An-Najah National University

Faculty of Graduate Studies

DEXMEDETOMIDINE AS A BLOCKING AGENT FOR INTERCOSTAL BLOCKS IN PATIENTS WHO UNDERGO VIDEO - ASSISTED THORACOSCOPIC SURGERY

By

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Dedication

This thesis dedicated for all who support me. My father the man who bare me I missed you too much, wish you with me. My mother who have all the thanks for supporting me (mom I did it “thank you”)

My family Ahmad, Omar & Eman wish you all the best, my soul mate in life

Acknowledgment

All the thank for my supervisor dr. Jamal Qaddoumi, I am grateful to whoever educates me.

Dr. Ali Abd-Alhaq thank you for all you efforts my kind full clinical supporter

Thanks for all who help me to finish my master degree path

At end I want to thank me to be standing with me in my master degree path

Declaration

I, the undersigned, declare that I submitted the thesis entitled:

DEXMEDETOMIDINE AS A BLOCKING AGENT FOR INTERCOSTAL BLOCKS IN PATIENTS WHO UNDERGO VIDEO -ASSISTED THORACOSCOPIC SURGERY

I declare that 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.

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ABSTRACT

Background: Local or regional anesthesia is one major fields in anesthesia. One technique to apply regional anesthesia is intercostal block, a type of regional anesthesia used in thoracic and upper abdominal surgeries to provide analgesia and to relieve pain due to rib-fracture, cancer, thoracic procedures and lung surgeries. Video -assisted Thoracoscopic Surgeries (VATS) has been began the late 20^{th} century. They have now become one of the most common preferred procedures for lung surgeries. Applying intercostal blocks in these surgeries yield good outcome on pain level post operatively. Many anesthetic blocking agents are used in regional anesthesia such as lidocaine and Marcaine. Dexmedetomidine is an alpha-2 adrenergic antagonist that works on the smooth muscles of viscera and has unique effect on pain control and sedation. Adding 1 microgram per kilogram of Dexmedetomidine for the formula has a strong effect on controlling level of pain.

Objectives: This study has assessed the effect of Dexmedetomidine as intercostal block agent on the level of pain, analgesia requirements, stability of hemodynamics and nausea and vomiting.

Methodology: randomized control clinical trial double-blinded design was used to assess 30 patients with a category of anesthesia (ASA 1, ASA 2 and ASA 3) who underwent VATS in referral center in Palestine. These patients were divided into two groups: intervention (experimental) and control. The control group (15 patients) was given Marcaine 1 mg/kg while, the intervention group was given 1 microgram/kg Dexmedetomidine with 1 mg/kg Marcaine on intercostal space.

Results: According to the results, there was an effect on the level of pain in the 3rd (p-value=0.04) 5th (p-value=0.01) 15th (p-value=0.1) minute post operation and after 24 hours of the procedure (p-value=0.01).

Conclusion: Using Dexmedetomidine as adjunct in intercostal block deceased the intensity of pain, conserved the vital signs (hemodynamics) on the normal lower limits for patient, and needed less analgesic requirement post-operatively. There was also no incidence of nausea and vomiting for patients who were administered Dexmedetomidine with Marcaine.

Keywords: Dexmedetomidine, intercostal block, regional anesthesia, pain, analgesia, hemodynamics.

Chapter One

Introduction

1.1 Anesthesia

Anesthesia is a state of intermittent mandatory controlled loss of sensation and consciousness induced by chemical agents for medical purpose, it consists of four elements the first is analgesia which is relieving of pain, second one is amnesia (loss of memory), third is immobility(loss of movement) and the last is loss of consciousness.(Sorrenti et al., 2021)

1.1.1 Analgesia

Is the term of blocking or reliving pain due to a stressful event to tissue this stressful event can be a disease, trauma, cut wound or due to surgical intervention to the body tissues. The most common type of pain that may occur for patients after an operation is chronic post-operative pain which is the pain that last for at least 3 months after the surgery and it has unique properties than the pre-operative pain and centralized in the surgical site with unknown etiology (Chen et al., 2021).

1.1.2 Amnesia

The goal of this element is to prevent patient from recalling the experience of surgical procedure due to the fear that can be happen from recalling that experience. Amnesia period onset is defined as by inability of patient from answering multiple choices questions and cannot recall the last image prior to propofol administration. Patient consider out of amnesic phase by answering three sequential multiple choice questions and recalling the last image after initial propofol dose (Schick et al., 2019). Also when amnesia achieved for patient the level of patient satisfaction will be increased (Steenholdt et al., 2020)

1.1.3 Immobilization

Immobilization during surgery can be achieved by administrating muscle relaxants such as propofol. Maintain of immobility during surgery is crucial because any movement can cause an injury to the patient. Also, by immobilization there is stress-free environment for patient and health team (Brown et al., 2018).

1.1.4 Loss of consciousness

The yield of all steps before surgery called loss of consciousness analgesia, immobility, amnesia and hypnosis. All of these effects called loss of conscious ness. Loss of consciousness is the most important thing that should be gained before starting the surgery (Siddiqui & Kim, 2020)

1.2 types of anesthesia

There are two general types of anesthesia which are general anesthesia and local anesthesia(Butterworth et al., 2018).

1.2.1 General anesthesia

It is defined as a reversible state that consist of the four elements of anesthesia and it is drug induced, on other hand, physiological ability should be conserved. To achieve these four elements there are several drugs than can be administer.

At first the analgesia phase, opioids is the most common drugs that can be given to achieve. Regardless that they have several side-effects such as respiratory depression, Nausea and vomiting, urinary retention and paralytic ileus.

The second one is amnesia, the desired effect can be achieved by administer hypnotics such as midazolam which has a synergistic effect with propofol.

Immobility is the third element that can achieved by administer muscles relaxants such as non-depolarizing muscular relaxants such as rocoronium, by inhalation such as ether or by using propofol (Brown et al., 2018)

For the final element which is unconsciousness, by achieving all the first 3 elements unconsciousness will be achieved.

So to summarize a combination of drugs is being given to achieve general anesthesia, muscles relaxants, hypnotics, opioids and sedative agents.

1.2.2 Regional anesthesia

Regional anesthesia is one of the most preferred techniques in anesthesia in these days when the patient's ASA state increased, the avoidance of general anesthesia is preferred(Gupta & Hopkins, 2012) and consider a subtype of local anesthesia. Local

anesthesia is being done by infiltration of the neuro-muscular blocking agents near sensory, motor or sensory-motor neuronal tissues endings or plexus that inhibits their function (Butterworth et al., 2018).

Local anesthesia or regional is one of the major fields in anesthesia in which firstly describes by Carl Koller who is an ophthalmologist in way that he use cocaine for topical anesthesia for eye. At this point many physicians start the use of local anesthesia in their work. The first physician started to use cocaine as a local anesthesia out of ophthalmic is William Halsted, he use cocaine by intradermal infiltration and nerve block such as facial nerve, brachial plexus, pudendal nerve and posterior tibial nerve, all of these ideas were firstly showed in 1884 (Butterworth IV et al., 2013).

Then the evolution of local anesthesia has been started by inventing new drugs and medication, the first drug was DIBUCAINE in 1930 and then the new drug stated to emerge from TETRACAINE in 1932 to LEVOBUPIVACAINE in 1999. Also, and additional drugs has been started to administer with these agents such as epinephrine to increase the time of local anesthesia. (Butterworth IV et al., 2013).

The main purpose of local anesthesia is to decrease the sensation of pain during surgical procedures in which describes by analgesia also it leads to decrease in stress response, analgesic requirements, side effects of opioids and general anesthesia in addition to the possibility of decreasing the chronic pain in post-operative period at this point anesthesiologists start to use regional anesthesia. It depends on a group of drugs that inhibit some or all sensory, motor, or autonomic nerve functions by applying these drugs near neural tissues. so based on type of procedure or surgery the selection of nerve block is determined such as brachial plexus block, interscalene block, celiac block, paravertebral block, ankle block and intercostal block in addition to many types of nerve blocks. (Butterworth IV et al., 2013).

While general anesthesia is the most common type that used for patients, to achieve general anesthesia the four elements should be achieved (Butterworth et al., 2018).

1.2 Intercostal block

1.2.1 Definition

Intercostal block is type of regional block that used in thoracic and upper abdominal surgeries to provide analgesia also to relief of pain due to rib-fracture and cancer. For applying this block the need for individual injection of local anesthetics to more than single site in the field of procedure. To block the intercostal nerve in which innervate from the dorsal and ventral rami of the thoracic spinal nerves to the groove of corresponding rib. Due to the position of intercostal nerve while intercostal artery and vein is next to it superiorly so it is located at the inferior aspect of artery and vein. When a blocking agents is infiltrated in intercostal nerve the high concentration of blocking agent is found in blood stream so when doing this technique care must be taken to prevent toxic level of local anesthetic in blood stream. Moreover local anesthesia has many types and techniques such as paravertebral block, brachial plexus block, femoral block and etc…(Butterworth IV et al., 2013).

1.2.2 Epidural thoracic block

In the past before using intercostal block epidural thoracic block was used instead, by administering analgesics and local anesthetics in the epidural space to apply sympathetic block. Thus, produce less pain response to any stimuli occur. Applying epidural thoracic block has many advantage such as reducing incidence of acute coronary syndrome, increasing intestinal oxygen perfusion and optimum effect of intra and post-operative pain control (Freise & Van Aken, 2011).

1.2.3 Disadvantages of epidural thoracic block

But on other hand, it has disadvantages that may put patients in harm and this can be increased when patient has chronic diseases or multi medications use especially anti-coagulation and anti-platelet drugs. Risk for bleeding, infection and over sympathetic block effect these are the most critical consequences that may occur due to the application of epidural thoracic block. Multi punctures to the epidural space especially for patients who are advanced in age; degeneration of vertebral spaces, or obese people all of these are challenges for applying epidural thoracic block. Applying epidural thoracic block needs a sterile area to guarantee patient safety but there is an incidence for infection which increases the mortality for this procedure. Over dose of drugs or

continuous infusion of analgesics and local anesthetics to the epidural space can increase the area of blockage and increasing the intensity of blockage and this yield to over sympathetic block effect and produce cardiovascular and neurological side-effect such as impairment in cardiovascular function and neurological functions (Freise & Van Aken, 2011)

1.2.4 Using inter-costal block instead of epidural thoracic block

Along the direction of using minimally invasive procedures for lung surgeries, the use of intercostal block become common and it is considered superior to thoracic epidural block because by applying inter-costal block the risks of epidural thoracic block decrease and many studies conducted that when using inter-costal block the consumption of opioids was decreased and less harm for patients (Guerra-Londono et al., 2021).

1.2.5 Benefit of intercostal block

Using intercostal block instead of epidural thoracic block gives many advantages to the patient, the frequency of intubation within patients who got intercostal block where less than patients who got epidural thoracic block. Moreover, ICU staying period where less than other patients.

The consequences of epidural thoracic block such as cardiovascular and neurological injuries were also less than others who got epidural thoracic blocks (Gerner et al., 2022).

When harm was assessed for patients who got intercostal block in comparison with thoracic epidural block, there are many advantages and less harm for patients. Opioid consumption was decrease, incidence of nausea and vomiting decreases, cardiovascular complications were less in intercostal block and incidence of arterial hypotension was less than epidural thoracic block. Moreover length of stay was less than thoracic epidural block when compared with intercostal block in Thoracoscopic surgeries (Guerra-Londono et al., 2021).

1.3 local anesthetic agents

1.3.1 Pharmacology of local anesthetic agents

For local anesthesia there are many agents that may be used to achieve the desired effect which is pain control throughout working on sodium-potassium pump by inhibiting the influx of sodium to the cell and this prevent the propagation of pain stimulation via nerve fibers in other words by diminishing the depolarization process of action potential. These agent divided to two categories the ester- chain group which is metabolized in plasma by pseudo-cholinesterase and the yield metabolites eliminated by urine but due to the metabolism process one of the metabolites is para-amino benzoic acid which is responsible for the allergic reaction. The other one is amid- group which is metabolized by liver and due to that process patients which have renal disease the awareness for administer these type of local anesthetic is vital.(Cherobin & Tavares, 2020).

Regional anesthesia via neuro-axial pathway or peripheral nerve block become widely speared common as an analgesic way for relieving of pain especially the technique of opioid sparing analgesia is common in these days and thus enhance the recovery process. (Rao & Rajan, 2021).

1.3.2 Types of local anesthetics

As mentioned above there are many blocking agents that used for regional anesthesia such as lidocaine, bupivacaine and heavy bupivacaine, Sometimes an additive drugs added to blocking agent to increase the duration of analgesia and enhance the quality of pain management also to improve patient safety while practicing regional anesthesia. These agents such as dexamethasone, alpha-2 agonists, non-steroidal anti-inflammatory drugs, epinephrine, midazolam, ketamine, magnesium sulfate and sodium bicarbonate. (Prabhakar et al., 2019).

In 2011 FDA approved the use of bupivacaine (Marcaine “trade name in Palestine”) for pain management via infiltration to surgical site in adults (Ilfeld et al., 2021). Marcaine is a local anesthetic agent that block sodium channels and can be used in spinal, epidural and caudal anesthesia. And can be given as adjunct to pain management protocols post operatively and it is safe on children (Moga et al., 2020).

1.3.3 Non-opioid local anesthetics

Non-opioids analgesics such as alph-2 agonist can be used as adjuvant for blocking agent for example clonidine and Dexmedetomidine (DEXMED) those agents are the most commonly used in these days from alpha-2 agonist class. DEXMED is an alpha-2 agonist seven times selective than clonidine with analgesic and sedative effect. (Prabhakar et al., 2019).

1.4 Dexmedetomidine

1.4.1 Mechanism of action

In the last decades, Alpha-2 agonist interest has been aroused due to their multi-effect that can be produces by single agent instead of using multi-agents these effects are sedation, analgesia, preoperative sympatholytic, anesthetic sparing and hemodynamics stability in addition with less side-effects than other agents, which is the most important benefit is conserving respiratory function.(Grewal, 2011).

It's mechanism of action is being happen by hyperpolarization of noradrenergic neurons and this inhibits the firing from locus ceruleus in addition to inhibition of releasing of norepinephrine. By this activation the triggers of sympathetic pathways will be inhibited and provide a decline in release of histamine and this the mechanism of hypnosis. And by suppression of noradrenergic pathways that control nociception neurotransmission which make it has analgesic effect. In addition to these benefit also it improves glomerular filtration rate, inhibition of salivation and decreasing shivering threshold. These benefits are one of the most important things that took in consider in the critically ill patients in intensive care units. (Grewal, 2011).

1.4.2 Effect of DEXMED

It is first approved in 1999 by food and drug federation as sedative and analgesic agent for mechanically ventilated patients in intensive care units for less than 24 hours. It has a half-life of 2 hours and if infused continuously to patient half-life become 6 hours. And by this way make it good choice in intensive care units and operation rooms. Also it has another effects on patients such as decreasing the incidence of delirium after sedation. Another important thing is that any sedative agent should be discontinued in

case of extubation but using Dexmedetomidine there is ability to continue infusing this agent. (Grewal, 2011).

There is consideration that must be taken in consider such as volume depletion and heart blocks due to the effect of Dexmedetomidine as sympatholytic agent that produce hypotension and bradycardia. (Grewal, 2011).

Also it considered as a sole of sedative procedures and can be used in most of anesthetic techniques and procedures from using it in general anesthesia to local anesthesia to regional anesthesia and peripheral nerve blocks. (Grewal, 2011).

But the concern is that due to the activation of alpha-2 receptors in the post-synaptic cleft make it a sympatholytic agent and this produce hypotension and bradycardia.

Dexmedetomidine is highly selective alpha-2 agonist with multi-unique effects which are sedation, analgesia, sympatholytic and respiratory function preserver. It has many uses for example sedation intensive care units intubated patients, short term sedation, procedures that patient should be lightly sedated. (Lee, 2019).

Sedative effect of Dexmedetomidine is unique which called arousal sedation which mean that patient who get Dexmedetomidine for a certain procedure has the ability of transition from sedation to wakefulness by light stimulation. It works on the locus ceruleus in the brain stem by suppression of noradrenergic neuronal firing. (Lee, 2019).

Moreover due to it propriety as a respiratory muscle preserver the time of intubation was less than other patients who get PROPOFOL; which is one of sedative agents that works through inhibition of neurotransmitter γ-aminobutyric acid (GABA) at the GABAA receptor (Sahinovic et al., 2018). Also using Dexmedetomidine instead of PROPOFOL conserve the heart rate of patient on the lower normal limit which is 60 beats per minute and decrease the need for analgesic requirements. Also Dexmedetomidine can be given as a local anesthetic when given via neuro-axial route that works on somatic and visceral pain sensation. And for instance Dexmedetomidine prove that it can be given for patients who have neuropathic pain and prove its effectiveness (Lee, 2019).

1.4.3 Side-effects of DEXMED

Dexmedetomidine has minimal side effects when compared to other adjuncts for anesthesia due to its unique proprieties. For cardiovascular it conserve the heart rate and the incidence of hypotension is lower than other adjuncts. Respiratory system muscle function was conserved and this helps patient to get easily extubated and f Dexmedetomidine given as an analgesic instead of opioids it will keep the respiratory function because opioids inducing respiratory depression (Lee, 2019)

Dexmedetomidine can be used as adjunct to regional anesthesia because it proved its effectiveness in synergizing of analgesic effect, with minimal side-effects, increase the duration of analgesic time, decrease analgesic requirements post-operatively and the applicability for administered via multi-modes and types of regional blocked such as plexus blocks. (Rao & Rajan, 2021).

1.5 Pain sensation

1.5.1 Definition

Pain first defined by international association for the study of pain in 1978, pain is “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”(Raja et al., 2020). Intensity of pain is high at the first 24 hours post-surgery and if pain didn’t manage well, many complication might happened such as chronic pain, immune suppression, infection and impaired wound healing. Also severity and intensity of pain depending on many factors which are the size of injured tissue, location of surgery, direction of incision and anesthetic technique that used during surgery (Zubrzycki et al., 2018).

Pain sensation is the most common side-effect that happened due the surgical intervention, a study was conducted in United States of America showed that 61% -70% of patients who had thoracotomy procedure got the feel of pain.

1.5.2 Physiology of pain

During surgical procedures when the incision done there are many molecules that released such as nerve growth factor and cytokines to the primary sensory neurons in the dorsal ganglia, thus are the main reason for the hypersensitivity for pain also these factors are playing a role in wound healing, immune response and inflammatory

process. These molecules are released in both incision of skin and muscle, especially nerve growth factor which is the one of the most important factor in initiating pain hypersensitivity. Also local cytokines especially interleukin 1β and the chemokine are also important in the pathways of incisional pain, these factor are the cause of peripheral sensation and this sensation transmitted to the central sensation via the afferent neurons in the spinal cord, this sensation also called memory pain sensation and this responsible for secondary hyperalgesia that can be defined as the increase sensation of pain away from the site of pain site. Also there is a factor that the most crucial factor in central pain sensitivity called brain-derived neurotrophic factor that activate the extracellular signal-regulated kinases which is regulate the pain due to the incision.(Richebé et al., 2018).

Sensation of pain induced by any injury to the cell it may be trauma, surgery or chemical agent, these injuries stimulate the release of pro inflammatory molecules and thus initiate the depolarization of cell by binding to the nociception nerves. This will induce the release of kinase and that will stimulate and reinforce of depolarization, and when the depolarization is strong to activate the sodium-voltage channels by that way the nerve fibers will be stimulated. (Armstrong & Herr, 2019).

When a stressful event occur due to an any surgical intervention, catechol-amines release increase lift ventricular afterload and produce tachycardia therefore the time of coronary perfusion decreased. Moreover, releasing of corticotropin hormone due to stress produce endothelial dysfunction in the endothelium of coronaries and yield to pro-coagulatory state due to stress. Along with these events a plaque will be induced in the coronaries which produce acute coronary syndrome (Freise & Van Aken, 2011).

There are four types of nerve fibers which are alpha, beta, delta and C- fibers, each one has special characteristics but to summarize the most fast one is alpha-fibers and if the stimulation is enough C-fibers will be activated. These nociception neurons are part of peripheral nervous system and when a stimulus happened the signals will be carried out to high-orders brain center via different routes. The viscera which contain the organs connected to central nervous system by sympathetic and parasympathetic pathways and this creates to routs of signals to the central nervous system. Parasympathetic nervous system utilize certain cranial nerves and the parasympathetic pathway utilize thoracic, lumber and certain cranial nerves. (Armstrong & Herr, 2019).

1.5.3 Physiology of local anesthesia in pain control

The idea from local anesthesia as a pain controlling managements is blocking the neuronal pathway of action potential and preventing it to arrive to the central nervous system. By blocking voltage-gated sodium channels the impulse that fired by the stimulus prevented to be transmitted in the neuronal pathway. So sensation of pain decreased (Taylor & McLeod, 2020).

1.6 Video assessed Thoracoscopic surgeries (VATS)

1.6.1 History of VATS

VATS is a type of surgeries that is being done instead of thoracotomy for treating certain disorders in pleura from obtaining biopsy to tissue resection. This idea first describes by Jacobeaus in 1910 for treating effusion due to tuberculosis, after this procedure the development of cameras and scopes started to emerge to enhance the view definition during surgery. The advantages that gives the VATS the preference are less post-operative pain, less post-operative complications, short hospital stay, low finances early immobilization and lower overall morbidity. Also it can be done for healthy patients and for high risky patients for thoracotomy more over in VATS the surgeon has the ability to access all the structures of chest therefore many procedures were replaced by VATS. (Усенко et al., 2019).

1.6.2 Advantages of VATS

Due to the difficulties of practicing Thoracoscopic due to the technological limitation such as no cameras and scopes to do this surgery, the practice of VATS abandon till the early 1990’s at that point fiber optic technique started to be emerged which makes VATS procedure more easy to be applied. And so, an acceptable variety of diagnostic procedures and diseases become feasible to be done and treated for patients who have a diseases such as plural diseases, cancers of pleura, mediastinal tumors and some of pericardial diseases.(Kim et al., 2021).

VATS decrease the pain score for the first 90 min than posterolateral thoracotomy (PLT) moreover there were less analgesic requirements, significant vital capacity (VC) and 1st second expiratory volume (FEV1) recovery in comparison to PLT. (Pu et al.,

2013). And for hospital stay and post-operative pain was significantly less than thoracotomy. (Landreneau et al., 1993).

Also, VATS make it possible to let patient discharged from hospital earlier than open technique. Patients who undergo VATS lobectomy instead of open technique has short log of say in hospital in comparison with open technique in which 7.7 ± 3.8 versus 8.3 ± 4.3 days. But the cost is higher than open technique(Mei et al., 2019)

VATS in these days has been used widely for treating spontaneous pneumothorax instead of thoracotomy technique, using VATS decrease the hospital stay post-operatively, relief of pain, time of operation and minimizing the complications (Hong et al., 2019).

1.7 Anesthesia and VATS

Before anesthetizing patient for any procedure or surgery there should be assurance for patient's safety and health condition that patient is fit for anesthesia and procedure also the wellness of patient to have the surgery. VATS can be done by two ways the first one is by local anesthesia for incisional site and light sedation by PROPOFOL but the challenging thing in that technique is that patient should be breath spontaneously. The second way is being under general anesthesia and inserting a double lumen tube instead of single lumen to make the control of lung volume easy because of surgical field which is lung should be clear and this is done by collapsing the affected side. After surgery proper pain control is important not just for patient but also it is important for proper cough mechanism to let sputum go out of lung because while patient in pain the sputum is conciliate at the base of lung which is affect the good prognosis for surgery(Cohen, 2011).

Pain control can be done by many ways such as patient control analgesia method, intravenous administration of opioids, around clock pain killers, when needed pain killers, transcutaneous electrical nerve stimulator and regional blocks. Regional block can be done in variety of ways such as paravertebral block, sub-clavicular block, epidural block and intercostal block by adding medications such as opioids, sodium channel blockers or alpha-2 agonists such as clonidine (Cohen, 2011).

1.8 Problem statement

Pain is the most common side-effect that can be happen due to any operation, using of intravenous analgesics frequently can lead to serious side-effects to the kidney and liver due to that their metabolism and detoxification of these drugs occur in liver and kidney when used frequently as pain control management. The protocol for pain management for patients who will undergo VATS is administration of MARCAIN 1 mg/kg in the intercostal region at the end operation and administration of PARACETAMOL 1g intravenously with OPTALGIN 1 g intravenously 3 times per day. Using of these drugs has an effect on liver due to that their metabolism occur in liver and this can lead to hepatotoxicity. More over when the dose missed or can't be given due to certain cause such as contraindication for administer this drug make pain intensity increase. Increasing the pain intensity make a challenge for the health team and interfere with patient prognosis post-operatively, using adjuncts to local anesthetics for pain control become one of the most preferred ways in pain management. This leads to decrease the number of intravenous analgesics and prolog the effect of pain control post- operatively. And by this way patient satisfaction, hospital stay time and pain control will be improved, more over a less amount of intravenous analgesics will be used to control pain, instead of giving this drugs frequently, they can be given when needed in case pain score become worse according to the guidelines of the hospital.

In this study we proposed that using DEXMED 1 microgram/kg with 1 mg/kg Marcaine as a blocking agents via intercostal block can enhance pain control and decreases analgesic requirements in comparison with Marcaine 1 mg/kg alone.

1.9 Framework

1.9.1 Introduction

This chapter demonstrates all the fields that has been assessed in the study and how assessment has been done. Conceptual framework of the study was built based on the literature review and evidence-based studies about pain control using intercostal block as a tool to manage pain for patients who undergo VATS.

Neuman's nursing theory was used to build the conceptual framework of the study as this theory focused on the internal and external factors that alter patient life-style due an event of and procedure that has been done for the patient.

1.9.2 Dependent variable

1.9.2.1 Pain

The main dependent variable that has been assessed in this study because pain is a reaction to an action and this action is the surgical procedure which is VATS. Moreover, dose of anesthetic medications and analgesics play a role in intensity of.

1.9.2.2 Nausea and vomiting

Nausea and vomiting is a reaction to pain, medications or any procedure for patient. So the incidence of nausea and vomiting depends on how patient medical condition controlled during hospitalization.

1.9.2.3 Analgesia requirement

Dose and frequency of analgesic depend on pain score of patient. When patient is free of pain there is no need for analgesics. On other hand, when there is pain, pain assessment should be done to administer the proper amount of analgesia for pain control. Analgesics can be given in frequencies of when needed according to patient condition.

1.9.2.4 Systolic blood pressure

There is a relation between pain and systolic blood pressure, in which SBP increases when pain score increases. Also, there is a significance between SBP and type of drug that has been administered in which one of side effects for local anesthetic is decreasing in blood pressure.

1.9.2.5 Diastolic blood pressure

Also, there is a significance between increasing on pain score and diastolic blood pressure. Increasing in pain intensity increases diastolic blood pressure due to catecholamine release.

1.9.2.6 Heart rate

Pain intensity and type of drug administered has a relation to heart rate, due to that heart rate is connected to release of catecholamine due to surgical stress.

1.9.2.7 Other variables

Respiratory rate and saturation of O2 in blood also considered one of dependent variables that pain and type of drug can contribute for them.

1.9.3 Independent variables

In this study, correlation between sociodemographic which represented by age and gender with pain score. Also, the intervention of the study considered one of independent variables which are Marcaine and Dexmedetomidine.

1.9.4 Conceptual framework

According to Neumann's nursing theory health defined as an optimal system stability that can be achieved after stressful that can be modified by internal and external factors that affect patient's life style to obtain the optimum physiological, emotional and environmental stability.

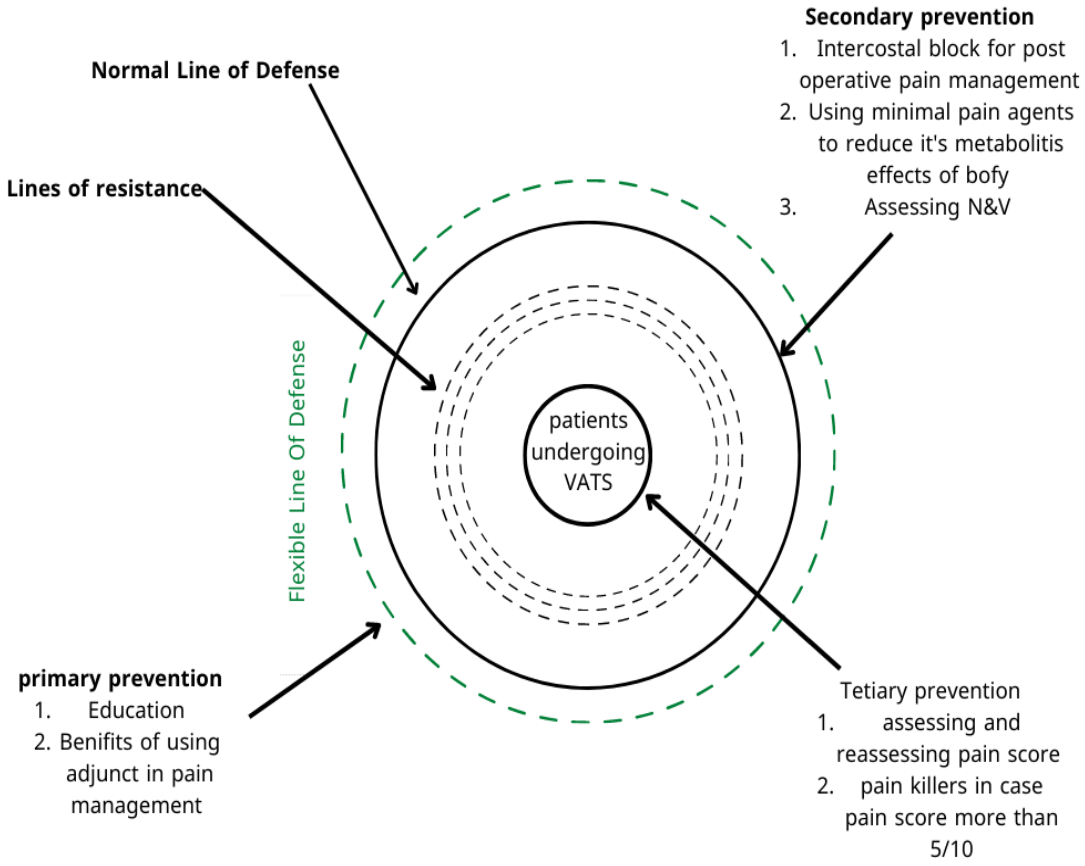
According to the theory, for each human has a normal line of defense in which any internal or external factors occur, the self-defense mechanism starts to work to prevent these factors to cross this line.

These factors can be internal such as disease or disorder happened to body or can be external due to a stimulus from outside the body such as stress, clashes or trauma.

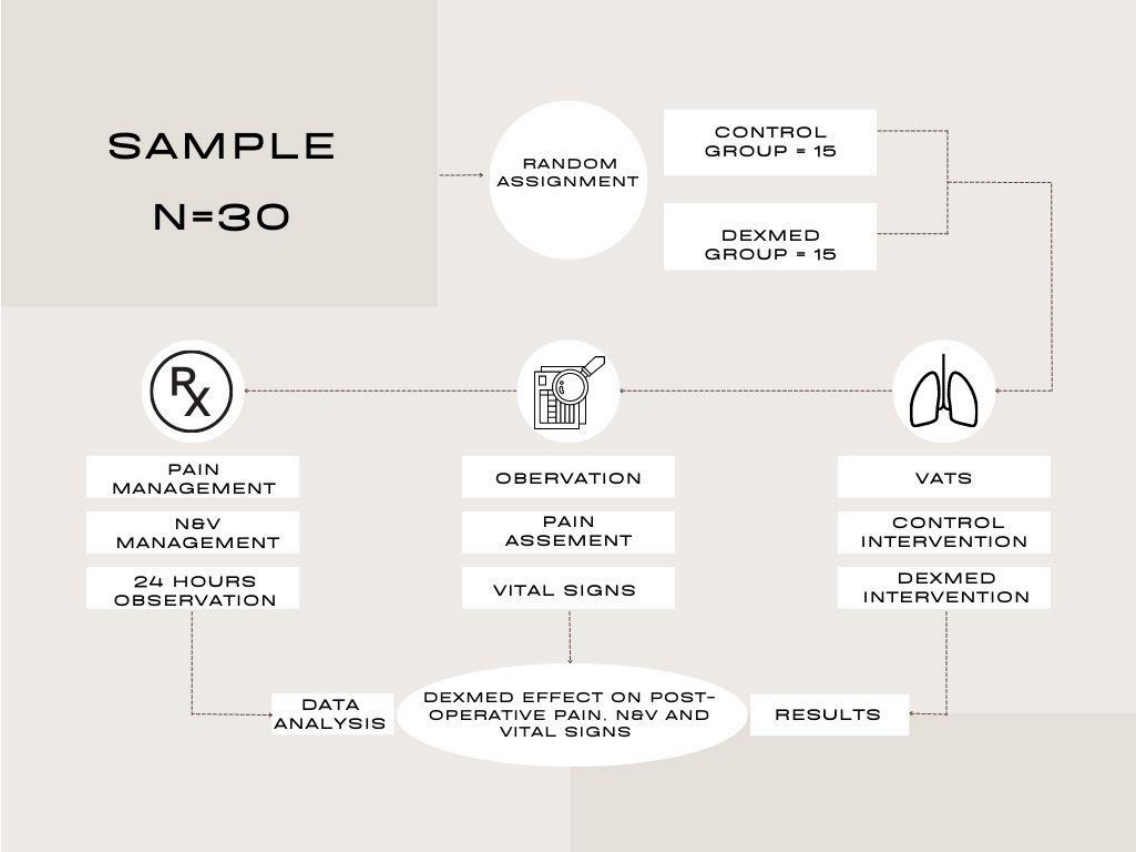
By crossing the normal line of defense, there are 3 lines of defense. First line is adjusted by applying primary prevention techniques such as education. The second line called secondary prevention and can be achieved by an intervention from.

Figure 1

Neumann's theory conceptual framework



1.9.2 Operational framework



1.10 Literature review

A systematic review searched for the gold guide-lines for analgesia in Thoracoscopic surgeries. Especially that VATS in these days is one of the most common easy ways in treating some of lung problems that need a surgical intervention, one of the most causes is tumors and cancer. Furthermore, oncological problems needs special analgesic techniques due to the nature and pathophysiology of tumors. Some analgesic interventions for these patients are paravertebral and block and thoracic epidural analgesia but these ways are so expensive and not cost effective in contrast with VATS because it is minimal invasive procedure. The recommendation of this systematic review is finding new ways for analgesia in patients who will undergo VATS (Steinthorsdottir et al., 2014).

Dexmedetomidine effect was evaluated as adjunct agent with remifentanil as infusion of intercostal block. They found that using minimal dose of Dexmedetomidine prolonged the effect of analgesia in the post-operative period and stabilize the heart rate of patients during surgery. According to Cheng et. al. intercostal block is feasible and cost effective

way for the analgesia for patients who will undergo VATS post-operatively when thoracic epidural analgesia not performed. (Cheng et al., 2021).

Nociception process during VATS emerged from two sources one from phrenic nerve that responsible for the lung and diaphragm so any intervention that affect lung phrenic nerve will be stimulated leading to the feel of pain. The other source of pain is the vagus nerve due to that it is go through trunk and has endings in the viscera layers of the organs (Novak Janković & Potočnik, 2015).

DEXMED has two features of nociception effect one is it has an effect of decreasing noradrenergic excitatory inputs to the cortex and thalamus. The second, "activating inhibitory interneurons that synapse onto projection neurons in the spinal dorsal horn" (Cheng et al., 2021).

There are many studies conducted to evaluate the effect of DEXMED as adjunct to local blocking anesthetic agent with comparison with other adjuncts. A study was conducted Assessing the different administration routs of DEXMED with ROPIVACAINE 0.5%, it revealed that group who get DEXMED perineural 0.5 micrograms/kg with 0.5% ROPIVACAINE was significantly has low numerical rating scale for pain than other groups who get DEXMED intravenous or ROPIVACAINE 0.5% alone. (Yao et al., 2020).

A study was done on patients who underwent arthroscopic of rotator cuff repair by using suprascapuler nerve block and axillary nerve block in comparison between DEXMED 50 microgram with 9.5 ml of 0.75% ROPIVACAINE and ROPOVACAIN 0.75% with normal saline they found that using DEXMED with ROPIVACAINE has significantly lower the visual analog score of pain from the control group in which mean plasma interleukins were lower in group of DEXMED than control group also more patient satisfaction in group of DEXMED. On other hand, rebound pain post operatively was later in DEXMED group than control group (Lee et al., 2021).

ROPIVACAINE with normal saline 0.9% or DEXMED 1 microgram/kg or dexamethasone 10 mg or DEXMED 1 microgram/kg with dexamethasone 10 mg tested on patient who underwent VATS. The result was that DEXMED enhanced the duration of analgesia in comparison with ROPIVACINE with normal saline 0.9% (8-11 hours, 5-

9 hours respectively) but groups of ROPIVACINE with dexamethasone or dexamethasone and DEXMED have more duration of analgesia. Also use of additive analgesia was low in DEXMED group in comparison with ROPIVACINE with normal saline 0.9% group. (Zhang et al., 2019).

Another study in 2018 conducted that using DEXMED 1 microgram/kg with 0.375% ROPIVACAINE in thoracic para-vertebral block for VATS increase the duration of post-operative analgesia and increase patient's satisfaction post operatively with no any significant side effects in a dose of 1 microgram/kg (Xu et al., 2018).

A meta-analysis conducted to compare clonidine with DEXMED on single injection brachial plexus block. They found that using DEXMED has an advantage over clonidine by duration of sensory block, time of onset for sensory block, duration of motor block, motor block onset and duration of analgesia (549.5 min, 6.4 min, 497.3 min, 9.9 min and 652.1 min for DEXMED) (361.1 min, 8 min, 335.2 min, 11.6 min and 447.2 for clonidine) which means that using DEXMED is better than clonidine for sensory block effect (El-Boghdadly et al., 2017).

Dexmedetomidine was administer as adjunct to bupivacaine via continuous infusion in the epidural space and compared with administer bupivacaine alone for patients who have rib fractures due to traumas, the result showed that the pain control within the Dexmedetomidine and bupivacaine was significant. In addition, arterial blood gases especially PO2 was significantly improved in comparison with bupivacaine group (Agamohammdi et al., 2018).

A study was conducted to compare the techniques of regional anesthesia in patients who underwent breast cancer surgeries, these techniques are pectoral nerve block, local anesthesia, paravertebral block and erector nerve block. They found that using Dexmedetomidine in addition to the local anesthetic agent reduce the consumption of using opioids and provide better pain control post operatively and this was a secondary result in which the main purpose of study is to compare between these techniques in controlling pain intra and post operatively(Elshanbary et al., 2021).

When Dexmedetomidine was infused intravenously in addition to pectoral nerve block type 1 and type 2 in a case report study conducted by Nakanishi et al. (2019), they found that using Dexmedetomidine infusion intravenously with pectoral nerve block can be used instead of general anesthesia in these patents and that is due to the multi-functions of Dexmedetomidine which are sedation, analgesia and hypnosis.

Also Dexmedetomidine effect as regional anesthetic agent for patients who underwent modified radical mastectomy and they found adding 1 microgram per kilogram of Dexmedetomidine provide superior post-operative analgesia without any side effects (Duan et al., 2021).

Due to the features of Dexmedetomidine it was assessed in a true experimental double-blinded study when using it as adjunct to LEVOBUPIVACAINE in regional anesthesia in anterior serratus plan block for patient who underwent thoracotomy. Time of analgesia was assessed and found that analgesia time was promoted in Dexmedetomidine and LEVOBUPIVACAINE in comparison with LEVOBUPIVACAINE alone. Also a proper sedation was achieved in Dexmedetomidine group, the dose of Dexmedetomidine is 1 microgram per kilogram (Abdallah et al., 2019).

Another study was conducted by Hong et al. (2019) to assess the effect of Dexmedetomidine as adjunct to ROPIVACAINE on post-operative pain in patients who underwent VATS and they found that pain control was significant in Dexmedetomidine and ROPIVACAINE group with less opioids consumption.

Effect of Dexmedetomidine as adjunct with ROPIVACAINE was assessed against dexamethasone and ROPIVACAINE in erector spinae plane block on post-operative pain on patients who underwent VATS. Using Dexmedetomidine instead of dexamethasone provide pain relief, prolonged the duration of analgesia, less analgesic requirements and decrease hospital stay (Gao et al., 2019).

Dexmedetomidine effect was assessed as adjunct to ROPIVACAINE against ROPIVACAINE alone in patient who underwent open thoracotomy for esophageal cancer resection using erector spinae plane block as regional anesthesia technique. There was a significant in pain relief and decrease in post-operative opioids

consumption with no incidence of adverse effects such as hypotension and bradycardia (Wang et al., 2022).

Also effect of Dexmedetomidine as adjunct with ROPIVACAINE versus ROPIVACAINE alone versus normal saline 0.9% to bilateral dual-transverses abdominis plane blocks on patients who underwent cytoreductive surgery; this surgery is done for women who have ovarian cancer, the way of surgery by resection of microscopic tumors in combination of chemotherapy. The effect of Dexmedetomidine was consistent with previous study that has been mentioned in this literature review. Dexmedetomidine as adjunct to ROPIVACAINE via bilateral dual-transverses abdominis plane blocks was provide a pain relief for 48 hours post-operatively in comparison with ROPIVACAINE group or normal saline 0.9% group (Zhang et al., 2022).

From the literature the direction of using Dexmedetomidine was widely spread these days and become one of the excellent protocol by adding it as adjunct to local anesthetics. A variety of regional anesthesia protocols efficacy was assessed by adding Dexmedetomidine as adjunct to local anesthetic agents, this provide long duration of analgesia with minimal side-effects and decrease in post-operative analgesic requirements. Due to poor evidence-based article and studies about DEXMED as adjuvant to regional anesthesia especially on intercostal block for VATS, this study has been stablished to investigate and evaluate the effect of DEXMED as adjuvant to regional anesthesia agents in intercostal block for patients who underwent VATS.

1.11 Aims of study

1. To assess the effectiveness of DEXMED on the first 24 hours post-operative pain when using it as a intercostal blocking adjunct agent for patient undergo video assessed Thoracoscopic surgeries (VATS).

2. To evaluate the amount of analgesic requirements in the first 24 hours post-operative period when using DEXMED as adjunct intercostal block agent as for patients undergo VATS

3. To assess the effect of DEXMED as adjunct in regional anesthesia on the stability of vital signs for patients who will undergo VATS

4. To assess the incidence of nausea and vomiting when using DEXMED as adjunct in regional block for patients who will undergo VATS

1.12 Hypothesis of study

1. Using DEXMED as an intercostal blocking agent in patients who undergo VATS decreases the analgesics requirements post- operatively in patients who will undergo CABG.

2. Using DEXMED as an intercostal blocking agent in patients who undergo VATS decreases pain score in comparison with control group.

3. Using DEXMED as adjunct agent in intercostal block in patients who will undergo VATS will stabilize the vital signs of patients post operatively.

4. Using DEXMED as adjunct agent in intercostal block will not induce nausea and vomiting post operatively.

Chapter Two

Methodology

2.1 Study design

A prospective quantitative randomized control clinical trial double-blinded design was conducted in this study. Where the three components of true-experimental design were achieved.

First one there were two groups control and intervention groups, first group was control who get Marcaine 1 mg/kg and the second group is interventional one who get DEXMED 1 microgram/kg.

Second component is randomization: to achieve this component a random assignment of groups was done, due to that the type of samples has the same characteristics/

Third component is intervention: DEXMED 1 microgram/kg with Marcaine 1 mg/kg injection via intercostal space.

It is true that true experiential is the most effective design in research but when using the double-blinded method in doing the intervention and assessment which mean that patient don't know if he will get the control agent or intervention agent and by that way we excluded the emotional and mental believe that make patient feel less pain or high pain score, this is the first thing in double blinded designs. The second one is that the researcher who will did the assessment don't know if the patient get the control or intervention agent and this excluded the false belief that make researcher miss-assess the patient state based on that patient get the intervention who mean that the score of pain will be lower than the control group.

2.2 Settings

The study conducted at Al-Makassed Islamic Charitable hospital, which considered one of the big referral hospital in Palestine that has multi branches of health science that benefit all the layers of Palestine community from Gaza and west-bank. Also it has one of the most special branches of health which is thoracic surgeries and this is was the reason from choosing this referral center. Moreover, there is a residency program which

is cardiothoracic surgery and this was one of the advantage that this hospital was chosen (Leyland & Goldstein, 2001).

2.3 Study population

Population of study was all the patients underwent VATS but the sample was based on inclusion and exclusion criteria. Inclusion criteria of patients level of anesthesia ASA1, ASA2 and ASA 3 and this was the most important thing in this study. American society of anesthesiologist divided patient to six categories based on the health condition of patient, these categories are ASA 1, ASA 2, ASA 3, ASA 4, ASA 5, ASA6 each one has special characteristics. The main categories of this study was ASA 1 which mean that patient is free from any chronic disease and not a smoker, ASA 2 meant that patient has chronic disease in which it is control via drug or health management and if patient is smoker but its free from chronic disease consider ASA 2, ASA 3 means that patient has chronic diseases that it is not controlled via health management or drug or the patient has cancer.

In our study, it has special thing which is the first study that include ASA 3 level according to the evidence-based literature. Other inclusion criteria is that patient should be free from mental disease according to medical history and has normal level of cognition that let patient can explain pain. Exclusion criteria are patient refusal, death during surgery and patients who developed ASA 4 and ASA 5 level in hospitalization time.

2.4 Sample size

The calculated participant in this study is 12 participant based on effect size 1.12 according to (Zhang et al., 2019), But due to high effect size an adjustment was done for effect size and decreased to 0.5, alpha error probability 0.05 with power of 80%. So estimated sample size is 30 participants in which 50% of participants were a control group and the other 50% participants were interventional group. Participant were chosen based on the inclusion criteria as mentioned above mentioned above. A random assignment will be done for the choice of intervention or control.

2.5 Instruments

Numerical pain score (NPS) scale was used to assess level of pain post-operative and according to Myles et al. (2017) test-retest reliability was 0.79. Nausea and vomiting was assessed by researcher in case they happened and for analgesic requirements assessed by the amount of analgesia given in the first 24 hours post-operatively. The intervals of assessment are zero time, 3rd minute, 5th minute, 15th minute, 30th minute, 1st hour, 3rd hour, 6th hour, 12th hour and 24th hour.

2.6 Data analysis plan

SPSS program was used for entering the data and for statistical analysis descriptive data such as age, sex, patient medical history, NPS score, incidence of nausea and vomiting and analgesic requirements was presented as mean, standard deviation, max and min.

Two-tailed t-test was used to interfere that data as these data is a parametric data and can be interfered by two-tailed t-test. Significance level should be p-value <0.05, with confidence interval more than 95%. Mann-Whitney test was used for non-parametric values.

2.7 Ethical consideration

Each patient was informed about study by surgeon, anesthesiologist and researcher. The selection of groups was done by anesthesiologist randomly and the patient was told that he may be in a control group or interventional one. Patient was informed about risks and benefits by anesthesiologist. After agreeing of patient an informed consent signed.

Confidentiality and anonymity was assured. The data was secured in a safe place and the allowed people who can view this data are who just enrolled in research who are researcher, physicians that visit patient and study supervisor. The participant was presented as numbers and no one can identify the person that this information belongs to.

2.8 Study protocol and data collection

Once participants agreed to enroll in study every participant have to sign consent form, preoperative evaluation was done to assess fitness for surgery. When entering operation room cardiac monitor, pulse oximetry, noninvasive blood pressure cuff were applied to

patient for baseline vital signs readings. Arterial line was applied for invasive blood pressure monitor during surgery. Then induction with ESMIRON 0.6 mg/kg, PROPOFOL 1-2 mg/kg, FENTANYL 2 mcg/kg, DORMECUM 0.05 mg/kg were given IV, then a double lumen bronchial tube was applied for patient to control lungs volumes during surgery. FENTANYL 100 mcg was given IV prior to incision, ISOFLORANE 1 MAC will be started for anesthesia maintenance. After completion of surgery an intercostal block was done by DEXMED 1 mcg/kg and 1mg/kg MARCAINE 0.5% for intervention group and for control group 0.5% MARCAIN 1 mg/kg and N/S 0.9%. After full recovery from operation patient transferred to surgical ward or cardiothoracic intensive care unit for evaluation. Evaluation was done by researcher himself at according to time schedule of zero time, 3^{rd} min, 5^{th} min, 15^{th} min, 30^{th} min, 1^{st} hour, 3^{rd} hour, 6^{th} hour, 12^{th} hour and 24^{th} hour post-operative. Pain, nausea, vomiting and analgesic requirements were assess in that time schedule.

PARACETAMOL 1g IV or OPTALGIN 1g was given to patient in case of pain score more than 5/10 and the priority is for PARACETAMOL, and for nausea and vomiting METOCLOPRAMIDE 10 mg IV will be given when needed.

Chapter Three

Results

This thesis constructed and implemented to figure out and evaluate the effect of DEXMED as adjuvant to regional anesthesia patient undergo video assessed Thoracoscopic surgeries (VATS).

Specifically, to assess the effectiveness of DEXMED on the first 24 hours post-operative pain when using it as a intercostal blocking agent for patient undergo video assessed Thoracoscopic surgeries (VATS). Furthermore, to evaluate the effect of DEXMED on hemodynamics including BP, HR, RR, SPO2 during the first 24 hours post-operative period when using DEXMED for patients undergo VATS.

3.1 Demographic patient undergo video assessed Thoracoscopic surgeries (VATS) Gender and age of participants

The analysis of gender variable revealed that male percentage was higher than female percentage among patients underwent (70% vs. 30% respectively).

A chi-square test of independence showed that there was no significant association (X^2 [2, N = 60] = 1.42, p = .23) between gender and groups (DEXMED vs. control). Although the proportion of male is higher in intervention group than female but there was not a statistically significant association between the two variables (two-tailed p = .427) as Fisher's exact test was used to determine if there was a significant association between gender and group preference.

Table 1

Association between gender and group preference

			Group			
		Total	Intervention	Control	X^2 (*p* value)	Fisher's exact test
Gender	Male	21 (70.0%)	12 (80.0%)	9 (60.0%)	1.42 (.23)	*p* = .427
	Female	9 (30.0%)	3 (20.0%)	6 (40.0%)		
Total		30 (100.0%)	15 (100.0%)	15 (100.0%)		

Mann-Whitney U statistical test revealed that there was no statistically significance difference between the median of age between the intervention (DEXMED) and control groups (47 years vs. 55.5 years respectively) U ($N_{INTERVENTION} = 15$, $N_{CONTROL} = 15$,) = 80.5, Z= -.464, *P*= .657. See table 2.

Table 2

Age between the intervention and control groups

	Group	N	Mean	SD		Mean Rank	Mann-Whitney U	Z	Exact Sig. (2-tailed)
Age (years)	Intervention	15	44.3	21.2	47	13.37	80.5	-.464	.657
	Control	12	45.8	18.0	55.5	14.79			

3.2 DEXMEDOTOMIDINE effect on Post-operative pain level

It is clear by looking at Table No. 3 and Figure No.1 that the DEXMED group participants suffered a lower post-operative pain level than the participants in the control group, especially at the third, fourth, fifth and tenth readings (NPS mean= 0.93, 0.93, 0.60 VS. 2.80, 3.00, 2.33 respectively). Additionally, by using M-WU statistical test, the difference in post-operative pain level between the two groups was statistically significant during those periods (0.046, 0.016, & 0.015 respectively).

Table 3

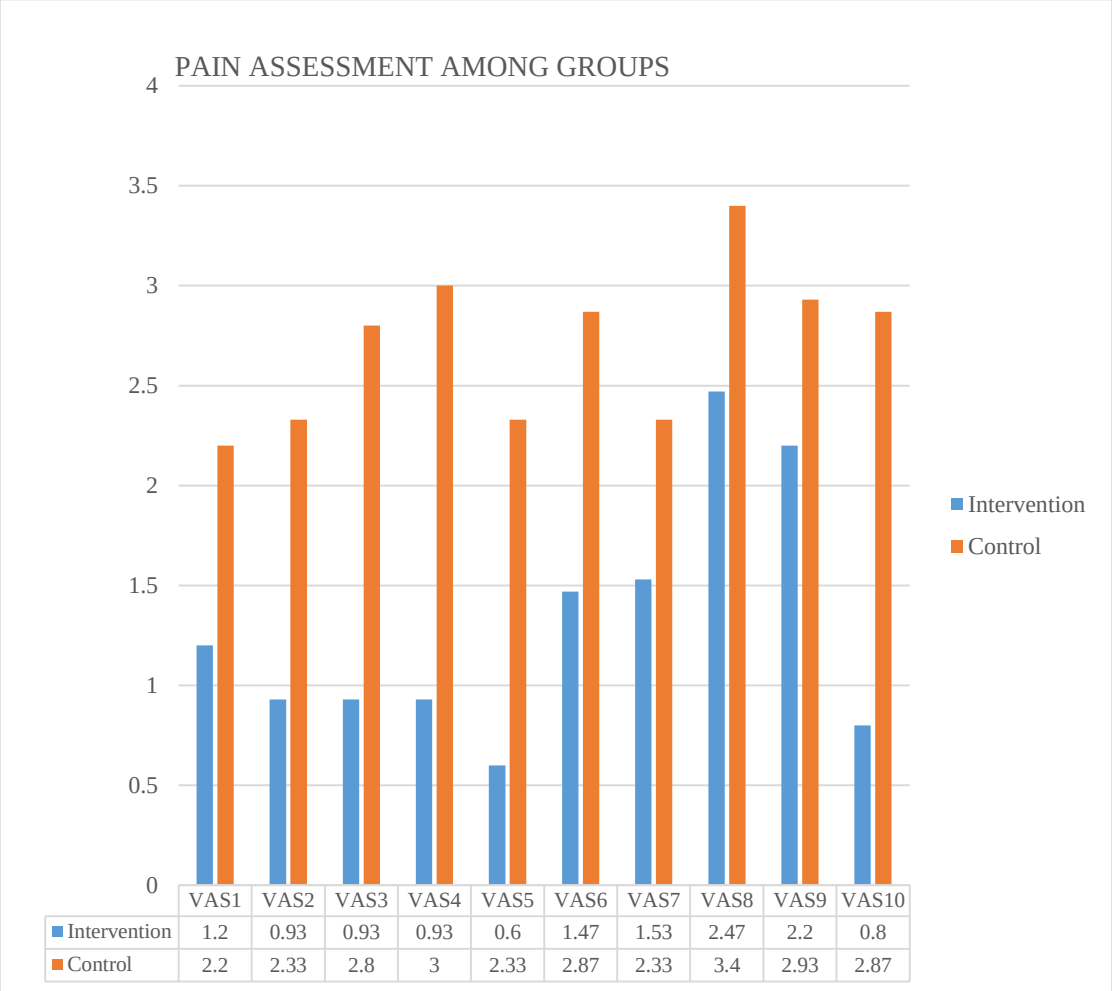
NPS mean scores comparisons between the two groups (DEXMED vs. control)

	Group	Mean	SD	N	M-W U	Z	Sig. (P Value)
NPS1	Intervention	1.20	2.18	15	83.0	-1.318	0.187
	Control	2.20	2.54	15			
NPS2	Intervention	0.93	1.71	15	74.5	-1.717	0.086
	Control	2.33	2.72	15			
NPS3	Intervention	0.93	1.53	15	67.5	-1.999	0.046
	Control	2.80	2.98	15			
NPS4	Intervention	0.93	1.22	15	56.0	-2.416	0.016
	Control	3.00	2.65	15			
NPS5	Intervention	0.60	0.83	15	57.0	-2.424	0.015
	Control	2.33	2.32	15			
NPS6	Intervention	1.47	1.46	15	72.5	-1.698	0.090
	Control	2.87	2.36	15			
NPS7	Intervention	1.53	2.03	15	84.5	-1.197	0.231
	Control	2.33	2.09	15			
NPS8	Intervention	2.47	2.42	15	88.5	-1.011	0.312
	Control	3.40	2.61	15			
NPS9	Intervention	2.20	2.43	15	86.5	-1.094	0.274
	Control	2.93	2.22	15			
NPS10	Intervention	0.80	1.15	15	57.0	-2.410	0.016
	Control	2.87	2.53	15			

M-W U: Mann-Whitney U.

Figure 2

NPS mean scores comparisons between the two groups (DEXMED vs. control)



	VAS1	VAS2	VAS3	VAS4	VAS5	VAS6	VAS7	VAS8	VAS9	VAS10
Intervention	1.2	0.93	0.93	0.93	0.6	1.47	1.53	2.47	2.2	0.8
Control	2.2	2.33	2.8	3	2.33	2.87	2.33	3.4	2.93	2.87

3.3 DEXMED effect on Post-operative Systolic Blood Pressure level

SBP was assessed for the interventional group who got DEXMED as adjunct to MARCAIN via intercostal block in comparison with control group (MARCAIN group) with controlling the effect of the characteristics of participants using ANCOVA statistical test, it was found that there is a statistically significant difference (*P* value = 0.016) with a high effect size (ηp2= .27) between the two groups with respect to the SBP measure. There was a statistically significant difference in SBP mean scores between the two groups (F (between groups DF=1, within groups DF=28) = [F-value=6.60], p = [0.016]).

On other hand, the rest of the characteristics of the study participants did not have a statistically significant effect (*P* value > 0.05) on the level of pain post operatively. See table 4.

Table 4

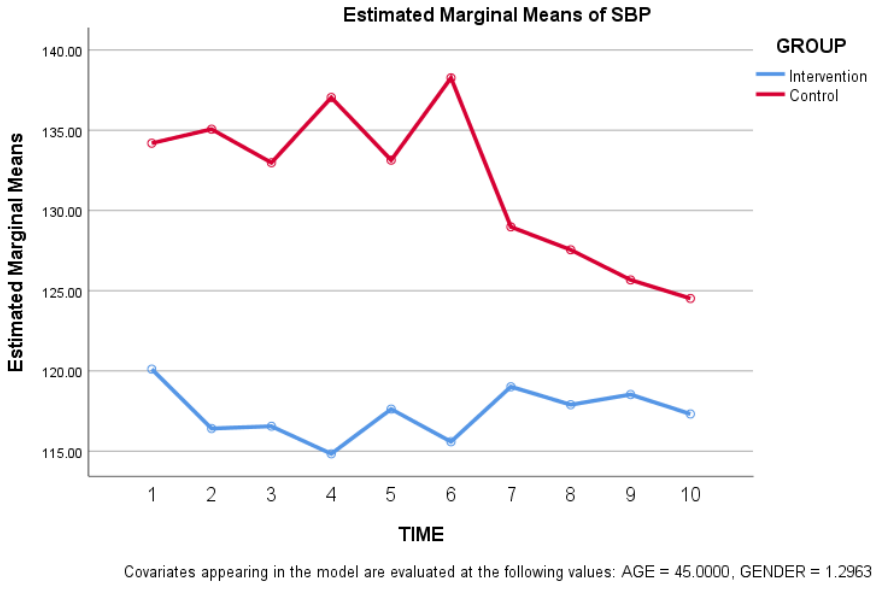
Effect of DEXMED on the level of SBP was analyzed for the two groups with controlling the effect of the characteristics of the patients participating in the study using the ANCOVA statistical test

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	161060.3	1	161060.3	110.3	.000	.827
Age	1316.4	1	1316.4	.902	.352	.038
Gender	2584.0	1	2584.0	1.77	.196	.071
Group	12828.7	1	12828.7	8.78	.007	.276
Error	33579.3	23	1459.9			

a Computed using alpha = .05

Figure 3

SBP mean scores comparisons between the two groups (DEXMED vs. control)



3.4 DEXMED effect on Post-operative Diastolic Blood Pressure level

DBP was assessed for the interventional group who got DEXMED as adjunct to MARCAIN via intercostal block in comparison with control group (MARCAIN group) with controlling the effect of the characteristics of participants using ANCOVA statistical test, it was found that there is a statistically significant difference (P value =

0.007) with a high effect size (ηp2= .28) between the two groups with respect to the DBP measurement in the post-operative period after the operation. There was a statistically significant difference in DBP mean scores between the two groups (F (between groups DF=1, within groups DF=28) = [F-value=8.91], p = [0.007]).

When assessing the effects of characteristics of participants , it found that there is no significant effect of age of the study participants (p value > 0.05) on the level of DBP post operatively, on other hand, gender of participants has significant effect (*p* value = 0.05) on the level of DBP post operatively. See table 5.

Table 5

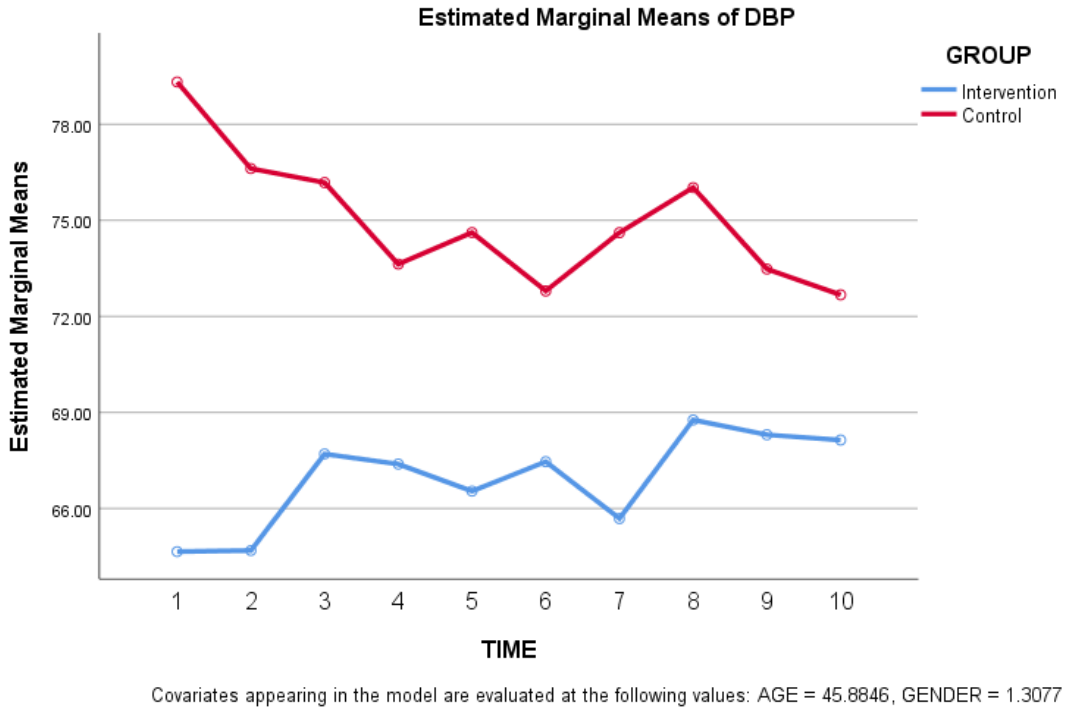
Effect of DEXMED on level of DBP was analyzed for the two groups with controlling the effect of the characteristics of the patients participating in the study by using the ANCOVA statistical test

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	73025.8	1	73025.8	163.3	.000	.881
Age	447.5	1	447.5	1.001	.328	.044
Gender	2600.5	1	2600.5	5.817	.025	.209
Group	3983.7	1	3983.7	8.911	.007	.288
Error	9835.7	22	447.0			

a Computed using alpha = .05

Figure 4

DBP mean scores comparisons between the two groups (DEXMED vs. control)



3.5 DEXMED effect on Post-operative Heart Rate level

HR rate was assessed on the two groups intervention and control one with controlling the characteristics of the patients who enrolled in study by using the ANCOVA statistical test, it was found that there is NO statistically significant difference (*P* value = 0.082) and low effect size (ηp2= .126) between the two groups with respect to the HR measurement in the post-operative period after the operation. There was not a statistically significant difference in HR mean scores between the two groups (F (between groups DF=1, within groups DF=28) = [F-value=3.30], p = [0.082]).

Moreover, the rest of the characteristics of the study participants did not have a statistically significant effect (*p* value > 0.05) on the level of HR post operatively. See table 6.

Table 6

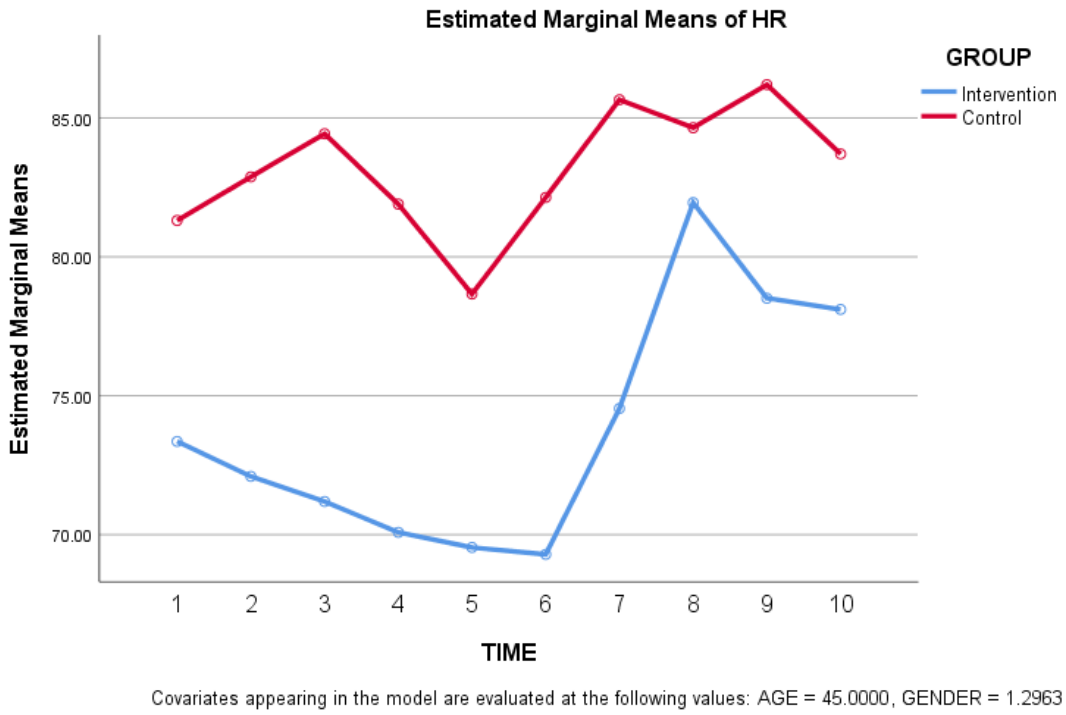
Effect of DEXMED medication intervention (groups) on the level of HR was analyzed for the two groups with controlling the effect of the characteristics of the patients participating in the study by using the ANCOVA statistical test

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	82865.4	1	82865.4	51.01	.000	.689
Age	48.4	1	48.4	.030	.864	.001
Gender	49.4	1	49.4	.030	.863	.001
Group	5371.0	1	5371.0	3.306	.082	.126
Error	37363.6	23	1624.5			

a Computed using alpha = .05

Figure 5

HR mean scores comparisons between the two groups (DEXMED vs. control)



3.6 DEXMED effect on Post-operative Respiratory Rate level

DEXMED effect was analyzed on the group of medication intervention (groups) on the level of RR with controlling the effect of the characteristics of the patients participating in the study by using the ANCOVA statistical test for the two groups, it was found that there is NO statistically significant difference (*P* value = 0.555) and nearly no effect size (ηp2= .016) between the two groups with respect to the RR measurement in the

post-operative period after the operation. There was not a statistically significant difference in RR mean scores between the two groups (F (between groups DF=1, within groups DF=28) = [F-value=0.360], p = [0.555]).

Furthermore, the rest of the characteristics of the study participants did not have a statistically significant effect (*p* value > 0.05) on the level of RR post operatively. See table 7.

Table 7

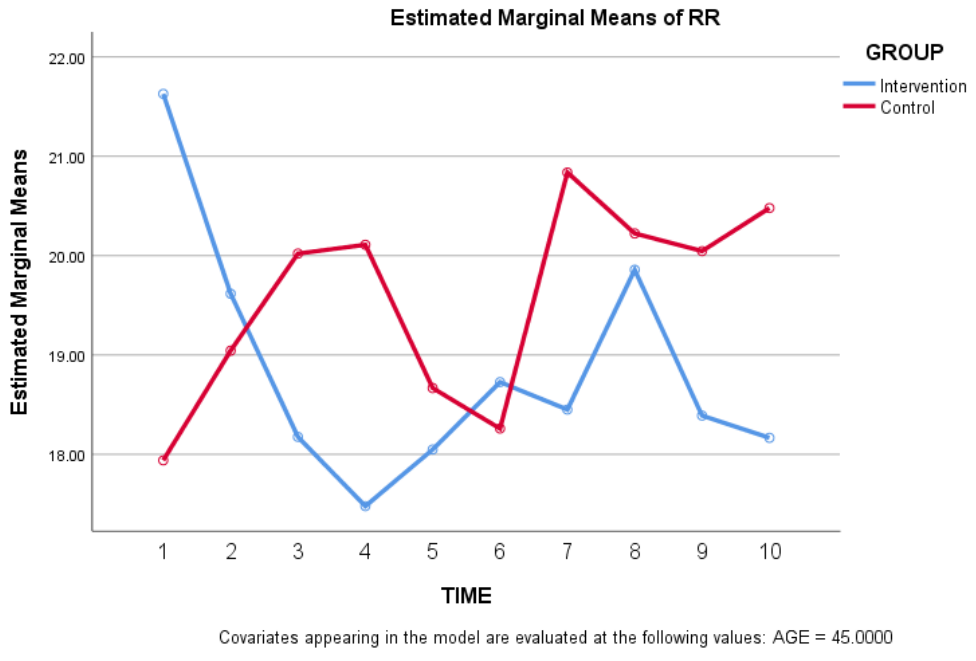
Effect of DEXMED medication intervention (groups) on the level of RR was analyzed for the two groups with controlling the effect of the characteristics of the patients participating in the study by using the ANCOVA statistical test

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	17529.9	1	17529.915	247.402	.000	.918
Age	109.6	1	109.675	1.548	.227	.066
Group	25.4	1	25.479	.360	.555	.016
Gender	31.5	1	31.515	.445	.512	.020
Error	1558.8	22	70.856			

a Computed using alpha = .05

Figure 6

RR mean scores comparisons between the two groups (DEXMED vs. control)



3.7 DEXMED effect on Post-operative SPO2 level

SPO2 was analyzed for the two groups the control one and the group who get DEXMED (intervention group) 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 NO statistically significant difference (*P* value = 0.599) and nearly no effect size (ηp2= .013) between the two groups with respect to the SPO2 measurement in the post-operative period after the operation. There was not a statistically significant difference in SPO2 mean scores between the two groups (F (between groups DF=1, within groups DF=28) = [F-value=0.285], p = [0.599]).

Moreover, the rest of the characteristics of the study participants did not have a statistically significant effect (*p* value > 0.05) on the level of SPO2 post operatively. See table 8.

Table 8

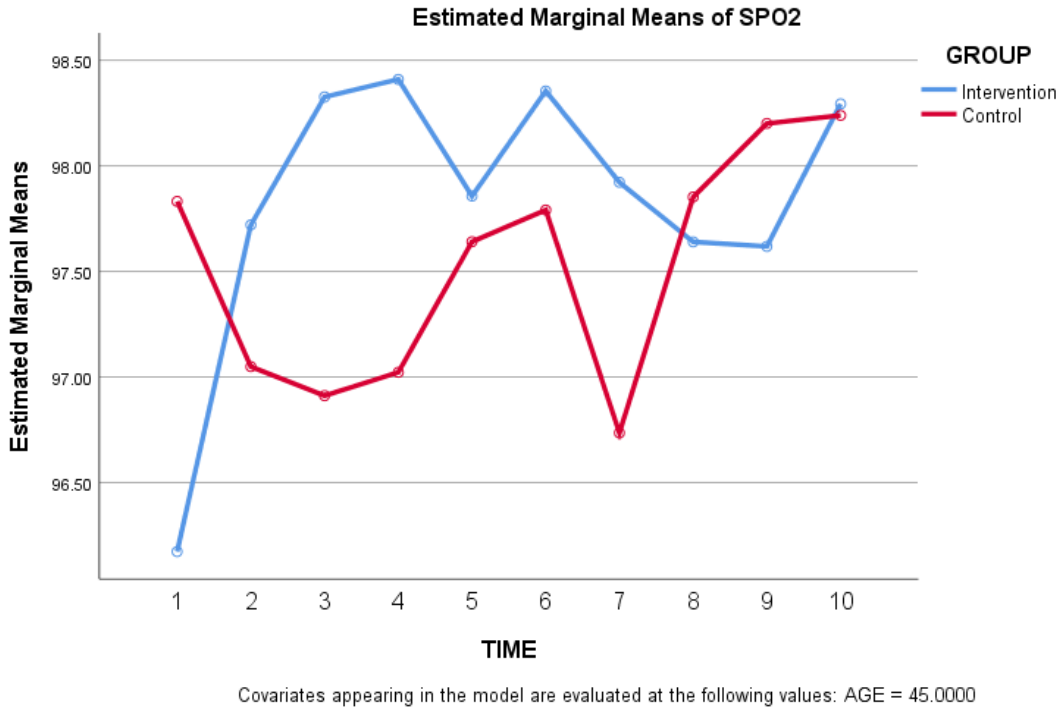
Effect of DEXMED medication intervention (groups) on the level of SPO2 was analyzed for the two groups with controlling the effect of the characteristics of the patients participating in the study by using the ANCOVA statistical test

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	378400.468	1	378400.4	22958.0	.000	.999
Age	44.415	1	44.4	2.69	.115	.109
Group	4.693	1	4.69	.285	.599	.013
Gender	1.491	1	1.49	.090	.766	.004
Error	362.610	22	16.48			

A Computed using alpha = .05

Figure 7

SPO2 mean scores comparisons between the two groups (DEXMED vs. control)



3.8 DEXMED effect on Post-operative analgesic requirements

The use of analgesics post-operatively was assessed in both groups, the interventional group has low administration doses of analgesics were 80% of patient don't need analgesic post operatively in contrast with control group where 55% was given analgesics considering NPS >5 as indication to administer analgesics.

3.9 DEXMED effect on Post-operative nausea and vomiting

In interventional group there was no incidence of nausea and vomiting in contrast with control group where 3 patients developed incidence of nausea and vomiting especially when pain score was more than 7/10 according to NPS.

Chapter Four

Discussions and Conclusions

4.1 Discussion

In this study, effect of DEXEMD and Marcaine on post-operative pain, N&V and post-operative vital signs was assessed in contrast with using Marcaine alone. According to the results of this study there was minimal side effects using DEXMED with Marcaine which consist Zhang et al. (2019) results. Also, vital signs were more stabilized in patients in intervention group more than patients in control group.

According to the results that emerged from this study there is no association between age and gender on the effect of and DEXMED on post-operative pain. This revealing that using DEXMED with Marcaine as blocking agents reduce the level pain in these intervals 5^{th} minutes, 10^{th} minute, 30^{th} minute and 24^{th} hour in comparison with control group according to table.1 also the amount of analgesia that used in DEXMED group was less than Marcaine group which this partially consistent with Mahmoudi et al. (2021)

4.2 Blood pressure

Blood pressure is one of the important vital sign that has been taken in consider when the patient is being anesthetized, any alteration in blood pressure affect patient stability in all operation period from the beginning of assessing patient until patient discharged from hospital. Anesthetic and analgesic agents decrease blood pressure in general but according to the dose of agent when applying a dose that is more than patient requirement it causes blood pressure to be declined. On other hand, conservation in the dose of these agents has harmful circumstances for example if there is a decrease in the anesthetic agents dose patient will awake from sedation and then neuro-blocking effect will diminished, this stimulate sympathetic nervous system causing increase in blood pressure due to the vasoconstriction (Kawasaki et al., 2018). Also conservation in analgesic has the same effect on sympathetic nervous system, so administer the right agent and dose will prevent patient from harm due to the surgery(Nie et al., 2021)

In this study blood pressure was assessed in both groups, the results revealed that in control group level of pain was more that the intervention group, take in consider that anesthetic protocol was the same in both groups which means that the effect of DEXMED with Marcaine was potent and give a good outcome. Pain is produced by any injury or trauma and this considered sympathetic stimulant that causing release of catechol-amines and norepinephrine which causing hypertension. Using DEXMED inhibits sympathetic nerves and by reducing sympathetic stimuli, controlling of blood pressure is achieved. Also using of Dexmedetomidine conserving hemodynamics. (Zhao et al., 2020).

Another result was emerged from the study. Blood pressure was on the normal lower limit which means that stability of blood pressure was conserved post operatively and this is one of the most important outcome when administration of analgesic agents and this consistent with Zhao et al. (2020). At all, using DEXMED with Marcaine decrease level of pain and conserve blood pressure on the normal lower limit at the first 24 hours post VATS. Also according to figure 2 systolic blood pressure in control group started from a high limit than intervention group and start to decrease within the period of assessment, on other hand in interventional group systolic blood pressure start from a limit less than control group and blood pressure conserved within normal limit and this revealing that using Dexmedetomidine as adjunct to Marcaine in intercostal nerve block stabilize the systolic blood pressure.

When diastolic blood pressure was assessed, in control group diastolic blood pressure start from high limit and then dropped but within the normal range of diastolic blood pressure. In contrast with interventional group blood pressure start from low limit than control group and then started to rise but within constant rise. By using Dexmedetomidine as adjunct to Marcaine in intercostal nerve block diastolic blood pressure was conserved. From the figure 3 the baseline reading in control group was higher than interventional group which mean that Dexmedetomidine decrease blood pressure but it decreased within the normal lower limits and conserve it. By this way patient safety was conserved. Patient safety is the most important thing that must be guaranteed before patient anesthetized.

4.3 Heart rate

Heart rate has been assessed in both groups. Heart rate considers one of the indicators for pain level in patient due to the stimulation of sympathetic nervous system due to pain (Riganello et al., 2019). Conservation of heart rate is crucial during operation, because any dysrhythmia will cause decrease in cardiac output, any decrease in cardiac output puts patient in fatal condition especially intra- or post- operation due to the high incidence of bleeding. Decrease in blood volume with cardiac output mortality rate will be increased (Butterworth et al., 2018).

When giving patient the optimum dose of analgesic agent conserves heart rate due to the inhibition of stimulants that activate sympathetic nervous system.(Ammar et al., 2021)

In this study heart rate was evaluated in both groups. The results revealed that in control group heart rate was less stable on the high normal limit and when patient level of pain more than 5 from 10 heart rate was increased in contrast with lower pain scores. On other hand, in intervention group heart rate conserved and was more stable on a level near lower normal limit. This yield to that using DEXMED with Marcaine instead of Marcaine alone decrease the level of pain in contrast with control group, this make heart rate more stable and when heart rate is stable the incidence of harm decreased and when harm is decreased then the core of anesthesia which is safety of patient during intra- and post- operative has been achieved.

4.4 Respiratory rate

Respiratory rate was assessed also, the results showed that there is variability in respiratory rate readings among both groups. This consider one of the limitation of study, this limitation may be due to the depending on cardiac monitor reading because patient over movement alter the reading.

In this study according to the results there was no effect of DEXMED with Marcaine on the respiratory rate which is consistent with the control group.

To prevent this limitation from happening in future studies, the use of prime way in accounting respiratory rate may be the best way when assessing respiratory rate. Reliability of the way is more than accounting respiratory rate using cardiac monitor.

4.5 Oxygen saturation

Due to the effect of DEXMED which is conservation of respiratory muscle oxygen saturation was assessed in both group. The results revealed that in both groups there was stability in oxygen saturation but there was a significant conservation of oxygen saturation among interventional group.

This leads that using DEXMED with Marcaine improve the respiratory muscle function and ventilation especially VATS which a procedure is done for the lung. If conservation of respiratory muscle during procedures in lungs this will improve the function of lung to be less affected by the surgery.

Conservation of oxygen saturation also is important during and after surgery. Low oxygen saturation leads to ischemia of the cells and the ischemia consider one of the harmful side effects for desaturation of oxygen in bod cells. Especially body cells work on the aerobic respiration

While assessing nausea and vomiting for patients post operatively there was no incidence in both groups. This show us that using DEXMED has no effect as emitting agent, nausea and vomiting is one of the most common side-effect of anesthetic agents that makes aesthetics take in consider for patient safety this s due to the relaxation of airway muscles(Butterworth et al., 2018).

Even that the intervals of study were not consistent with other studies but there was a stability in vital signs post-operatively in pulse, diastolic blood pressure, systolic blood pressure and saturation of oxygen in blood except respiratory rate. In comparison with control group the vital signs in DEXMED group were within the normal lower limits and were stabilized all over the period of assessment. Due to that vital signs reflects the condition of patient they can be used to approximate the intensity of pain and initiate further assessment for pain intensity (Shahiri & Gélinas, 2022).

Vital signs were normal and lower than the control group this leads us that using DEXMED decrease the intensity of pain in some intervals post-operatively. The core of anesthetic management is maintain the hemodynamic stability within operation and post-operative period.

Most of results that emerged from study are consistent with literature about the side-effects of Dexmedetomidine, there were no adverse effects when Dexmedetomidine was used as adjunct to local anesthetic agent.

4.6 pain

The results in our study revealed that patients who received DEXMED 0.1 mcg/kg with MARCAIN 0.5% 1 mg/kg has low NPS than the control group who received MARCAIN 0.5% 1 mg/kg via intercostal rout without the need of rescue analgesics such as PARACETAMOL or OPTALGIN 1g and this results was consistent with a study conducted by Yao et al. (2020) that revealed patients who gets DEXMED as adjunct to MARCAIN via intercostal rout has low NPS than control group.

Also Xin-qi et al. (2021) conducted a study to assess DEXMED administration in the intercostal space with a dose of 4 mcg/kg for patients who underwent single port Thoracoscopic lobectomy. the results revealed that patients got optimum analgesic effect after the surgery and when DEXMED infusion was added the time of analgesia time was prolonged. The results of this study was consistent with our study when pain score was compared between them.

At the end, DEXMED approved it’s ability to control the pain post operatively for patients who will undergo VATS without any side-effects that may occur to patient.

4.7 Conclusion

Non-opioid analgesic has become the most favorable agents than opioids in controlling pain. Dexmedetomidine is a selective alpha-2 agonist and has special effects such as sedation, analgesia and hypnosis and the use of this agent become common in surgical and radiographic procedures. There are several studies that assess the use of Dexmedetomidine as adjunct to local anesthesia for controlling of pain such as paravertebral block and brachial plexus block. In this study the effect of using Dexmedetomidine 1 mcg/kg as adjunct to MARCAIN 1 mg/kg via intercostal space for patient who underwent VATS in was assessed and we found that when adding Dexmedetomidine to Marcaine as intercostal-blocking agents in patients who will undergo VATS; core of anesthetic management was achieved. By decreasing intensity of pain, decreasing analgesic consumption, maintaining the hemodynamic stability

moreover there was no incidence of nausea and vomiting in all patients that took DEXMED.

4.8 Limitations of study

This study is the first study in Palestine that assess effect of DEXMED as intercostal blocking agent and according to literature review it one of the few studies that has been done to assess the effect of Dexmedetomidine as adjunct to bupivacaine via intercostal nerve block worldwide in term of VATS combined with intercostal block analgesia.

VATS surgeries is being done in just two hospitals so in order to make more evaluation of effect DEXMED it is preferred to apply study in more than one health center in Palestine.

Also one of the problems that faced us in this study is the reliability of respiratory rate accounting using cardiac monitor. In future study changing the tool of assessing respiratory rate is preferred.

DEXMED uses in Palestine is rare due to its special properties which are sedation, analgesia and muscle relaxation. So when it used as adjunct in operations or in ICU's many consideration is being toke in mind to prevent any consequences such as hypotension, therefore there is a conservation in administering DEXMED to patients.

4.9 Recommendations

In Palestine VATS surgeries become common and it is been done by Palestinian teams. So the number of sample can be increased to get new literature about the use of Dexmedetomidine as adjunct to local anesthesia medications. For instance there are many drugs can be added to Dexmedetomidine as adjunct such as dexamethasone and clonidine, by assessing these agents with Dexmedetomidine a multi factorial analysis study can be done to assess the effect of these medication on pain managements epically there are new direction in these days to do surgical procedures with minimal anesthetic protocols and minimally invasive procedures.

Further studies are recommended to assess the effect of Dexmedetomidine as adjunct to local anesthetic and non-opioid analgesics and may be assessed in other surgical procedures not only VATS.

Moreover, DEXMED can be used in other fields not in just operation rooms, DEXMED can be used in ICU's for patients on mechanical ventilators or patients who need sedation, also, DEXMED can be used in radiographic procedures such as computed tomography and magnetic resonance image.

List of Abbreviations

Abbreviation	Meaning
ASA	Association of anesthesia
ANCOVA	Analysis of covariance
BP	Blood pressure
DBP	Diastolic blood pressure
DEXMED	Dexmedetomidine
FDA	Food and drug administration
FEV1	1st second expiratory volume
HR	Heart rate
NPB	Numerical pain score
PLT	Posterolateral thoracotomy
RR	Respiratory rate
SBP	Systolic blood pressure
SPO2	Saturation of oxygen
VATS	video assessed Thoracoscopic surgery
VC	Vital capacity

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Appendices

Appendix A

Consent form

نموذج طلب موافقة على المشاركة في بحث علمي

عنوان الدراسة: تأثير استخدام دواء الديكسوميدوتومودين في تخدير العصب الموجود بين الاضلاع في عمليات الرئة باستخدام الناظور ودرجة الالم بعد العملية

اسم الباحث الرئيسي: موسى محمد موسى معروف

اسم المشرف على البحث: د.جمال القدومي

اسم المشرف الاكلنيكي: د. علي عبد الحق

ملخص البحث:

عمليات ناظور الرئة باستخدام الفيديو من العمليات الحديثة التي تستخدم في العديد من المجالات مثل استئصال الاورام او اخد عينات للتحليل، ولها العديد من الايجابيات مثل تقليل نسبة الالم بعد العملية، تقليل مدة المبيت داخل المشفى، تقليل نسبة الاصابة بالالتهاب بعد العملية. تتم من خلال ادخال ناظور عن طريق فتحة في الصدر وقبل نهاية العملية يتم تخدير العصب بين الاضلاع لتقليل الالم حيث ان هناك العديد من الادوية المستخدمة. الديكسوميدوتوميدين من الادوية الحديثة وهذه الدراسة تدرس اثر استخدام هذا الدواء في تخدير العصب بين الاضلاع حيث ان هناك دراسات قليلة عليه وتثبت هذه الدراسات انه من الادوية الفعالة في تقليل الالم.

معلومات عن العينة المنتقاة والفترة الزمنية المقدرة لاستكمال المقابلة أو الاستبيان:

تم اختيار المرضى الذين سوف يعملون عمليات ناظور الرئة باستخدام الفيديو لانهم الفئة المستهدفة من الدراسة، حيث ان فترة الدراسة لكل مريض هي فقط يوم واحد بعد العملية.

المخاطر المتوقعة والخصوصية:

بالنسبة للمخاطر التي ممكن ان تحدث للمريض هي فقط مخاطر العملية وليس استخدام دواء الديكسوميدوتومودين لانه لا يوجد له اثآر جانبية على المريض في حال استخدامه في تخدير العصب بين الاضلاع. المعلومات الخاصة بكل مريض سوف تحفظ حفظا تاما بحيث انه لا يمكن لاي احد الموصول الى هذه المعلومات سوى اصحاب الشأن في الدراسة ولن يتم معرفة هوية المريض في حالة نشر نتائج الدراسة.

للمريض الحق في الانسحاب من الدراسة في اي وقت شاء سواء كان قبل بداية الدراسة او خلالها او بعد الانتهاء من جمع المعلومات او قبل البدأ بعملية تحليل البيانات.

طريقة التواصل مع الباحث:

يمكنك التواصل مع (موسى محمد موسى معروف) عن طريق (رقم الهاتف0595224195) أو عنوان البريد الإلكتروني mosakarajah@gmail.com إذا كانت لديك بعض الأسئلة عن الدراسة.

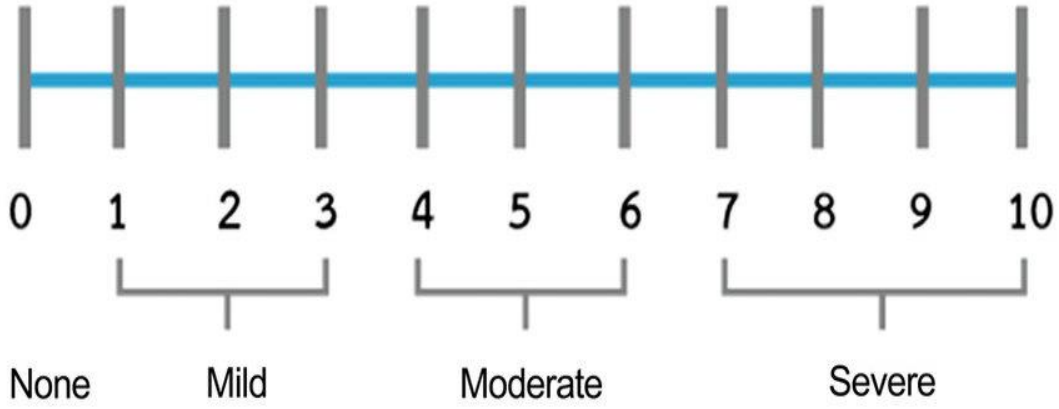
موافقة أو توقيع المشارك في البحث:

الاسم:

التوقيع:

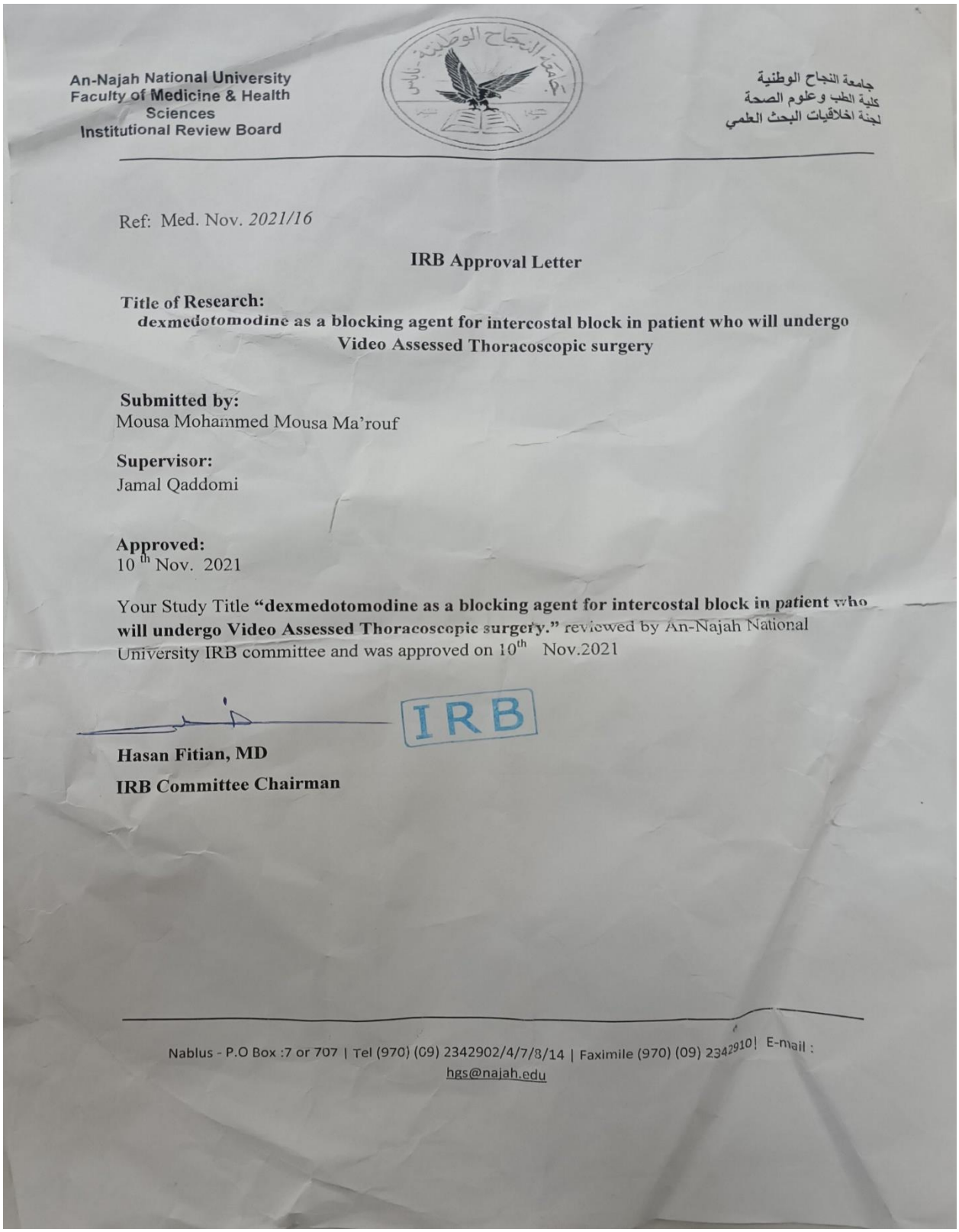
Appendix B

Numerical pain scale



Appendix C

IRB approval paper



An-Najah National University
Faculty of Medicine & Health Sciences
Institutional Review Board

جامعة النجاح الوطنية
كلية الطب وعلوم الصحة
لجنة اخلاقيات البحث العلمي

Ref: Med. Nov. *2021/16*

IRB Approval Letter

Title of Research:
dexmedotomodine as a blocking agent for intercostal block in patient who will undergo Video Assessed Thoracoscopic surgery

Submitted by:
Mousa Mohammed Mousa Ma'rouf

Supervisor:
Jamal Qaddomi

Approved:
10 th Nov. 2021

Your Study Title **"dexmedotomodine as a blocking agent for intercostal block in patient who will undergo Video Assessed Thoracoscopic surgery."** reviewed by An-Najah National University IRB committee and was approved on 10th Nov.2021

IRB

Hasan Fitian, MD
IRB Committee Chairman

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جـامعـــة النجاح الوطنية

كليـــة الدراســـات العليـــا

الديكسميدوتومودين كعامل مانع في التخدير بين الاضلاع لمرضى عمليات جراحة تنظير الصدر بمساعدة الفيديو

إعداد

موسى محمد موسى معروف

إشراف

د. جمال قدومي

قدمت هذه الرسالة استكمالا لمتطلبات الحصول علي درجه الماجستير في تمريض التخدير، من كلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس– فلسطين.

2022

الديكسميدوتومودين كعامل مانع في التخدير بين الاضلاع لمرضى عمليات جراحة تنظير الصدر بمساعدة الفيديو

إعداد

موسى محمد موسى معروف

إشراف

د. جمال قدومي

الملخص

الخلفية: التخدير الموضعي أو النحي هو أحد المجالات الرئيسية في التخدير. هناك العديد من التقنيات لتطبيق التخدير الموضعي، ومن بين هذه الطرق الحصار الوربي وهو نوع من التخدير الموضعي يستخدم في جراحات الصدر والجزء العلوي من البطن لتسكين الآلام أيضًا لتسكين الألم الناتج عن كسر الضلع والسرطان وإجراءات الصدر والرئة و العمليات الجراحية.

ظهرت جراحات التنظير الصدري في القرن العشرين وأصبحت واحدة من أكثر الإجراءات المفضلة شيوعًا في جراحات الرئة، حيث يؤدي تطبيق الكتلة الوربية في هذه العمليات إلى نتائج جيدة على مستوى الألم بعد الجراحة. هناك العديد من عوامل التخدير التي يمكن استخدامها في التخدير الموضعي مثل ليدوكائين وماركين. الديكسميدوتودين هو مضاد أدرينالي ألفا −2 يعمل على العضلات الملساء للأحشاء وله تأثير فريد للتحكم في الألم والتخدير. عن طريق إضافة 1 ميكروجرام لكل كيلوغرام من ديكسميديتوميدين للصيغة له تأثير قوي على السيطرة على مستوى الألم.

الأهداف: استخدمت هذه الدراسة لتقييم تأثير عقار ديكسميديتوميدين Dexmedetomidine كعامل إحصار وربي على مستوى الألم، ومتطلبات التسكين، واستقرار ديناميكا الدم، والغثيان والقيء.

المنهجية: تصميم تجريبي حقيقي مزدوج التعمية يستخدم لتقييم 30 مريضًا يعانون من فئة التخدير (1 و2 و3) الذين خضعوا لعمليات جراحات التنظير الصدري في احدى المستشفيات في فلسطين. هؤلاء المرضى

مقسمون إلى مجموعتين كل مجموعة 15 مريضا. أعطيت المجموعة الضابطة 1 ميلي جرام/ كيلوجرام، وأعطيت مجموعة التدخل 1 ميكروجرام / كيلوجرام ديكسميدوتومودين مع 1 ميلي جرام/ كيلوجرام ماركائين على الفضاء الوربي.

النتائج: وفقًا للنتائج كان هناك تأثير على مستوى الألم في الدقيقة الثالثة (القيمة الاحتمالية = 0.04) الخامسة (القيمة الاحتمالية = 0.01) الخامس عشر (القيمة الاحتمالية = 0.1) دقيقة بعد العملية و24 ساعة (ع– القيمة = 0.01).

الخلاصة: استخدام ديكسميديتوميدين كعامل مساعد في التخدير الوربي قلل من شدة الألم بعد العملية، والحفاظ على العلامات الحيوية (ديناميكا الدم) على الحدود الدنيا الطبيعية للمريض، ومتطلبات أقل للتسكين بعد الجراحة، وعدم حدوث حالات الغثيان والقيء للمرضى الذين أعطوا ديكسميديتوميدين مع ماركائين.

الكلمات المفتاحية: الديكسميديتوميدين، الألم، جراحات التنظير الصدري بمساعدة الفيديو.