excreted virtually unchanged by the kidneys(16).

Pregabalin has no drug-drug interaction

Pregabalin has a very little potential for drug– drug interactions since it is neither metabolized nor bound to plasma protein, There is no rationale to suppose drug– drug interactions to occur by these mechanisms in clinical practice. Studies using human liver microsomes have confirmed that pregabalin does not affect the cytochrome P450 system at therapeutic doses, neither should it affect the metabolism of drugs eliminated by this route (16).

Advers effects: Somnolence, dizziness, peripheral edema, dry mouth, weight gain, fatigue, visual disturbances, ataxia, non-peripheral oedema, vertigo, euphoria(17).

Chapter Two

Litreture review

Pre-emptive effects of gabapentin and pregabalin on postoperative pain have been studied combined with different anesthesia techniques as general, spinal, or spinal-epidural technique(18-20). This pre-emptive effect was studied on various patient with spicefic conditions and surgeries such as coronary artery bypass graft surgeries, Laparoscopic Cholecystectomies, lumber spine surgeries, total abdominal hysterectomies, lower limb orthopedic surgeries, modified radical mastectomies and others (18-30).

All of the previously mentioned studies are highly controlled randomized studies, which included ASA grade I and II, and adopted similar methods in administering various doses of pregabalin and gabapentin. All studies divided patients into 3 groups (pregabalin group, gabapentin group and placebo group). Most of the studies administered the drugs one and a half hour before the induction of anesthesia. Postoperative pain was assessed by the Visual analogue score along with expected side effects immediately and then at a periodical manner lasting for the first 24 hours.

Postoperative assessment of the drugs effect showed that pre-emptive oral pregabalin and oral gabapentin significantly decrease the severity of pain postoperatively. Also that Pregabalin caused more sedation than gabapentin (18, 19, 21-24, 31), and significantly reduced the need of postoperative rescue analgesia such as Tramadol, Diclofenac sodium and epidural top-

ups (20, 25, 26), without any intraoperative hemodynamic alterations(20, 21) or additional major side effects beside sedation(30).

Sedation didn't alter the hemodynamics and consequently, pregabalin and gabapentin can be used safely(25). A study found a decreased postoperative nausea and vomiting with pre-emptive pregabalin and gabapentin(27). The results were consistent even when pregabalin and gabapentin were combined with other drugs as IV paracetamol(32). When pregabalin and gabapentin were administered with intrathecal bupivacaine in spinal-epidural blocks it revieled a new binifit by increasing the duration of postspinal anesthesia(20, 26).

A comprehensive literature search of articles revealed that the analgesic effect of pregabalin and gabapentin may be dose related.It also showed an incidence of adverse reactions varying with different doses of Pregabalin and Gabapentin.(28)

Regarding lumber spine conditions; The most common persistent symptoms after lumber spine surgeries are pain, motor deficit, and decreased functional status. Postoperative Gabapentinoids administration effectively reduce the opioid consumption and opioid-related adverse effects after surgery. Pregabalin is associated with less pain intensity on acute postoperative pain and has more pronounced effect on economic and functional improvement as compared with gabapentin in the long term(33). Pre-emtive Pregabalin has showed a better analgesic profile and delayed time for requirement of first dose of rescue analgesic when compined with

IV Paracetamol compared to Gabapentin with IV Paracetamol in a study done on patients undergoing lumber spine surgeries(32).

Chapter Three

Methodology

Study design and Setting: This study is a true experimental randomized, double-blind, placebo controlled, prospective study. The study is projected to compare the pre-emptive analgesic effectiveness of oral gabapentin versus oral Pregabalin in patients undergoing lower lumber spine surgeries under general anesthesia. The study design is chosen to be the most suitable for the study objectives as well as the intervention given related to the intervention outcomes measured(34). The study is conducted in operation unit, post anesthesia care unit, and post-surgical wards at Rafedia Government Surgical Hospital in Nablus, Palestine.

Study population: All adult patients undergoing elective lumber spine surgeries under department of neurology at Rafedia Government Surgical Hospital and satisfying the following inclusion criteria.

Inclusion criteria

1. Patients undergoing elective lumber spine surgeries under department of neurology.
2. American Society of Anesthesiologists (ASA) physical status I and II patients
3. Age group 18 to 70 years
4. Male and female

Exclusion criteria

1. Patients of grads ASA 3 and above.
2. Patient refusal
3. History of allergy to gabapentin and Pregabalin
4. History of drug and /or alcohol abuse
5. Patients who have been prescribed Pregabalin or gabapentin for other indications
6. History of chronic pain and chronic daily intake of analgesics
7. History of epilepsy and other neurological disorders
8. Pregnancy and breast-feeding mothers
9. Liver or renal disease
10. History of psychological co-morbidity

Study Sampling and sample size

Male and female patients undergoing elective lumber spine surgeries under department of neurology. American Society of Anesthesiologists (ASA) physical status I and II patients, Age ranging from 18 to 70 years at Rafedia Government Surgical Hospital. The estimated sample size is withdrawn from literature by using the time for first rescue analgesia requirement as the main variable to calculate the medium effect size 1.3 (21, 30, 35). Based on the 1.3 medium effect size, alpha 0.05, power 80%, and using G power, 20 patients in each group. Patients were enrolled in the study by

random assignment due to the lack of cases number. Randomization was done by the researcher.

Study Variables

The comparison of the postoperative effect of oral Pregabalin and gabapentin on pain is studied regarding to variables summarized as following:

Table 3.1: Study Variables

Independent variables:	**Dependent variables:**
Age (year)	Postoperative pain (Visual analogue scale)
Sex (male/female)	Postoperative sedation (Ramsey sedation score)
Weight (kg)	First time of rescue analgesia
Height (meter)	Total amount of rescue analgesia in the first 24 hours post surgically
Body mass Index	Incidence of nausea, vomiting.
Duration of surgery (minute)	

Study tools

Postoperative pain assessment:

It is vital and obligatory to measure the degree of pain experienced by the patient in the postoperative period. Pain assessment is an important vital sign in postoperative patients and must checked periodically. Postoperative pain assessment includes preoperative patient education of postoperative pain. The preoperative education aids to increase the patient knowledge which assists to decreases the anxiety and fear regarding pain. It also helps

in the development of positive approach towards pain, by this means improving satisfaction of the patient. Postoperative pain assessment aids in the process of quantitating the intensity of pain, to frame analgesic regimen and to assess the patient response to the treatment administered. There are various pain assessment methods. Pain assessment tools must be simple and understandable without difficulty by the patients. Common used pain scales are Visual analogue scale, numerical rating scale, verbal rating scale and Wong baker faces rating scale(36).

Visual analogue scale (VAS):

The VAS is presented as a 10-cm line, anchored by verbal descriptors, usually ‘no pain’ and ‘worst imaginable pain’. The patient is asked to mark a 100 mm line to indicate pain intensity. The score is measured from the zero anchor to the patient’s mark. Using a millimeter scale to measure the patient’s score will provide 101 levels of pain intensity. One of the limitations of the VAS is that it must be administered on paper or electronically. Caution is required when photocopying the scale as this can lead to significant changes in its length. VAS is proven to be reliable and valid and statistically the strongest compared with The Numerical Rating Scale and The Verbal Rating Scale, as it can provide ratio level data(37). Postoperatively all patients were assessed for the level of pain using the Visual analogue scale periodically after 2, 4, 6, 9,12, and 24 hours of endotracheal extubation, by a trained health care team member.

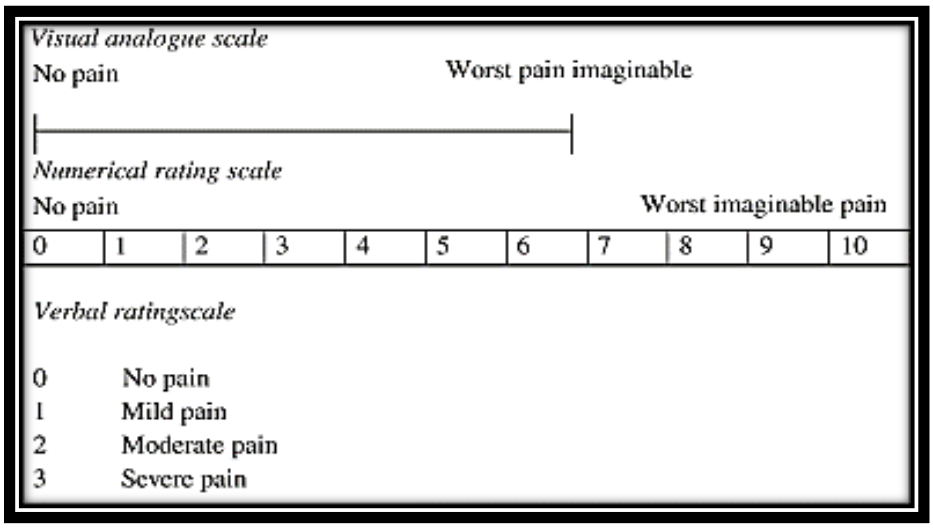

Figure 3.1: A picture demonstrating the visual analogue scale for pain assessment (37).

Ramsay sedation scale:

This scoring system was described in 1974 for the purpose of monitoring sedation. It continues to be the most widely used scale for monitoring sedation in daily practice, as well as in clinical research. This instrument identifies situations of agitation or sleep visually. This method has good reliability, with good interobserver agreement. This qualifies this scale as sufficiently reproducible for clinical practice(38).

Response	Level
Awake and anxious, agitated, or restless	1
Awake, cooperative, accepting ventilation, oriented, or tranquil	2
Awake, responds only to commands	3
Asleep, brisk response to light, glabella tap, or loud noise	4
Asleep, sluggish response to light, glabella tap, or loud noise	5
Asleep, no response to light, glabella tap, or loud noise	6

Figure 3.2: A picture displaying Ramsay Sedation Scale (38).

Postoperatively all patients were assessed for the level of sedation using Ramsay sedation score periodically after 1, 2, 4, 6, 9,12, and 24 hours of endotracheal extubation, by a trained health care team member.

Time for the first rescue analgesia:

Postoperatively all patients were monitored for pain scores periodically. When the pain score is 4 or greater, patients were given 100 ml of Paracetamol (10mg/ml) intravenously (IV) as initial dose.

Total amount of rescue analgesia administered in first 24 hours postoperatively:

In this study, the mean of dosage of rescue analgesic Paracetamol IV (gm. /24 hours) administered in the first post-operative 24 hours were calculated.

Incidence of nausea and vomiting:

Postoperative nausea and vomiting (PONV) are defined as any nausea, retching, or vomiting taking place during the first 24– 48 hours after surgery(39). It has been shown that post-operative pain increases the occurrence of emesis(40). In this study, the patients were asked if nausea or vomiting have occurred during the first 24 hours postoperatively.

Study protocol

Medication administration: In this study, 60 patients underwent lower lumber spine surgeries under general anesthesia were enrolled and randomly allocated into 3 group: Group received Pregabalin 150 mg, Group received Gabapentin 300 mg and Group received placebo with sips of water one hour before surgery by a trained health care team member.

Gabapentin was shown to reduce postoperative pain and prolong postoperative analgesia when administered as a single dose preoperatively(29). Pregabalin was also proven to decrease postoperative pain and prolong postoperative analgesia when administered as a single dose preoperatively(41). Thus, the drugs were given to patients before surgery. Drugs were administered one hour preoperatively. This is based on the time of maximal plasma concentration of Pregabalin which is 71 minutes, nearly 1 hour(16). And the time of peak plasma concentration of Gabapentin, which is around 2 to 3 hours(15).This is similar to a recent study conducted by Sidharth et al (23), where 75 patients undergoing lower spine surgeries were selected and allocated into 3 groups (Pregabalin group, Gabapentin group and Placebo group. Capsules specially manufactured to have identical shape and color were unavailable and hard to be attained due to high cost of manufacturing small number of them, so we had to use the available forms available in public pharmacies. None of the patients exhibited allergic reactions to any of the administered drugs.

Blinding:

Patients, all employees included in patient care and the persons who are collecting the data weren't aware of the treatment group's allocation.

Randomization:

The patients enrolled in the study were randomly assigned to one of the three previous mentioned groups by simple randomization by using lottery method.

Anesthesia protocol

Preoperatively, all patients were in fasting state for 8 hours and fluid maintenance were obtained with N.S 0.9% according to surgical ward protocol. Inside the operating room, standard hemodynamic monitors were placed (electrocardiogram, heart rate, pulse oximeter oxygen saturation, noninvasive blood pressure, capnography, and temperature monitoring). Bladder was catheterized to monitor urine output. One Intravenous 18G cannula was established. Pre-oxygenation was done by face mask for 3 minutes at 3 L. Anesthesia induction was obtained with 2 mg/kg of fentanyl and 2 to 4 mg/kg of Propofol, followed by 0.5 mg/kg of Atracurium, to facilitate tracheal intubation and ventilation. The ventilation was mechanically controlled and modified to preserve end-times of Carbonic dioxide between 35 and 40 mmHg and anesthesia was maintained by Isoflurane to maintain end tidal concentration 1 minimum alveolar concentration. After anesthesia induction, patients were put in prone position for the entire time of surgery. Intraoperative intravenous fluid maintenance were obtained with Ringer lactate. Atracurium and fentanyl were administered as clinically indicated. Neuromuscular block was reversed to repeal muscle relaxation and the endotracheal tube removal by atropine 0.01 mg / kg and Neostigmine 0.05 mg / kg IV.

After surgery is done, patients were put at supine position. Then when fully awake, were extubated and moved to recovery room. There, oxygen saturation, noninvasive blood pressure, and pulse were monitored. Oxygenation was maintained by face mask 3L. After 30 minutes, patients

were transferred to post-surgical wards. The first pain assessment was done at the surgical ward when patient is fully awake and comprehensive.

In the post-surgical ward, patients were assessed for pain scores at 2, 4, 6, 9, 12 and 24 hours postoperatively by trained health team members using the VAS scale. Same persons recorded the time of first rescue analgesia and the total amount of rescue analgesia given to the patient in the first 24 hours. Also, the incidence of nausea and vomiting were recorded for each patient.

Data Analysis

The data was analyzed using SPSS software statistical package version 20. Means, standard deviations, percentages and frequencies were used to describe data for each group, Chi Square test was utilized to examine differences between Percentages, Post-Hoc test examined pairwise differences between means, ANOVA, ANCOVA and one Way Analysis of Variance (F-Test) was used to examine differences between means. Cross tabulation analysis and chi-Square test were used as a univariate analysis.

Ethical consederation

The study was conducted after Institutional review board (IRB) and ministry of health approval is obtained. Every patient included in the study was informed about the study purpose, the drugs and their action and side effects, the post-operative assessment, the information confidentiality, anonymity and there right to withdraw from the study at any time. After that, every patient was asked to sign a consent form allowing the research team to proceed with the study protocol.

Chapter Four

Results

This chapter presents the results of the answers to the questions and hypothesis of the present thesis, which were concerned with assessing the effectiveness of medications (Gabapentin, Pregabalin, & Placebo) when administered orally before the operation in reducing the post-operative pain level and consumption of rescue analgesia among patients underwent lumber spine surgeries under general anesthesia.

Additionally, to assess the effect of these medications on post-operative complications after lumber spine surgeries under general anesthesia. Furthermore, to assess if the demographic and characteristics of patients underwent lumber spine surgeries under general anesthesia could affect the correlation between these medications and post-operative pain level and consumption of rescue analgesia.

Demographic and anthropometric characteristics of participants

When a comparison was made for the participants within the three groups (Gabapentin, Pregabalin, & Placebo) in this thesis regarding their personal characteristics, it was revealed through the statistical tests that there were no statistically significant differences (p value > 0.05) with regard to the characteristics of the participants.

Although there were no statistically significant differences in demographics between the participants between the three groups (Gabapentin, Pregabalin, & Placebo) in this thesis, the average age of the participants in the

Gabapentin group (50.9 years) was relatively higher compared with the other two Pregabalin & Placebo groups (41.6&45.2 years respectively), as well as the percentage of females in the Pregabalin group was slightly higher compared with the other two Gabapentin and Placebo groups (55.0% vs. 40.0% &45.0% respectively).

As for anthropometrics, the participants in the Pregabalin group were lower in length and higher in weight in compare with participants' of Gabapentin (171.5cm &76.4 kg vs174.0cm &76.1kgrespectively) and Placebo group (171.5cm &76.4 kg vs. 172.8cm &72.7kgrespectively).

Furthermore, this was reflected in the body mass index (BMI) of the participants, as the BMI among the participants in the Pregabalin group was relatively higher in compare with Gabapentin (26 vs. 25.2respectively) and with Placebo (26 vs. 24.2respectively).

Table 4. 1: Demographic and anthropometric characteristics of three groups (Gabapentin, Pregabalin, & Placebo) participants

Variable	Categories	N	Mean	SD	Min	Max	F	Sig.
Age	**Gabapentin**	20	50.9	14.0	26	69	2.088	.133
	Placebo	20	45.2	15.0	21	67		
	Pregabalin	20	41.6	14.4	20	70		
	Total	60	45.9	14.7	20	70		
Height	**Gabapentin**	20	174.0	8.8	159	194	.363	.697
	Placebo	20	172.8	7.4	158	188		
	Pregabalin	20	171.5	10.6	155	190		
	Total	60	172.8	8.9	155	194		
Weight	**Gabapentin**	20	76.1	10.4	60	97	.432	.651
	Placebo	20	72.7	13.9	54	110		
	Pregabalin	20	76.4	16.5	50	110		
	Total	60	75.1	13.7	50	110		
BMI	**Gabapentin**	20	25.2	3.6	19.0	30.0	.796	.456
	Placebo	20	24.2	3.8	19.4	33.9		
	Pregabalin	20	26.0	5.5	17.4	40.0		
	Total	60	25.1	4.4	17.4	40.0		

Although there were no statistically significant differences between the three groups(Gabapentin, Pregabalin, & Placebo) due to medical history and ASA classification as shown in table 1, but the percentage of ASA 1 was slightly more among the participants in the Gabapentin group, compared to the Pregabalin (70.0% vs. 65.0%respectively) and Placebo (70.0% vs.65.0% respectively) groups.

Likewise, the percentage of diabetes patients was slightly higher among the participants in the Pregabalin group than Gabapentin (20.0% vs. 15.0%respectively), while the percentage of hypertensive patients was the opposite (15.0% vs. 20.0%respectively).

Table 4.2: Gender, ASA, and medical history of three groups (Gabapentin, Pregabalin, & Placebo) participants

			Group				
		Total	**Gabapentin**	**Placebo**	**Pregabalin**	X^2	**Sig.**
Gender	**Female**	28(46.7%)	8(40.0%)	9(45.0%)	11(55.0%)	.938	.626
	Male	32(53.3%)	12(60.0%)	11(55.0%)	9(45.0%)		
ASA	**1**	40(66.7%)	14(70.0%)	13(65.0%)	13(65.0%)	.150	.928
	2	20(33.3%)	6(30.0%)	7(35.0%)	7(35.0%)		
Comorbidity	**None**	40(66.7%)	14(70.0%)	13(65.0%)	13(65.0%)	1.50	.959
	DM	10(16.7%)	3(15.0%)	3(15.0%)	4(20.0%)		
	HTN	8(13.3%)	2(10.0%)	3(15.0%)	3(15.0%)		
	HTN, DM	2(3.3%)	1(5.0%)	1(5.0%)	0(0.0%)		

Baseline hemodynamics' parameters of three groups

ANOVA test results showed that the three groups (Gabapentin, Pregabalin, & Placebo) had very similar readings of the baseline hemodynamic' parameters, and there was no statistically significant difference (p value > 0.05) between the three groups due to the Baseline hemodynamic' parameters as shown in table 2.

In addition, the baseline hemodynamic' reading ranges parameters between groups were close, the baseline hemodynamic' readings were within the normal limit for the heart rate, O_2 saturation, and diastolic blood pressure. However, the average of systolic blood pressure was within normal, but it contained some high readings, which reached 140mmHg.

Table 4.3: Baseline hemodynamics' parameters of three groups (Gabapentin, Pregabalin, & Placebo) participants

		N	Mean	SD	Min	Max	F	Sig.
SBP	**Gabapentin**	20	126.5	10.4	100	140	.214	.808
	Placebo	20	127.9	7.5	110	140		
	Pregabalin	20	128.2	8.2	110	145		
	Total	60	127.5	8.7	100	145		
DBP	**Gabapentin**	20	75.9	10.2	60	90	.262	.770
	Placebo	20	76.3	8.2	65	92		
	Pregabalin	20	77.9	8.5	63	90		
	Total				60	76.7	8.9	60 92

HR	**Gabapentin**	20	79.6	10.7	64	98	.052	.950
	Placebo	20	80.1	7.5	68	91		
	Pregabalin	20	80.5	9.6	64	93		
	Total	60	80.0	9.2	64	98		
O_2 Sat %	**Gabapentin**	20	98.7	1.1	97	100	.111	.895
	Placebo	20	98.9	1.0	97	100		
	Pregabalin	20	98.8	0.9	97	100		
	Total	60	98.8	1.0	97	100		

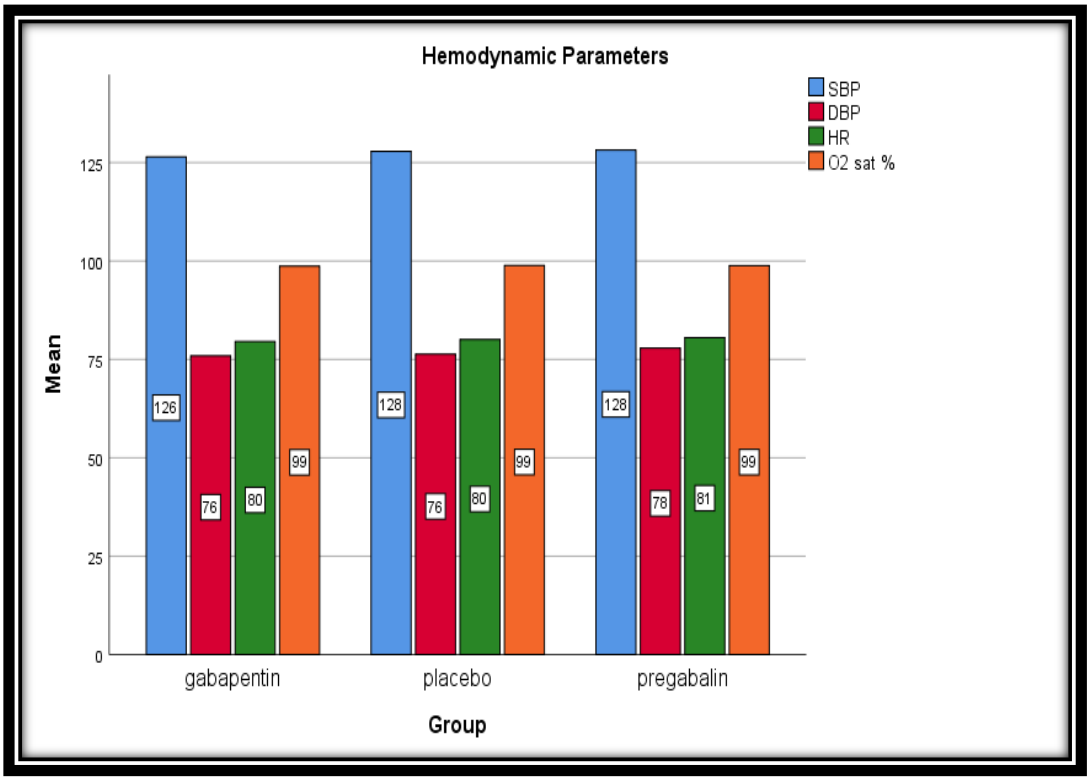

Figure 4.1: Baseline hemodynamics' parameters of three groups (Gabapentin, Pregabalin, & Placebo) participants

Duration of surgery, time of first rescue analgesia, total amount of rescue analgesia

Duration of surgery

By looking at figure 2 and Table No. 3, it appears that the three groups participating in the study did not have any statistically significant difference due to the duration of the operation, although there were small differences between groups as the average operation time was the highest in the Placebo group comparing to other 2 groups (120 vs. 113.6 &106.5) and the lowest in the Pregabalin group comparing to other 2 groups (106. 5 vs. 113.6 & 120).

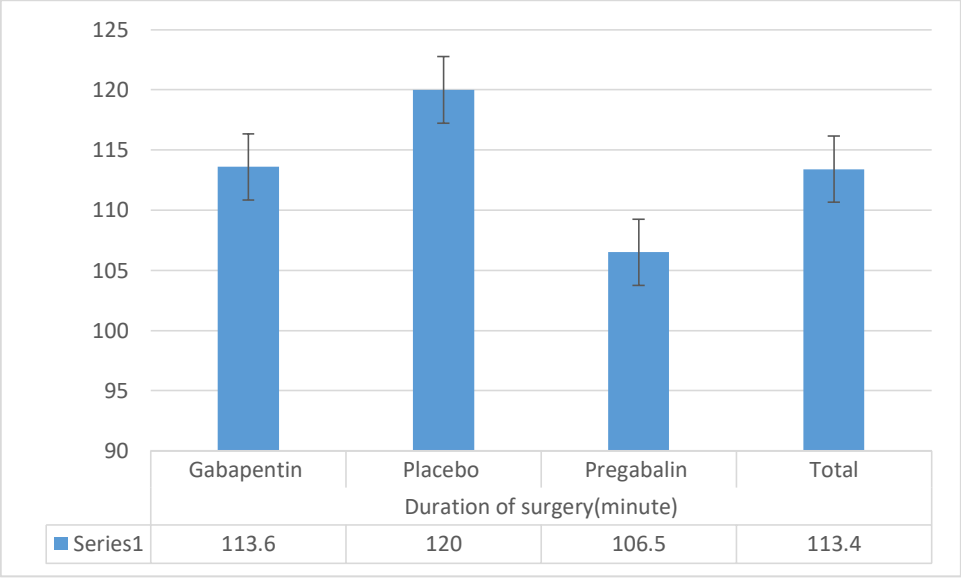

Figure 4.2: Duration of surgery of three groups (Gabapentin, Pregabalin, & Placebo)

Time of first rescue analgesia

The results by using ANOVA test showed that the three groups had a statistically significant difference in terms of time of administration of the

first dose of rescue analgesia (*p* value <0.001), and that the three groups was also a statistically significant difference in terms of the total amount of rescue analgesia (*p* value <0.001) given to relieve pain.

The placebo group gave the fastest group to request the first dose of rescue analgesia compared to the group of Pregabalin (125 vs. 520.8) and the group of Gabapentin (120 vs. 344), while on the other hand, the Pregabalin group was also the slowest in requesting the first dose of rescue analgesia compared to the Placebo group (520.8 vs. 125) and the Gabapentin group (520.8 vs. 344). Post hoc multiple comparison revealed that the three groups were sig. (p value > 0.05). For more details see figure 3 and table 3.

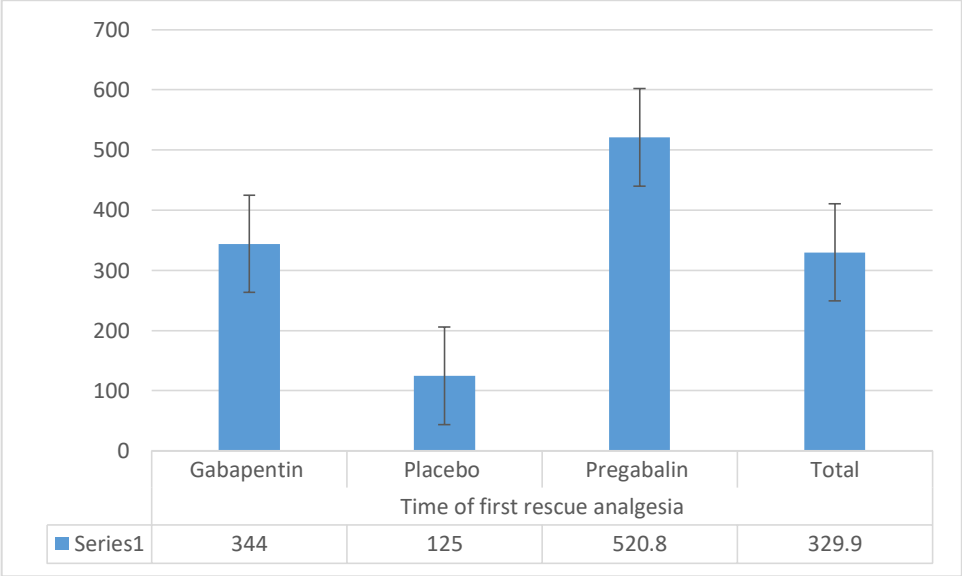

Figure 4.3: Time of first rescue analgesia of three groups (Gabapentin, Pregabalin, & Placebo)

Total amount of rescue analgesia

Figure 4 and Table No. 4 shows that the three groups participating in the study had a statistically significant difference due to the total amount of

rescue analgesia (gm.). additionally, the highest in the Placebo group comparing to other 2 groups (2.8 vs. 1.3 &2.0) and the lowest in the Pregabalin group comparing to other 2 groups (1.3 vs. 2.8 & 2.0).

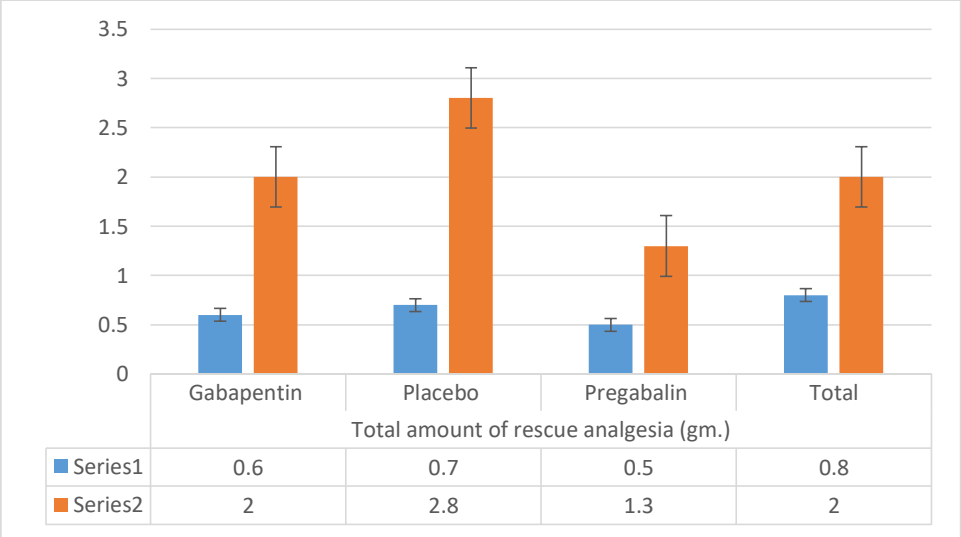

Figure 4.4: Total amount of rescue analgesia (gm.) of three groups (Gabapentin, Pregabalin, & Placebo)

Table 4.4: Duration of surgery, time of first rescue analgesia, total amount of rescue analgesia

		N	Mean	SD	Min	Max	F	Sig.
Duration of surgery(minute)	Gabapentin	20	113.6	30.5	60	160	1.10	.339
	Placebo	20	120.0	22.1	80	160		
	Pregabalin	20	106.5	32.7	60	180		
	Total	60	113.4	28.8	60	180		
Time of first rescue analgesia	Gabapentin	20	344.0	88.7	230	560	65.64	<.001
	Placebo	20	125.0	89.9	40	360		
	Pregabalin	20	520.8	141.3	60	720		
	Total	60	329.9	195.5	40	720		
Total amount of rescue analgesia (gm.)	Gabapentin	20	2.0	0.6	1	3	30.04	<.001
	Placebo	20	2.8	0.7	2	4		
	Pregabalin	20	1.3	0.5	1	2		
	Total	60	2.0	0.8	1	4		

Post-operative complication of three groups (Gabapentin, Pregabalin, & Placebo)

There were no complications after the operation among the participants in the three groups (Gabapentin, Pregabalin, & Placebo) except for a feeling of nausea and vomiting, as nearly 51.7 % of the participants reported that they experienced a feeling of nausea or vomiting after the operation as shown in table 5.

The Chi-Square statistical test showed that there are statistically significant differences between the three groups in terms of the percentage of nausea and vomiting (p value =0.008), as the percentage of nausea and vomiting among the participants in the Placebo group was higher compared with the participants of the Gabapentin group (80% VS 40%) and the Pregabalin group (80% VS 35%).

Also, the experience percentage of nausea and vomiting among the participants in the Pregabalin group was lower compared with the participants in the Gabapentin group (35% vs. 40%) and the control group (35%vs 80%).

Table 4.5: Post-operative complication of three groups (Gabapentin, Pregabalin, & Placebo)

			Group				
		Total	**Gabapentin**	**Placebo**	**Pregabalin**	X^2	**Sig.**
Incidence of nausea & vomiting	No	29(48.3%)	12(60.0%)	4(20.0%)	13(65.0%)	9.74	.008
	Yes	31(51.7%)	8(40.0%)	16(80.0%)	7(35.0%)		
Surgery	Discectomy	2(3.3%)	0(0.0%)	1(5.0%)	1(5.0%)	1.03	.596
	Laminectomy	58(96.7%)	20(100.0%)	19(95.0%)	19(95.0%)		
Complications	No	60(100.0%)	20(100.0%)	20(100.0%)	20(100.0%)	NA	
Diagnosis	Back pain	60(100.0%)	20(100.0%)	20(100.0%)	20(100.0%)	NA	

To measure the effect of the personal characteristics of the participants within the three groups, as well as the effect of medications on the occurrence of post-operative complications, the tabulation and chi-Square test were used as a univariate analysis. The results showed that there are statistically significant differences between the groups and occurrence of post-operative complications (*p* value= 0.008) as well as between co-morbidity and occurrence of post-operative complications (*p* value= 0.015), while gender and baseline did not make any statistically significant difference on the occurrence of post-operative complications (*p* value= 0.20 & 0.46 respectively) as shown in table 6.

Table 4.6: Cross tabulation for Post-operative complication and patients' characteristics of the three groups (Gabapentin, Pregabalin, & Placebo)

			Incidence of nausea & vomiting			
		Total	**No**	**Yes**	X^2	**Sig.**
Group	**Gabapentin**	20 (33.3%)	12 (60.0%)	8 (40.0%)	9.74	.008
	Placebo	20 (33.3%)	4 (20.0%)	16 (80.0%)		
	Pregabalin	20 (33.3%)	13 (65.0%)	7 (35.0%)		
Gender	**Female**	28 (46.7%)	16 (57.1%)	12 (42.9%)	1.63	.201
	Male	32 (53.3%)	13 (40.6%)	19 (59.4%)		
ASA	**1**	40 (66.7%)	18 (45.0%)	22 (55.0%)	.534	.465
	2	20 (33.3%)	11 (55.0%)	9 (45.0%)		
Co-morbidity	**None**	40 (66.7%)	18 (45.0%)	22 (55.0%)	10.44	.015
	DM	10 (16.7%)	8 (80.0%)	2 (20.0%)		
	HTN	8 (13.3%)	1 (12.5%)	7 (87.5%)		
	HTN,DM	2 (3.3%)	2 (100.0%)	0 (0.0%)		

Post-operative Ramsay Sedation Score comparison between groups

It is clear, looking at table number 7, that Ramsay Scores were different between the three groups (Gabapentin, Pregabalin, & Placebo), and this difference had statistical significance and continued through the first, second, fourth and sixth hours *(p* values= 0.001, 0.001, 0.001, 0.005 respectively), while from the ninth hour after the operation, the readings were nearly the same and the statistical significance difference between the groups disappeared (*p* values= 0.37, NA, NA).

Table 4.7: Post-operative Ramsay Sedation Score comparison between groups:

Variable		**Gabapentin**	**Placebo**	**Pregabalin**		
	Time	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**F**	**Sig.**
Ramsay Sedation Score	**1st h**	2.65 (0.49)	2.00 (0.32)*	2.80 (0.41)	21.14	<.001
	2nd h	2.00 (0.00)	1.65 (0.49)	2.45 (0.60)*	15.94	<.001
	4th h	1.75 (0.44)	1.05 (0.22)*	1.90 (0.45)	27.60	<.001
	6th h	1.10 (0.31)	1.00 (0.00)*	1.35 (0.49)*	5.83	.005
	9th h	1.00 (0.00)	1.00 (0.00)	1.05 (0.22)	1.00	.374
	12th h	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	NA	-
	24th h	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	NA	-

NA: not applicable

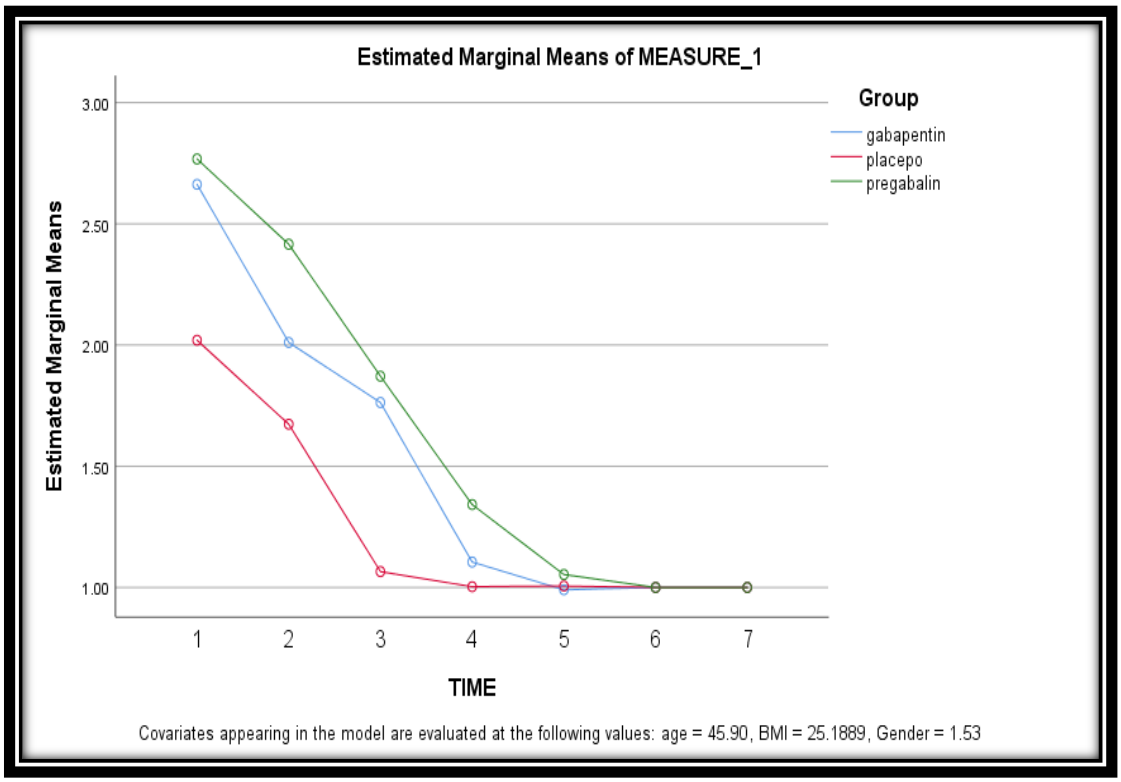

Figure 4.5 : Post-operative Ramsay Sedation Score comparison between groups

Post-operative Visual Analog Scale (VAS) comparison between groups

When the level of pain among patients was measured using a visual analog scale, it was found that there was a statistically significant difference in the level of pain between the three groups (Gabapentin, Pregabalin, & Placebo) during the second (*p* value <0.001), fourth (*p* value = 0.001) and sixth hours(*p* value = 0.001), while from the ninth (*p* value =0.77), twelfth (*p* value <0.56), and twenty-four hours (*p* value =0.88), the differences disappeared in the level of pain between the participants of the three groups.

Post hoc multiple comparison revealed that the placebo group was the group which did the significance (*p* value > 0.05) and had a higher post-

operative pain level in comparing with Gabapentin and Pregabalin groups at the 2nd (6.7 vs. 2.1& 2.2 respectively) and 4th (4.3 vs. 3.3 & 2.5) post-operative. Furthermore, at 6th post-operative hour, placebo group had a significance (*p* value > 0.05) higher post-operative pain level in comparing with Pregabalin groups (5.7 vs. 3.3 respectively).

Although there were no statistically significant differences at 9th (*p* value = 0.77) 12th (*p* value = 0.56) and 24th (*p* value =0.88) post-operative pain level between the three groups, the placebo group exhibited a higher post-operative pain level in comparing with Gabapentin and Pregabalin at 9th, 12th , and 24th post-operative pain level as shown in table 8.

Table4.8: Post-operative Visual Analog Scale (VAS) comparison between groups:

Variable		**Gabapentin**	**Placebo**	**Pregabalin**		
	Time	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**F**	**Sig.**
Visual Analog Scale (VAS)	**2nd h**	2.1(0.6)	6.7(2.1)*	2.2 (1.2)	69.4	.000
	4th h	3.3(0.9)	4.3(1.6)*	2.5(0.5)	14.6	.000
	6th h	4.8(2.1)	5.7(2.2)*	3.3(1.7)*	7.38	.001
	9th h	5.1(2.6)	5.6(2.2)	5.5(2.2)	.254	.776
	12th h	5.8(1.9)	6.0(1.9)	5.3(2.1)	.577	.565
	24th h	4.7(2.2)	4.9(2.1)	4.5(2.4)	.121	.886

*POST HOC MULTIPLE COMPARISON SIGNIFICANT

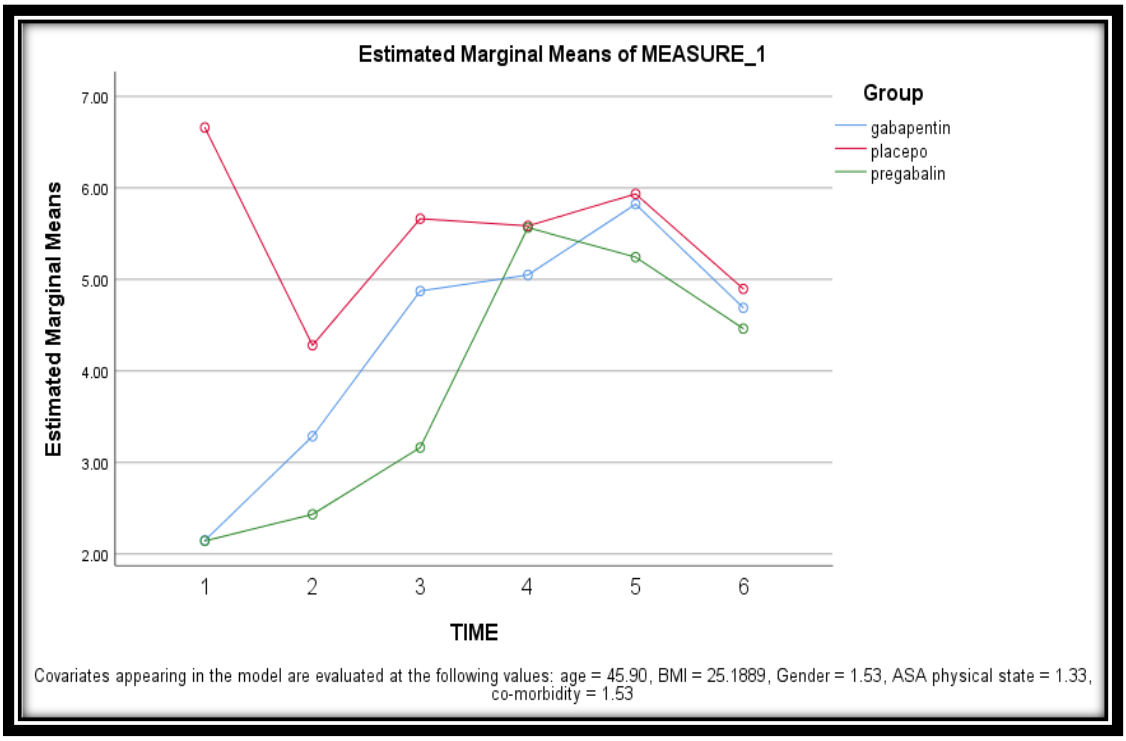

Figure 4.6: Post-operative Visual Analog Scale (VAS) comparison between groups

When the effect of medication intervention (groups) on the time of first rescue analgesia was analyzed for the three groups with controlling the effect of the characteristics of the patients participating in the study by using the ANCOVA statistical test, it was found that there is a statistically significant difference (P value < 0.001) with a high effect size (ηp2= .707) between the three groups with respect to the time of first rescue analgesia used after the operation to relieve pain.

Through the post hoc multiple comparisons, it was found that the three groups are different, and by return to the means of the time of first rescue analgesia, we find that the Placebo group has the least time of first rescue analgesia in comparing to Pregabalin and Gabapentin groups, while the Pregabalin group has the highest time of first rescue analgesia in comparing to Placebo and Gabapentin groups (125.0, 344.0, & 520.8).

While the rest of the characteristics of the study participants did not have a statistically significant effect (p value > 0.05) on the time of first rescue analgesia post operatively as shown in table 9.

Table 4.9: Post-operative time of first rescue analgesia comparison between groups and controlling effect of participants' characteristics:

Source		**Time of first rescue analgesia**			
	df	**Mean Square**	**F**	**Sig.**	**ηp2**
Intercept	1	164547.9	5.61	.059	.501
Group	2	766027.685	62.6	**<.001**	**.707**
Age	1	205.967	.017	.897	.000
BMI	1	1142.580	.094	.761	.002
Gender	1	23415.001	1.91	.172	.036
ASA physical state	1	6119.553	.501	.482	.010
Comorbidity	1	206.113	.017	.897	.000

MS: Mean Square; **ηp2**: Partial Eta Squared

When the effect of medication intervention (groups) on the time of first rescue analgesia was analyzed for the three groups with controlling the effect of the hemodynamic parameters of the patients participating in the study by using the ANCOVA statistical test, it was found that there is a statistically significant difference (P value < 0.001) with a high effect size (ηp2= .687) between the three groups with respect to the time of first rescue analgesia used after the operation to relieve pain.

Through the post hoc multiple comparisons, it was found that the three groups are different, and by return to the means of the time of first rescue analgesia, we find that the Placebo group has the lowest amount of time of

first rescue analgesia in comparing to Pregabalin and Gabapentin groups, while the Pregabalin group has the highest time of first rescue analgesia in comparing to Placebo and Gabapentin groups (125.0, 344.0, & 520.8).

While the rest of the hemodynamic parameters of the study participants did not have a statistically significant effect (p value > 0.05) on the time of first rescue analgesia post operatively as shown in table 10.

Table 4.10: Post-operative time of first rescue analgesia comparison between groups and controlling effect of participants' hemodynamics:

Source		**Time of first rescue analgesia**			
	df	**Mean Square**	**F**	**Sig.**	**ηp2**
Intercept	1	2344.509	.182	.672	.003
Group	2	731450.320	56.953	**<.001**	**.687**
Systolic blood pressure	1	191.176	.015	.903	.000
Diastolic blood pressure	1	1481.625	.115	.735	.002
HR	1	10595.118	.825	.368	.016
O2 sat	1	1676.763	.131	.719	.003
Duration of Surgery	1	40.637	.003	.955	.000

MS: Mean Square; **ηp2**: Partial Eta Squared

When the effect of medication (group) was analyzed for the three groups with controlling the effect of the personal characteristics of the patients participating in the study and using the ANCOVA statistical test, it was found that there is a statistically significant difference (P value <0.001) with a high effect size (**ηp2= .527)** between the three groups with respect to the total amount of rescue analgesics used after the operation to relieve pain.

Through the post hoc multiple comparisons, it was found that the three groups are different, and by return to the means of the total amount of rescue analgesia, we find that the Placebo group has the highest amount of total rescue analgesia in comparing to Pregabalin and Gabapentin groups, while the Pregabalin group amount of total rescue analgesia in comparing to Placebo and Gabapentin groups (2.75 gm., 2.00 gm., &1.30 gm.).

While the rest of the personal characteristics of the study participants did not have a statistically significant effect (p value > 0.05), with the exception of gender, where it was found that there is a high effect size (ηp2= .088) and statistically significant (p value = 0,029) relationship between gender and the amount of total rescue analgesia post operatively as shown in table 11.

Table 4.11: Post-operative total amount of rescue analgesia comparison between groups and controlling effect of participants' characteristics:

Source		**Total amount of rescue analgesia**			
	df	**Mean Square**	**F**	**Sig.**	**ηp2**
Intercept	1	8.517	14.945	.002	.567
Group	2	10.092	28.923	**<.001**	**.527**
Age	1	.040	.115	.736	.002
BMI	1	.052	.148	.702	.003
Gender	1	1.757	5.036	**.029**	**.088**
ASA physical state	1	.003	.008	.930	.000
Comorbidity	1	.003	.009	.923	.000

MS: Mean Square; **ηp2**: Partial Eta Squared

When the effect of medication intervention (groups) on the total amount of rescue analgesics was analyzed for the three groups with controlling the effect of the hemodynamic parameters of the patients participating in the study by using the ANCOVA statistical test, it was found that there is a statistically significant difference (P value = 0.001) with a high effect size (ηp2= .244) between the three groups with respect to the total amount of rescue analgesics used after the operation to relieve pain.

Through the post hoc multiple comparisons, it was found that the three groups are different, and by return to the means of the total amount of rescue analgesia, we find that the Placebo group has the highest amount of total rescue analgesia in comparing to Pregabalin and Gabapentin groups, while the Pregabalin group amount of total rescue analgesia in comparing to Placebo and Gabapentin groups (2.75 gm., 2.00 gm., &1.30 gm.).

While the rest of the hemodynamic parameters of the study participants did not have a statistically significant effect (p value > 0.05) on the amount of total rescue analgesia post operatively as shown in table 12.

Table 4.12: Post-operative total amount of rescue analgesia comparison between groups and controlling effect of participants' hemodynamics:

Source		**Total amount of rescue analgesia**			
	df	**Mean Square**	**F**	**Sig.**	**ηp2**
Intercept	1	.255	.737	.395	.014
Group	2	2.843	8.212	**.001**	**.244**
Systolic blood pressure	1	.434	1.252	.268	.024
Diastolic blood pressure	1	1.246	3.600	.063	.066

HR	1	.324	.935	.338	.018
O2 sat	1	.092	.266	.608	.005
Duration of Surgery	1	.059	.171	.681	.003

MS: Mean Square; **ηp2**: Partial Eta Squared

Chapter Five

Discussion

Chapter five includes a discussion of the previous chapter, deals with the discussion and summary of research findings. It also includes the research conclusion, implication and recommendation for upcoming research. The results are interpreted based on the literature review. Statistical significance is interpreted based on the P value < 0.05, which indicates a statistical significance. The research questions are also reproduced in the discussion. The present study is conducted to identify and assess the relationship between preoperative administration of Pregabalin and Gabapentin and their effect on acute postoperative pain.

The major findings of the study were organized under the following

- Demographic data and related findings.
- Duration of surgery and related findings.
- Dosage and administration of Pregabalin and Gabapentin.
- Pain assessment by VAS scores.
- Ramsey sedation scores.
- Time of first rescue analgesia.
- Dosage of Paracetamol administered in the first 24 hours.
- Incidence of nausea and vomiting.

This study was a prospective, randomized, double blinded study conducted by the Department of Anesthesiology, An-Najah National University in collaboration with Department of Neurology at Rafedia Government Surgical Hospital.

Demographic and hemodynamic data

In this thesis, it was revealed through the statistical tests that there were no statistically significant differences (p value > 0.05) with regard to the personal characteristics (gender, age, height, weight, hemodynamics & BMI) of the participants between the three tested groups. Moreover, there were no statistically significant differences between the three groups due to medical history, ASA classification or preoperative hemodynamic state. By that, we exclude any effect caused by the patients' characteristics on the drugs performance.

Duration of surgery

In similar to the present study result, a study conducted by Sidharth et al (23) on lower lumber spine surgery patients, the duration of surgery was 110.9 vs. 113.6 minute in gabapentin group, 109.2 vs. 106.5 minute in Pregabalin group & 109.3 vs. 120 minute in placebo group, which didn't make any statistical significance. The three groups participating in the study did not have any statistically significant difference due to the duration of the operation. By that, we exclude any effect of the duration of surgery on the drugs performance.

Dosage and administration of Pregabalin and Gabapentin

In consistence with (19, 29) studies, the present study administered Gabapentin and Pregabalin preoperatively and it was shown that they reduce postoperative pain and prolong postoperative analgesia when administered as a single dose preoperatively. In the present study, drugs were administered one hour preoperatively based on a study conducted by Sidharth et al (23), with a dose of 300 mg gabapentin and a 150 mg Pregabalin similarly to a study conducted by Acharya et al (25) in 2019. It was shown in these studies that these doses in this timing significantly lowered the postoperative pain scores and are safe on hemodynamics and does not alter them.

Pain assessment

After the patients were taught about VAS before surgery, pain assessment started at 2, 4, 6, 9, 12 and 24 hours post operatively. This is similar to a study conducted in 2019 by Vasanthy et al (18), in which compared the preemptive effect of Pregabalin and Gabapentin for post-operative analgesia on lower limb surgeries under spinal anesthesia at 1, 2, 4, 6, 9, 12 and 24 hours. In the present study, pain assessment at first postoperative hour was excluded because it wasn't applicable in the present study to use the VAS at this time due to the sedation effect of Pregabalin and Gabapentin.

In the present study, the VAS scores were significantly less in both Pregabalin and Gabapentin groups compared to placebo group, this is similar to the results of many recent studies (18, 20, 21, 23, 25-27).

Our study results revealed that Pregabalin group had a significant lower VAS scores for longer interval (up to 6 hours post-operatively) than gabapentin group compared to placebo group. This result may be explained by increased binding affinity for the alpha-2-delta protein found is Pregabalin, which makes it a more potent analgesic in neuropathic pain compared with gabapentin. Moreover, there is a difference in gabapentin absorption, in which gabapentin absorption is saturable and Pregabalin is not. Which causes a non-linear pharmacokinetic profile for gabapentin. So when gabapentin doses increase, the area under the curve (AUC) does not follow proportionally. Adding to what previously mentioned, the bioavailability of generic gabapentin formulations is about 80% at lower doses such as 100 mg every 8 hours, but only 27% bioavailable at doses of 1600 mg every 8 hours. On the other hand, Pregabalin has a greater than 90% bioavailability through 75 mg to 900 mg daily in divided doses. Variability in Gabapentin's bioavailability among patients ranges between 20% to 30% and only 10% to 15% with Pregabalin(42).

Sedation scores

In the present study, all patients were evaluated for the level of sedation postoperatively by Ramsay sedation score at 1, 2, 4, 6, 9, 12, and 24 hours. Sedation scores were higher in the first 6 hours postoperatively in

Pregabalin and Gabapentin groups compared to placebo group. The sedation effect of the drugs is related to the elimination half time of Gabapentin which is 4.8 to 8.7 hours(15) and the mean elimination t1/2 of Pregabalin which is 6.3 hours (16). It's also important to mention that the Pregabalin group had higher sedation scores when compared with Gabapentin group, which can be explained by the better lipid solubility in Pregabalin, which causes increased diffusion across blood brain barrier and better pharmacokinetic properties(43). The higher sedation effect of Pregabalin has been seen repeatedly in other studies, most recently in a study conducted in 2020 by Khetarapal et al(26).

Time of first rescue analgesia

It was revealed in the present study that the time interval for first dose of rescue analgesic is 520.8 minutes in Pregabalin group, 344 minutes in Gabapentin group and 125 minutes in placebo group. (p value <0.001), which reflects a significant prolonged pain relief in Pregabalin and Gabapentin groups compared to placebo group and a significant longer pain relief provided by Pregabalin when compared to gabapentin alone. This result may be explained by increased binding affinity for the alpha-2-delta protein found is Pregabalin. Which makes it a more potent analgesic in neuropathic pain compared with gabapentin. Moreover, there is a difference in gabapentin absorption, in which gabapentin absorption is saturable and Pregabalin is not. Which causes a non-linear pharmacokinetic profile for gabapentin. So when gabapentin doses increase, the area under the curve (AUC) does not follow proportionally. Adding to what previously

mentioned, the bioavailability of generic gabapentin formulations is about 80% at lower doses such as 100 mg every 8 hours, but only 27% bioavailable at doses of 1600 mg every 8 hours. On the other hand, Pregabalin has a greater than 90% bioavailability through 75 mg to 900 mg daily in divided doses. Variability in Gabapentin's bioavailability among patients ranges between 20% to 30% and only 10% to 15% with Pregabalin (42). This is result is similar to the discoveries of numerous other studies (18, 20, 21, 23, 25-27, 30, 44).

Dosage of Paracetamol administered in the first 24 hours

In the present study, the highest amount of administered Paracetamol was in the Placebo group compared to the Pregabalin & gabapentin groups (2.8 vs. 1.3 &2.0). The lowest in amount of administered Paracetamol was in Pregabalin group. This result may be explained by increased binding affinity for the alpha-2-delta protein found is Pregabalin. Which makes it a more potent analgesic in neuropathic pain compared with gabapentin. Moreover, there is a difference in gabapentin absorption, in which gabapentin absorption is saturable and Pregabalin is not. Which causes a non-linear pharmacokinetic profile for gabapentin. So when gabapentin doses increase, the area under the curve (AUC) does not follow proportionally. Adding to what previously mentioned, the bioavailability of generic gabapentin formulations is about 80% at lower doses such as 100 mg every 8 hours, but only 27% bioavailable at doses of 1600 mg every 8 hours. On the other hand, Pregabalin has a greater than 90% bioavailability through 75 mg to 900 mg daily in divided doses. Variability in

Gabapentin's bioavailability among patients ranges between 20% to 30% and only 10% to 15% with Pregabalin (42). This result is similar to the discoveries of numerous other studies (18, 20, 21, 23, 25-27, 30, 44).

Incidence of nausea and vomiting

In present study, the percentage of nausea and vomiting among the participants in the Placebo group was higher compared with the participants of the Gabapentin group (80% VS 40%) and the Pregabalin group (80% VS 35%). This result can be related to the higher postoperative pain scores in placebo group when compared to Pregabalin & gabapentin groups(39) and the effectiveness of pre-operative Pregabalin and Gabapentin in reduction of post-operative nausea and vomiting that has been proven in meta-analysis of randomized trials conducted by Grant et al (45, 46). The present result is also seen in previous similar studies (18, 20, 21, 23, 25-27, 30, 44).

The present study revealed an increased incidence of post-operative nausea and vomiting in relation with co-morbidity, which is supported with Sizemore et al (47) statement, that the frequency of post-operative nausea and vomiting can reach 80% in high-risk populations and 30% of the general population.

❖ **Study limitations**

- COVID 19 pandemic was a big limitation for the present study, it affected the timeline of the study due to the conversion of the surgical

wards to medical wards and the discontinuation of elective surgeries at Rafedia surgical hospital.

- Lack of funding, which made it hard to get the appropriate number of staff members for postoperative assessment.
- Unavailable and expensive manufactured identical Gabapentin, Pregabalin & placebo tablets, it was hard to obtain identical tablets due to the rejection of my request from many pharmaceutical companies.

❖ **Study strengths**

- Study design, this study is a true experimental randomized, double-blind, placebo controlled, prospective study.
- Study population size, the sample size (60 patients) is equal to the estimated sample size which revealed a high power and increase trust in the study results.
- Postoperative assessment period (24 Hrs.), which seems enough as the average elimination half time of Gabapentin and Pregabalin is around 6 hours (15,16).

❖ **Study recommendations**

- Usage of Gabapentin and Pregabalin as preemptive analgesics in lower lumber spine surgeries under general anesthesia on patients under ASA I and ASA II classification. To achieve reduced burden on the ministry of health as the preemptive drugs reduces the amount of rescue analgesia, reduction of nurses of work load and patient cost of health care

- Enforcing the hospitals continuing education committee to include sufficient education on multimodal and preemptive analgesia.
- Advice the curriculum developer at universities to include sufficient education on multimodal and preemptive analgesia.
- Suggest to indorse preemptive method of analgesia in government hospitals in the ministry of health.
- Further studies in the future regarding pain management methods and techniques.
- Further studies on preemptive Gabapentin and Pregabalin for patients above ASA I and ASA II classification.

❖ Conclusion

Preemptive Pregabalin (150 mg) is established to be more effective than Gabapentin (300 mg), in prolongation of postoperative analgesia with reduced rescue analgesic requirements. Although sedation is recurrently observed, and does not seem to cause any serious complications. Thus, Preemptive Pregabalin can be considered as a safe drug to reduce postoperative pain in lower lumber spine surgeries.

References

- Harsoor S. ***Emerging concepts in post-operative pain management***. **Indian Journal of Anesthesia**. 2011;55(2):101-3.
- Ghoneim MM, O'Hara MW. ***Depression and postoperative complications: an overview***. **BMC Surg**. 2016;16:5.
- Glare P, Aubrey KR, Myles PS**.** ***Transition from acute to chronic pain after surgery***. **The Lancet.** 2019;393(10180):1537-46.
- Dorow M, Lobner M, Stein J, Konnopka A, Meisel HJ, Gunther L, et al. ***Risk Factors for Postoperative Pain Intensity in Patients Undergoing Lumbar Disc Surgery: A Systematic Review***. **PLoS One.** 2017;12(1):e0170303.
- Joshi GP, Kehlet H. ***Postoperative pain management in the era of ERAS: An overview***. **Best Practice Research in Clinical Anesthesiology**. 2019;33(3):259-67.
- Kurd MF, Kreitz T, Schroeder G, Vaccaro AR. ***The Role of Multimodal Analgesia in Spine Surgery***. **J Am Acad Orthop Surg**. 2017;25(4):260-8.
- Rae A. ***Reasons for delayed patient discharge following day surgery: a literature review***. **Nurs Stand.** 2016;31(11):42-51.
- Brennan TJ. ***Pathophysiology of postoperative pain*****. Pain.** 2011;152(3 Suppl):S33-40.
- KEHLET H. ***The Endocrine-Metabolic Response to Postoperative Pain.*** **Acta Anaesthesiologica Scandinavica Fonden**. 1982;74:173-5.

- Ellison DL. ***Physiology of Pain***. **Crit Care Nurs Clin North Am.** 2017;29(4):397-406.
- Kehlet H, Dahl JB. ***The Value of "Multimodal" or "Balanced Analgesia" in Postoperative Pain Treatment.*** **Anesthesia & Analgesia.** 1993;77(5):1048-56.
- 12. Kehlet H, Werner M, Perkins F. ***Balanced Analgesia. What is it and what are its Advantages in Postoperative Pain?*** **Drugs**. 1999; 58(5):793-7. 13. GeorgeW. Crile. ***The kinetic theory of shock and its prevention through anoci-association (shockless operation).*** **The Lancet** 1913;182(4688):7-16.
- Kissin I. ***Preemptive Analgesia.*** **Anesthesiology.** 2000;93:1138-43.
- Rose MA, Kam PCA. ***Gabapentin: Pharmacology and Its Use in Pain Management.*** **Anesthesia** 2002;57(5):451-62.
- Ben-Menachem E. **Pregabalin Pharmacology and Its Relevance to Clinical Practice**. **epilepsia** 2004;45(s6):13-8.
- Onakpoya IJ, Thomas ET, Lee JJ, Goldacre B, Heneghan CJ. ***Benefits and harms of Pregabalin in the management of neuropathic pain: a rapid review and meta-analysis of randomized clinical trials.*** **BMJ Open**. 2019;9(1):e023600.
- Vasanthy DJ, Sandeep D. ***A comparative study of oral Pregabalin Gabapentin for post-operative analgesia in lower limb surgeries under spinal anesthesia.*** **PARIPEX – Indian Journal of Research.** 2019; 8(7):2250 - 1991.

- Surana DR, Chaturvedi DS, Jethava DD. ***Pre-Emptive oral Pregabalin for Pain Relief After Laparoscopic Cholecystectomy.*** **IOSR Journal of Dental and Medical Sciences.** 2017;16(06):55-60.
- Khetarpal R, Kataria AP, Bajaj S, Kaur H, Singh S. ***Gabapentin vs pregabalin as a premedication in lower limb orthopaedics surgery under combined spinal epidural technique.*** **Anesth Essays Res**. 2016;10(2):2627.
- Thakur N, Aggarwal V, Patidar S. ***Comparison of postoperative analgesic effect of oral Gabapentin and oral Pregabalin in patients undergoing total abdominal hysterectomy under spinal anesthesia.*** **International Journal of Scientific Research**. 2019;8(12):2277 - 8179.
- Tank T, Gosai N, Patel B, Vaidya V, Goswami P. ***To evaluate role of gabapentin as a preemptive analgesic in patients undergoing modified radical mastectomy.*** **Indian Journal of Clinical Anaesthesia**. 2016;3(4):497-501
- Routray SS, Pani N, Mishra D, Nayak S. ***Comparison of Pregabalin with gabapentin as preemptive analgesia in lumber spine surgery.*** **Journal of Aneasthesiology Clinical Pharmacology.** 2018;34(2):232-6.
- Magu A, Charan P, Ahmed DF. ***To compare analgesic effect of two different doses of Pregabalin as premedication in patients undergoing abdominal hysterectomy under spinal anesthesia.*** **International Journal of Scientific Research**. 2019 8(6):2277 - 8179.

- Maharjan R, Prasad JN, Singh SN, Bhattarai B, Ghimire A, Acharya U. ***Preemptive use of oral gabapentin or pregabalin for acute postoperative pain following lower limb orthopaedic surgery under spinal anaesthesia.*** **Journal of Kathmandu Medical College.** 2019;8(1):3-7.
- Khetapara R, Kataria AP, Singh S***. Gabapentin vs Pregabalin as a premedication in lower limb surgery under combined spinal epidural technique***. 2020.
- Eidy M, Fazel MR, Abdolrahimzadeh H, Moravveji AR, Kochaki E, Mohammadzadeh M. ***Effects of Pregabalin and Gabapentin on postoperative pain and opioid consumption after laparoscopic cholecystectomy.*** **Korean J Anesthesiol**. 2017;70(4):434-8.
- Hu J, Huang D, Li M, Wu C, Zhang J. ***Effects of a single dose of preoperative pregabalin and gabapentin for acute postoperative pain: a network meta-analysis of randomized controlled trials.*** **J Pain Res.** 2018;11:2633-43.
- Gogna RL, Dwivedi D, Tandon U, Sarin K, Bhatnagar V. ***Role of oral gabapentin as preemptive adjuvant with spinal anesthesia for postoperative pain in patients undergoing surgeries under spinal anesthesia.*** **Indian journal of Pain.** 2017;31(2):133-7.
- Gautam A, Tandon N, Masar R, Kothari D, Goyal P, Yadav S, et al. ***A Comparative Evaluation of Pre-Emptive Doses of Gabapentin and Pregabalin for Postoperative Relief of Pain in Patients Scheduled for***

Surgery under General Anaesthesia. **Journal of Evolution of Medical and Dental Sciences.** 2016;5(74):5459-62.

- Sebastian B, Talikoti AT, Krishnamurthy D. ***Effect of oral Pregabalin as preemptive analgesic in patients undergoing lower limb orthopedic surgeries under spinal anesthesia.*** 2020.
- Sharma A, Datta R, Sharma VB. ***Effect of Oral Gabapentin vs. Pregabalin as preemptive analgesic for postoperative pain in patients undergoing lumbar spine surgeries.*** **International Journal of Health Sciences and Research**. 2020;10(5):181-91.
- Khurana G, Jindal P, Sharma JP, Bansal KK. ***Postoperative pain and long-term functional outcome after administration of gabapentin and pregabalin in patients undergoing spinal surgery.*** **Spine (Phila Pa 1976**). 2014;39(6):E363-8.
- Polit DF, Beck CT. ***Nursing research-Principles and methods.*** **Lippincot Williems & Wilkins** 2003.
- Pal S, Dasgupta S, Mukhopadhyay S, Chauduri A**.** ***A comparative study between oral Pregabalin and Gabapentin on prolongation of postoperative pain relief after spinal anesthesia.*** **Indian Journal of Pain.** 2016;30(1):7-12.
- Fink R. ***Pain assessment: the cornerstone to optimal pain management.*** **Proc (Bayl Univ Med Cent).** 2000;13(3):236-9.
- Williamson A, Hoggart B. Pain: ***a review of three commonly used pain rating scales.*** **Journal of Clinical Nursing.** 2005;14:798–804.

- Carrasco G. ***Instruments for monitoring intensive care unit sedation.*** **Critical Care.** 2000;4:217–25.
- Pierre S, Whelan R***. Nausea and vomiting after surgery.*** **Continuing Education in Anaesthesia Critical Care & Pain**. 2013;13(1):28-32.
- Chia Y-Y, Kuo M-CL, Kang , Sun G-C, Hsieh S-W, Chow L-H. ***Does Postoperative Pain Induce Emesis?*** **The Clinical Journal of Pain.** 2002;18(5): 317-23.
- Ahmed F, Magu A. ***To Determine the Difference in Haemodynamic Parameter of Oral 75mg, 150mg Pregabalin Premedication and Control Group among Patients Undergoing Abdominal Hysterectomy.*** **International Journal of Medical and Biomedical Studies.** 2019;3(5).
- Bockbrader HN, DavidWesche, Miller R, Chapel S, Janiczek N, Burger P. ***A Comparison of the Pharmacokinetics and Pharmacodynamics of Pregabalin and Gabapentin***. **Clin Pharmacokinet.** 2010;49(10):661-9.
- Ghai A, Gupta M, Rana N, Wadhera R. ***The effect of Pregabalin and Gabapentin on preoperative anxiety and sedation: a double blind study.*** **anesthesia, pain & intensive care**. 2012;16(3):257-61.
- Bafna U, Rajarajeshwaran K, Khandelwal M, Verma AP. ***A comparison of effect op preemptive use of oral Gabapentin and Pregabalin for acute postoperative pain after surgery under spinal anesthesia.*** **Journal of Aneasthesiology Clinical Pharmacology.** 2014;30(3):373-3377.

- Grant MC, Betz M, Hulse M, Zorrilla-Vaca A, Hobson D, Wick E, et al. ***The Effect of Preoperative Pregabalin on Postoperative Nausea and Vomiting: A Meta-analysis.*** **Anesth Analg.** 2016;123(5):1100-7.
- Grant MC, Lee H, Page AJ, Hobson D, Wick E, Wu CL. ***The Effect of Preoperative Gabapentin on Postoperative Nausea and Vomiting: A Meta-Analysis.*** **Anesth Analg.** 2016;122(4):976-85.
- Sizemore DC, Singh A, Dua A, Singh K, Grose BW**.** ***Postoperative Nausea*** [Internet]. **PubMed. Treasure Island** (FL): StatPearls Publishing; 2021 [cited 2021 Aug 18]. Available from: https://pubmed.ncbi.nlm.nih.gov/29763205

Appendices

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بسم الله الرحمن الرحيم

جامعة النجاح
الوطنية
كليـة الطب وعـلـوم الصـحة
دائرة التمريض

كلية الدراسات العليا

موافقة للاشتراك في البحث العلمي:

الباحث: بشرى موسى عبد الجبار سمارة.

رقم الهاتف: 0597076447

أنت/ي مدعو/ة للمشاركة ببحث علمي سريري سيجرى في مستشفى رفيديا الجراحي في نابلس. الرجاء أن تأخذ/ي الوقت الكافي لقراءة المعلومات التالية بتأن قبل أن تقرر/ي إذا كنت تريد/ين المشاركة أم لا. بإمكانك طلب إيضاحات أو معلومات إضافية عن أي شيء مذكور في هذه الاستمارة أو عن هذه الدراسة ككل من الباحث.

عنوان الدراسة:

مقارنة بين التأثير الوقائي للبريجابالين والجابابنتين الفموي على الآلام الحادة بعد العملية الجراحية لدى المرضى الذين يخضعون لجراحات العمود الفقري القطني تحت التخدير العام.

الهدف من الدراسة:

تهدف هذه الدراسة إلى مقارنة الفعالية الوقائية لتسكين الالم للجابابنتين الفموي و البريجابالين الفموي في المرضى الذين يخضعون لجراحات العمود الفقري القطني تحت التخدير العام.

فترة المشاركة في الدراسة:

تبدأ مشاركتك في الدراسة من بدأ العملية الجراحية المخططة لك ومراقبة حالتك الصحية لمدة يوم كامل (24 ساعة) بعد انتهاء العملية.

اجراء الدراسة:

سيتم توزيع المشاركين في الدراسة الى ثلاث مجموعات عشوائيا، حيث ستتلقى المجموعة الأولى علاج ال "برجابالين"، والمجموعة الثانية سوف تتلقى علاج "جابابنتين", المجموعة الثالثة سوف تتلقى قرص الدواء الوهمي قبل بدء التخدير.

الفوائد المتوقعة للمشاركة في الدراسة:

التخفيف من حدة الألم بعد العملية.

التأثيرات السلبية المتوقعة للدراسة:

التأثيرات المتوقعة هي من الأعراض الجانبية للأدوية المستعملة في هذه الدراسة مثل النعاس والدوار. الأدوية سوف تعطى في جرعات خفيفة مما يقلل من الأعراض الجانبية لها، وفي حال حدوث هذه الأعراض سيتم تقديم العالج المناسب لها.

سرية المعلومات لحماية خصوصيتك:

سوف يتم تسجيل النتائج مع رمز سري. سوف يتم تسجيل فقط اسمك في نموذج الموافقة. وسيتم الإبقاء على الرمز السري المعين في ملف مغلق ومحمي بعناية .الوصول لهذه المعلومات يتم فقط من قبل الباحث الرئيسي للدراسة والأفراد المرخص لهم. مع ذلك، قد تتم مراجعة سجلات الدراسة من قبل اللجنة الأخلاقية التي تجري على البشر في جامعة النجاح الوطنية. ستتم مراقبة السجلات الخاصة بك ويمكن مراجعتها دون انتهاك السرية وأية بيانات يمكن ان تنتج عن هذه الدراسة لن تذكر أسماء المشاركين في الدراسة.

المشاركة الطوعية / الانسحاب:

اذا اخترت/ي عدم ان المشاركة في هذه الدارسة طوعية تماما، يمكنك سحب موافقتك في أي وقت. واذا اخترت/ي مشاركتك في الدراسة أو انسحابك في وقت لاحق من هذه الدراسة لن تتأثر الرعاية الطبية المقدمة لك او تتغير بأي شكل من الأشكال. إذا كنت/ي ترغب/ي في الانسحاب من الدراسة، يمكنك الاتصال بالباحث.

الاتصال للحصول على أجوبة على أسئلتك ومخاوفك وشكواك:

إذا كان لديك أي أسئلة، مخاوف أو شكاوى، يرجى الاتصال بالباحث الرئيسي للدراسة على الأرقام المدرجة على الصفحة الأولى من هذه الموافقة.

Assessment sheet

Study title: A comparison of pre-emptive effect of oral Pregabalin and Gabapentin on acute postoperative pain in patients undergoing lumber spine surgeries.

Patient number: _____ Age: _____ years

Height: ____meter

Weight: _____ Kg

Gender: Male/Female

Diagnosis:

_____

Surgery:

_____

ASA physical status:

_____

Co-morbidity:

_____

Pre-operation vital signs:

Bp: _____mmHg pulse: _____beat/min

SatO2: _____%

Duration of surgery: _____ minute

Post-operative pain score:

Time (PO)	**2 HRs**	**4 HRs**	**6 HRs**	**9 HRs**	**12 HRs**	**24 HRs**
Score						

Postoperative Ramsay sedation score:

Time (PO)	**1 hour**	**2 HRs**	**4 HRs**	**6 HRs**	**9 HRs**	**12 HRs**	**24 HRs**
Score							

Time for the first rescue analgesia: _____ minute

Total amount of rescue analgesia administered in first 24 hours postoperatively:

Time:					
Analgesic:					
Amount:					

Incidence of nausea and vomiting: yes/no

Other complications:

_____

_____

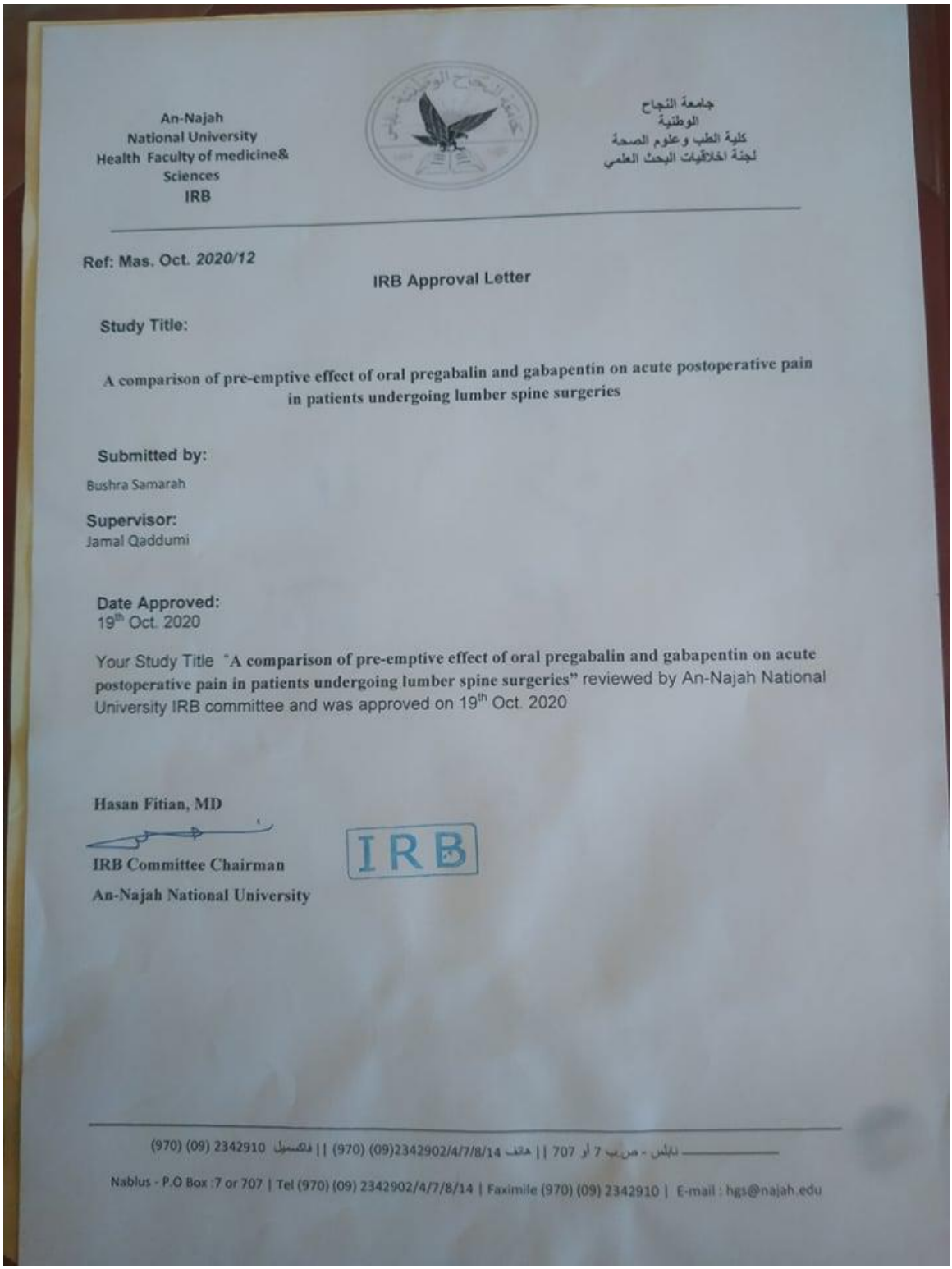
_____

_____

_____

_____

IRB approval



An-Najah
National University
Health Faculty of medicine&
Sciences
IRB

جامعة النجاح
الوطنية
كلية الطب وعلوم الصحة
لجنة اخلاقيات البحث العلمي

Ref: Mas. Oct. 2020/12

IRB Approval Letter

Study Title:

A comparison of pre-emptive effect of oral pregabalin and gabapentin on acute postoperative pain in patients undergoing lumber spine surgeries

Submitted by:

Bushra Samarah

Supervisor:
Jamal Qaddumi

Date Approved:
19th Oct. 2020

Your Study Title "A comparison of pre-emptive effect of oral pregabalin and gabapentin on acute postoperative pain in patients undergoing lumber spine surgeries" reviewed by An-Najah National University IRB committee and was approved on 19th Oct. 2020

Hasan Fitian, MD

IRB Committee Chairman

An-Najah National University

IRB

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General Directorate of Education in Health

دولة فلسطين
وزارة الصحة– نابلس
الإدارة العامة للتعليم الصحي

Ref.: ....
Date:..................

الرقم: عجد/١٤٧٨/٢٠٢٠
التاريخ: ٢٢/١١/٢٠٢٠

الأخ مدير عام الادارة العامة للمستشفيات المحترم ،،،

تحية واحترام...

الموضوع: تسهيل مهمة بحث

لاحقا لموافقة معالي وزيرة الصحة، وبعد توصيات لجنة اخلاقيات البحث العلمي، يرجى تسهيل مهمة الطالبة: بشرى موسى عبد الجبار سماره، ماجستير تمريض التخدير، جامعة النجاح، لاجراء بحث التخرج بعنوان:

A comparison of pre-emptive effect of oral pregabalin and gabapentin on acute postoperative pain in patients undergoing lumber spine surgeries

حيث ستقوم الطالبة بعمل دراسة تتضمن تأثير ادوية على المرضى، مع العلم ان مشرف الدراسة: د. جمال قدومي و د. نور الدين المصري، وذلك في:

– مستشفى رفيديا

يرجى العلم ان الطبيب المشرف افاد للجنة الاخلاقيات انه قام باستخدام الادوية سابقا ولا مانع من استخدامها ان توفرت.

مع الاحترام...

د. عبد الله القواسمي
مدير وحدة التعليم الصحي
والبحث العلمي

جامعة النجاح الوطنية

كلية الدراسات العليا

مقارنة بين التأثير الوقائي للبريجابالين الفموي والجابابنتين على الآلام الحادة بعد العملية الجراحية لدى المرضى الذين يخضعون لجراحات الجزء السفلي للعمود الفقري

اعداد

بشرى سمارة

اشراف:

د.جمال القدومي

د. نور الدين مصري

قدمت هذه الأطروحة استكمالا لمتطلبات الحصول على درجة الماجستير في تمريض التخدير بكلية الدراسات العليا في جامعة النجاح الوطنية، نابلس – فلسطين.

2021

مقارنة بين التأثير الوقائي للبريجابالين والجابابنتين الفموي على الآلام الحادة التالية للعملية الجراحية لدى المرضى الذين يخضعون لعمليات جراحية في العمود الفقري.

اعداد: بشرى سمارة

اشراف:

د.جمال القدومي

د. نور الدين مصري

الملخص

المقدمة: تعتبر آلام أسفل الظهر سببًا رئيسيًا لعمليات العمود الفقري السفلي ، لذلك يخضع المرضى لهذا الإجراء لتخفيف الآلام المتوقعة. ومع ذلك ، فإن تلف الأنسجة أثناء الجراحة هو السبب الرئيسي لتطور آلام ما بعد الجراحة المزمنة ، وعندما يصبح الألم مزمنًا ، تحدث تغيرات أساسية في الأنماط الظاهرية للخلايا العصبية ودوائر الدماغ. يمكن أن تغير هذه التغييرات المراكز الحسية والعاطفية والتحفيزية في الدماغ وتتداخل مع عمل الأدوية المسكنة التقليدية. يعد الألم الحاد بعد الجراحة الذي يتم التحكم فيه بشكل سيئ مؤشرًا على تطور الألم المزمن بعد الجراحة. تبين أن إدارة الألم بعد الجراحة على المدى القصير ونتائجه على شدة الألم كان لها مؤشرا موثوقا للنتيجة طويلة المدى للألم المزمن بعد الجراحة في مرضى جراحة العمود الفقري.

وُصِف ألم ما بعد الجراحة على أنه أحد الأسباب الأربعة الرئيسية لتأخر الخروج من المستشفى بعد الجراحة اليومية بين الغثيان والقيء بعد الجراحة ، والتأخر في الذهاب إلى غرفة العمليات والعوامل الاجتماعية. لذلك ، يجب أن يكون تخفيف الآلام المناسب بعد الجراحة ونظام المسكنات متعدد الوسائط جزءًا لا يتجزأ من إدارة التخدير. الأدوية المتوفرة حاليًا لعلاج الألم الحاد غير فعالة في الغالب في الوقاية منه وغالبًا ما يتم الإفراط في استخدام المواد الأفيونية في فترة ما بعد العملية الجراحية، مما يتسبب في مضاعفات متعددة مثل الغثيان والقيء بعد الجراحة والدوخة والشلل التنفسي. يعد إعداد العلاج متعدد الوسائط الذي يتضمن فريقًا متعاونًا متعدد التخصصات ضروريًا

لتحقيق تخفيف كبير وطويل الأمد للألم ، والذي قد يؤدي بدوره إلى تعافي أسرع وتحسين النتائج على المدى الطويل.

التسكين الوقائي هو نموذج جديد للتسكين يتم تقديمه ودراسته في مستشفيات منطقتنا. علاوة على ذلك ، لا توجد أي دراسات منشورة تغطي الجابابنتينويد الفموي الوقائي في مستشفيات فلسطين.

تصميم الدراسة و طريقتها: تهدف هذه الدراسة إلى أن تكون دراسة استباقية عشوائية ، مزدوجة التعمية ، خاضعة للتحكم الوهمي. من المتوقع أن تقارن الدراسة فعالية المسكن الوقائي لجابابنتين عن طريق الفم مقابل بريجابالين الفموي في المرضى الذين يخضعون لعمليات جراحية في العمود الفقري السفلي تحت التخدير العام. تم اختيار تصميم الدراسة ليكون الأنسب لأهداف الدراسة بالإضافة إلى التدخل المقدم المتعلق بنتائج التدخل المقاسة. من المقرر إجراء الدراسة في وحدة العمليات ، وحدة التعافي ، وأجنحة ما بعد الجراحة في مستشفى رفيديا الحكومي الجراحي في نابلس ، فلسطين.

يشمل مجتمع الدراسة المرضى الذكور والإناث الذين يخضعون لعمليات جراحية اختيارية في العمود الفقري في قسم طب الأعصاب. الحالة الجسدية للمرضى الأول والثاني حسب تصنيف الجمعية الأمريكية لأطباء التخدير ، تتراوح أعمارهم من 18 إلى 60 عامًا ، ويخضعون لعمليات جراحية اختيارية في العمود الفقري في إطار قسم طب الأعصاب في مستشفى رفيديا الحكومي الجراحي وتلبية معايير التضمين.

تم تقسيم المرضى (60 مريضًا) الذين يستوفون معايير الاشتمال إلى 3 مجموعات بطريقة عشوائية بسيطة: تلقت المجموعة بريجابالين 150 مجم ، تلقت المجموعة جابابنتين 300 مجم وتلقي المجموعة العلاج الوهمي مع رشفات من الماء قبل ساعة واحدة من الجراحة من قبل احد أعضاء فريق الرعاية.

لم يكن المرضى ، وجميع الموظفين المشمولين في رعاية المرضى ، والشخص الذي يجمع البيانات ، والمحكمين على النتائج على دراية بتخصيص مجموعات العلاج.

تم تقسيم المرضى المسجلين في الدراسة بشكل عشوائي إلى واحدة من المجموعات الثلاث المذكورة سابقًا عن طريق التوزيع العشوائي البسيط باستخدام طريقة اليانصيب.

في جناح ما بعد الجراحة ، تم تقييم المرضى لمعرفة درجات الألم في 1 و 2 و 4 و 6 و 9 و 12 و 24 ساعة بعد الجراحة من قبل أعضاء الفريق الصحي المدربين باستخدام مقياس VAS. تم تسجل وقت التسكين الإنقاذي الأول والكمية الإجمالية للتسكين الإنقاذي المعطى للمريض في الـ 24 ساعة الأولى. كما تم تسجيل حالات الغثيان والقيء لكل مريض.

الهدف من الدراسة: بناءً على المعرفة المقدمة بشأن إدارة آلام ما بعد الجراحة ، تهدف هذه الدراسة إلى مقارنة الفعالية الوقائية المسكنة لجابابنتين عن طريق الفم مقابل بريجابالين الفموي في المرضى الذين يخضعون لجراحات العمود الفقري الخشبي تحت التخدير العام.

النتائج:

في هذه الدراسة ، كانت درجات الألم أقل بكثير في كل من مجموعتي البريجابالين و الجابابنتين مقارنة بمجموعة الدواء الوهمي . و كشفت نتائج دراستنا أن مجموعة البريجابالين لديها درجات أقل بكثير من الألم لفاصل زمني أطول (حتى 6 ساعات بعد الجراحة) من مجموعة الجابابنتين و مقارنة بمجموعة الدواء الوهمي.

تخفيف الآلام لفترات طويلة بشكل ملحوظ في مجموعتي البريجابالين و الجابابنتين مقارنة بمجموعة الدواء الوهمي وتخفيف الآلام بشكل ملحوظ لفترة أطول من البريجابالين عند مقارنته مع الجابابنتين وحده

كانت أعلى كمية من الباراسيتامول المسكن المعطى في مجموعة الدواء الوهمي مقارنة بمجموعتي بريجابالين وجابابنتين. و كانت أقل كمية من الباراسيتامول المعطى في مجموعة بريجابالين.

كانت نسبة الغثيان والقيء بين المشاركين في مجموعة الدواء الوهمي أعلى مقارنة بالمشاركين في مجموعة جابابنتين (80٪ مقابل 40٪) ومجموعة بريجابالين (80٪ مقابل 35٪).

كانت درجات التخدير أعلى في أول 6 ساعات بعد الجراحة في مجموعتي البريجابالين و الجابابنتين مقارنة بمجموعة الدواء الوهمي.

الخلاصة: ثبت أن بريجابالين الوقائي (150 مجم) أكثر فعالية من جابابنتين (300 مجم) ، في إطالة مسكنات الألم بعد العملية الجراحية مع انخفاض متطلبات مسكنات الإنقاذ. على الرغم من

ملاحظة التخدير ما بعد العملية بشكل متكرر ، إلا أنها لا تسبب أي مضاعفات خطيرة. وبالتالي ، يمكن اعتبار البريجابالين الوقائي دواءً آمنًا ورخيصًا لتقليل آلام ما بعد الجراحة في جراحات العمود الفقري السفلي.

الكلمات المفتاحية: البريجابالين , الجابابنتين , عمليات جراحة العمود الفقري السفلي , التسكين الوقائي.