An-Najah National University

Faculty of Graduate Studies

THE COMPARISON OF DEXMEDETOMIDINE AND MIDAZOLAM USED FOR SEDATION OF PATIENTS UNDERGOING UPPER GASTROINTESTINAL ENDOSCOPY: A PROSPECTIVE COMPARATIVE STUDY

By

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This Thesis is submitted in Partial Fulfillment of the Requirements for the Degree of Master of Nursing Anesthesia, Faculty of Graduate Studies, An-Najah National University, Nablus, Palestine.

2022

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Dedication

Praise be to God always and forever and praise be to God before and after To those who stood by me and humiliate the difficulties, and they have the credit after God for what I am in, my father and my mother, may God extend their life and enable me to honor them To my dear sisters and brothers To my dear wife Wafa To my daughtwsan, and my son Qasim

Acknowledgements

I would like to extend my thanks and appreciation to God always, and to Dr. Aidah Alkaissi for the effort and time that she spent to me and Dr. Wael Sadaqah for what he did to my

Dear wife, Wafaa Qaisi, the main supporter for me since the beginning of the journey

To An-Najah National University and represented by all graduate studies staff

To the management and staff of An-Najah National University Hospital

To everyone who helped me and gave me a helping hand

Declaration

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

THE COMPARISON OF DEXMEDETOMIDINE AND MIDAZOLAM USED FOR SEDATION OF PATIENTS UNDERGOING UPPER GASTROINTESTINAL ENDOSCOPY: A PROSPECTIVE COMPARATIVE STUDY

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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THE COMPARISON OF DEXMEDETOMIDINE AND MIDAZOLAM USED FOR SEDATION OF PATIENTS UNDERGOING UPPER GASTROINTESTINAL ENDOSCOPY: A PROSPECTIVE COMPARATIVE STUDY

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Abstract

Background: Endoscopic procedures are essential for diagnostic testing, examining, and treating a wide range of disorders like gastrointestinal tract blood loss, foreign object removal, and many other complicated procedures such as Endoscopic retrograde cholangiopancreatography. An endoscope is an irritating and painful procedure. during which patients should be anesthetized to avoid mobility, pain, coughing, gagging, and nausea. So, sufficient analgesia and sedation agents should be given and monitored with minimal side effects or complications. These agents can keep patients'response to pain and verbal stimuli without failing respiratory or cardiovascular function.

Objectives: The current study aims to compare and investigate the efficacy and safety of Midazolam versus Dexmedetomidine in terms of respiratory, hemodynamic, analgesia, sedation, patient satisfaction, endoscopist satisfaction, and adverse effects in patients undergoing upper endoscopy at An-Najah National University Hospital.

Methodology: A prospective observational study was performed on 68 patients (aged 18-60) undergoing upper endoscopy using theAmerican Society of Anesthesiologists (ASA) Physical Status Classification System (grades one and two). The study was conducted at An-Najah National University Hospital, Nablus-Palestine, between October 2021 and January 2022. All subjects received information about the purpose of the study, the study protocol, and the consent form was obtained from each subject.

Results: Regarding patient satisfaction, the Dexmedetomidine demonstrated much higher satisfaction, minor discomfort, and less anxiety than Midazolam with $P<0.05$. Regarding endoscopy specialists, the satisfaction, discomfort, gagging, retching, and technical difficulty showed that Dexmedetomidine outperformed the Midazolam with $P<0.05$.

Dexmedetomidine patients recovered faster than Midazolam patients with $p < 0.05$, Midazolam needs 2.4 ± 7.7 minutes to be sedated while Dexmedetomidine needs 9.5 ± 1.1 minutes , and this difference is significant since the $p < 0.05$. Regarding side effects occurrence, Dexmedetomidine had fewer side effects than the Midazolam, but with no statistically significant difference. Regarding vital signs, there is no significant difference between Midazolam and Dexmedetomidine.

Conclusions: Dexmedetomidine outperformed Midazolam in recovery time, patient satisfaction, endoscopy specialist satisfaction, discomfort, anxiety, and retching; Dexmedetomidine appears to be a useful alternative to Midazolam for sedating patients during upper endoscopy because it is both safe and effective.

Keywords: Dexmedetomidine, Midazolam, sedation, upper endoscopy.

Chapter One
Introduction

1.1 Introduction

In conscious sedation, patients can keep their response to pain and verbal stimuli without failing respiratory or cardiovascular function (Waring et al., 2003). This type of sedation merges a benzodiazepine, and opioid and is commonly used in minor surgeries and endoscopy (Huang, Chen, Yang, & Liu, 2012) (Ozel, Oncü, Yazgan, Guerbuez, & Demirtuerk, 2008).

Endoscopic procedures are essential for the treatment, diagnosis, and evaluation of many disorders like gastrointestinal tract bleeding, foreign body removal or in some complicated procedures like endoscopic retrograde cholangiopancreatography (ERCP), which uses x-ray guidance to accurately treat and diagnose diseases inside the pancreas, bile ducts, liver, and gallbladder. During the procedure, pain, anxiety, fear, and retching may let patients to be uncooperative, and it can induce harmful respiratory and cardiovascular effects (Eger et al., 2000). The endoscope is an irritating and painful procedure performed without analgesia and sedation (Riphaus, Stergiou, & Wehrmann, 2005). During endoscopy, patients should be anesthetized to avoid mobility, pain, coughing, gagging, and nausea. So, sufficient analgesia and sedation agents should be given and monitored (Demiraran et al., 2007). It is necessary to guarantee that the client's protective reflexes are intact but immobile. After this type of anesthesia, the patient can recover his reactions and return home on the same day. This benefits both the patient and the hospital so that the occupancy rate in hospitals is reduced and the hospital can receive more cases per day. Other advantages of this type of sedation over general anesthesia are the speed of recovery, ease of response of the patient to the nurse when he awakens and the increase in his level of satisfaction and comfort (K. H. Kim, 2014; Moon, 2014; Schweickert & Kress, 2008). While using sedative drugs, the study aimed to do analgesia, amnesia, and quick patient recovery to the same level of consciousness before the procedure (Wang et al., 2013).

Midazolam is one of the benzodiazepines family with a short duration and rapid onset of action (Triantafillidis et al., 2013). It triggers γ-aminobutyric acid receptors and causes

central nervous system depression (Yilmaz et al., 2014). Midazolam was the most common sedative agent used in critical care units (Chawla et al., 2014).

Dexmedetomidine is an antagonist and highly selective drug that works on alpha 2-adrenoceptor and has sedative, amnestic, sympatholytic, and analgesic properties (Bajwa & Kulshrestha, 2013). Dexmedetomidine started to be used in the critical care unit in 1998, then in other medical applications (Takrouri et al., 2002). Dexmedetomidine is a good surrogate to Midazolam in sedation (Ihmsen & Saari, 2012). With the increase in the use of Dexmedetomidine, many side effects appeared, such as bradycardia and hypotension (Bharati, Pal, Biswas, & Biswas, 2011). Beneficent clinical applications of Dexmedetomidine sedation are found in endoscopic procedures and retrograde cholangiopancreatography (Inatomi et al., 2018).

In terms of the respiratory system, compared to Midazolam, Dexmedetomidine has been statistically shown to be more effective. It has a lower effect on oxygen saturation in the blood and more respiratory stability. As it leads to faster recovery, it is recommended to be used as an alternative, especially for people who suffer from respiratory problems (F. Zhang, Sun, Zheng, Liao, & Liu, 2016) (Tellor, Arnold, Micek, & Kollef, 2012) (Huang et al., 2012).

Regarding the cardiovascular system, the most critical complication of Dexmedetomidine is bradycardia and hypotension (Jalowiecki et al., 2005). However, other studies found no effect of hypotension or bradycardia. (F. Zhang et al., 2016) (Yu, Li, Deng, Yao, & Qian, 2014). The slow flow of the drug for ten minutes showed that the drug does not lead to a decrease in blood pressure. Hence, the correct preparation and administration of the drug give positive results regarding the safety of the circulatory system (Cheung et al., 2007). However, caution should be exercised while administering this drug to people with slow heartbeat problems or heart block (Arain & Ebert, 2002).

And if the comparison between the two drugs was made from the perspective of anesthesia, Dexmedetomidine proved more effectiveness during endoscopy, as the degree of anesthesia that the patient reaches through Dexmedetomidine gives the patient the ability to respond to commands such as moving to the right or left (Gerlach et al., 2006; Snapir et al., 2006; Wijeysundera, Bender, & Beattie, 2009). in addition to the side effects that occur during anesthesia. Complications during endoscopic operations were more

minor when using Dexmedetomidine. The most important of which are respiratory failure and the need for pulmonary intubation. Therefore, the benefits gained from Dexmedetomidine exceed that of Midazolam during endoscopy (Coull, Jones, Egan, Frith, & Maze, 2004).

1.2 Background

1.2.1 Endoscopy:

In 2018, Ahlawat and Ross published Esophagogastroduodenoscopy (EGD). It is one of the most important medical procedures carried out by endoscopists, as it is considered a diagnostic and therapeutic procedure that allows viewing the components of the digestive system such as the stomach, esophagus, and part of the duodenum and conducting therapeutic intervention in these parts.

Some examples of diagnostic procedures performed through Esophagogastroduodenoscopy include dysphagia, persistent vomiting, mal-absorption, chronic diarrhea, constant upper abdominal pain, sudden weight loss, anorexia, and iron deficiency anemia. Examples of therapeutic interventions carried out through this procedure are esophageal variceal ligation, upper gastrointestinal bleeding control, foreign body removal, and insertion of draining or feeding catheters (Ahlawat, Hoilat, & Ross, 2018).

There are many cases in which this procedure is not allowed or forms high-risk, such as peritonitis, perforated bowel, severe neutropenia, and coagulopathy. The equipment used consists of the endoscope and accessories so that the patient's age is considered when choosing the appropriate size. As for the accessories, they consist of an imaging device, suction equipment, biopsy equipment, and others for the preparation of the endoscopy. It is necessary to consider several axes, which are diet, medication, anesthesia, monitoring, and the consent form. It is essential to refrain from eating food six hours before the endoscopy and drinking for two hours, as for regular medications, there is no objection to taking them with a bit of water, taking into account diabetes medications for fear of the sharp drop in blood sugar level with fasting in addition to the anticoagulant drugs, and consulting the doctor about the period that should stop taking them before the endoscopy, taking into account the patient’s medical history. Hypnotizing the patient without the need for a muscle relaxant should be considerd so that all vital signs are under

continuous monitoring and continuous clinical evaluation during the procedure and monitoring of any respiratory or circulatory disorders. Finally, there must be a consent form for the procedure and anesthesia, and the person himself must sign it or his legal representative, complications occur during the endoscopic procedure by less than 2%, as most of these complications are related to difficulties in the respiratory or circulatory system during sedation. Examples of respiratory complications include hypoventilation, hypoxemia, airway obstruction and aspiration. Examples of complications in the circulatory system include hypotension, hypertension, and arrhythmia. Another expected complication that may occur during the endoscopy is bleeding, especially in cases in which biopsies are taken from the wall of the digestive system and are less than 0.3%. These complications are treated with simple or complex interventions that may reach surgical intervention for repair (Ahlawat et al., 2018).

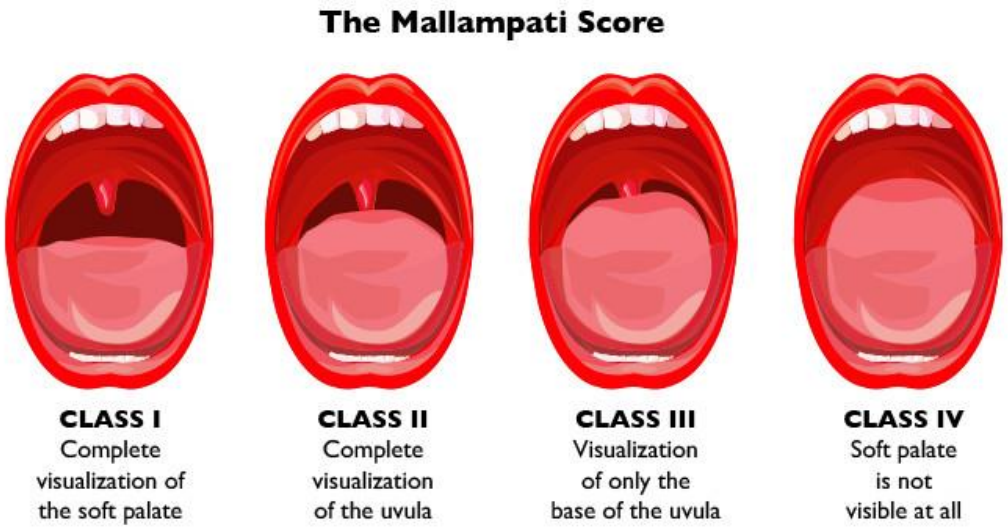
1.2.2 Procedural sedation

It is for the patient to be sedated using sedative and hypnotic drugs in addition to pain relievers or without them to give the patient the ability to tolerate the unwanted feeling during the procedure while maintaining the work of the respiratory and circulatory system in an efficient and safe airway, oxygen saturation of blood, blood pressure, respiratory rate, heart rate, pain degree, and others. Practically, the most widely used classifications for the depth of sedation are: minimal sedation (anxiolysis) during which the patient is relaxed and able to interact, moderate sedation (conscious sedation) during which the patient responds only to verbal order or touch stimuli but can breathe spontaneously, deep sedation during which the patient only responds to painful stimuli and breathing can be lost, and airway needs to be maintained and supported, finally dissociative sedation during which the patient does not feel pain and loses memory during the procedure and can respond to commands and does not lose control over the airway and respiratory system (Green et al., 2019). As mentioned previously about the complications resulting from the endoscopy procedure, it is crucial to assess the respiratory system anatomically and functionally. The most important things that must be evaluated are the airway and to note any abnormal differences in the airway. One of the essential tools that are used to assess the airway anatomically is the Mallampati score (figure 1:1), which is divided into four classes. In the first class the soft palate is visible and in the second class uvula appears. In the third class, only base of the uvula is visible while in the last type that soft

palate is not visible at all. Airway assesement enables us to observe any wounds or ulcers inside the oral cavity in addition to assessing the limited movement of the neck, obesity and examining the possibility of lying on supine position without respiratory problems or lack of oxygen saturation of the blood.

Figure 1:1

Mallampati Score



(Long et al., 2019).

To determine the type and depth of anesthesia, several criteria must be considered, which are the degree of pain that the patient may experience during the medical intervention, the stability of the patient during the procedure, the stability of vital signs, and also the medical history of each patient. One of the most critical systems used in clinical assessment is the American Society of Anesthesiologists (ASA) Physical Status scoring, Class one: healthy adult patient without organic, physiologic, or psychiatric disorder and tolerate exercise, Class two: mild systemic disease in one body system and controlled, Class three: severe systemic disease involving more than one body system, Class four: a severe systemic disease that represents a constant threat to life, Class five: patients not expected to survive over twenty-four hours without surgery, Class six: a brain-dead patient whose organs are being taken for donor purposes (Benzoni & Cascella, 2019).

1.2.3 Dexmedetomidine

1.2.3.1 Mechanism of action

Types of α2-adrenoceptor are A, B, and C. Each of them has a different activity. It is in the blood vessels, vital organs, autonomic, peripheral, and central nervous systems; Dexmedetomidine is an α2-adrenoceptor agonist, binds with G-Protein to do its effect. It was developed in the 1980s, and was clinically approved as a sedative and analgesic agent in 1999. It works as a sedative agent by affecting the Locus ceruleus in the brain stem, and works as an analgesic agent by affecting the spinal cord, acting through α2A subtype agonist. In the heart, it works by blocking the cardio-accelerator nerve through α2A subtype agonist, which results in vago-mimetic action. The bradycardia will be noticed, and tachycardia will be decreased (Fairbanks, Stone, & Wilcox, 2009) (Figure 2).

1.2.3.2 Pharmacokinetics

Absorption and distribution*:* Dexmedetomidine is a lipophilic medication (Giovannitti Jr, Thoms, & Crawford, 2015). with steady-state volume of distribution approximately one hundred eighteen litter and the mean total clearance of thirty-nine litter per hour (Afonso & Reis, 2012). It is a very high protein bound approximately (94%) (Bajwa & Kulshrestha, 2013). With a half-life of distribution needs six minutes and a half-life of elimination needs two hours, The drug can be administered intravenously and it is not recommended to be given orally, as the recommended dose during continuous administration of the drug intravenously is 0.2-0.7 mcg/kg/hr and that the duration of administration to the patient does not exceed 24 hours (Gertler, Brown, Mitchell, & Silvius, 2001). The extensive first-pass metabolism leads to poor bioavailability in oral administration, but in sublingual form the bioavailability is eighty-four percent, Therefore, among the applications available for the drug as a premedication or as a sedation for pediatric, there is a form of the drug as a lollipop (Anttila, Penttilä, Helminen, Vuorilehto, & Scheinin, 2003).

Metabolism and excretion: Direct N-glucuronidation and aliphatic hydroxylation mediated by cytochrome P-450 (CYP 2A6) result in biotransformation of Dexmedetomidine to inactive metabolites. Metabolites are eliminated in the urine 95% and 4% in the feces, Caution should be exercised while administering the drug to patients

with liver disease and adjust the dose and ensure that it is safe for these patients (Gertler et al., 2001).

Sedative and hypnotic effects: through the activation of α2-receptors in central presynaptic and postsynaptic in the locus coeruleus, Dexmedetomidine well impacts endogenous sleep aid pathways and causes hypnotic and sedative effects (Segal, Vickery, Walton, Doze, & Maze, 1988) (Vuyk, Sitsen, & Reekers, 2015), the use of Dexmedetomidine in intensive care departments was approved by the US Food and Drug Administration for 24 hours only, but many studies have shown that it can be used for more than 24 hours and for 30 days in intensive care units (Riker et al., 2009) (Jakob et al., 2012). Also, there are many applications for the use of Dexmedetomidine in the field of procedural sedation in diagnostic and therapeutic procedures, as well as in fiber-optic intubation, and it is also licensed for use in the United States of America for these procedures (Candiotti et al., 2010) (Bergese et al., 2010), in addition to the effect of sedation there is an effect as an analgesic, as Dexmedetomidine and its effect on alpha 2 receptors in the centeral and in the spinal cord by inhibiting the flow of pain in the human body, such as the inhibition of substance P and glutamate (Vuyk et al., 2015).

Cardiovascular system: In terms of the effect on blood pressure, Dexmedetomidine affects blood pressure in both directions, as it raises blood pressure for a short period at the beginning of administration, especially during rapid administration of the drug, and then the continuous hypotension stage during drug administration, as the two effects are responsible for the alpha two receptors that work in the human body in different pathways. For hypertension it is mediated by α-2B and in patients with a slowed heart rate and a high stimulation of vagal nerve, treatment with anticholinergic (glycopyrrolate and atropine) has been found to be highly effective (Philipp, Brede, & Hein, 2002).

Central nervous system: Dexmedetomidine decreases cerebral blood flow and oxygen metabolic demand; however, its impact on intracranial pressure (ICP) is unknown. Through the α 2-adrenergic receptor, Dexmedetomidine modifies spatial working memory, improving cognitive function while also acting as a anxiolytic, analgesic and sedative (Franowicz & Arnsten, 1998),

Studies have found that it may have neuro-protection by lowering circulation and brain catecholamine levels, so regulating the ratio of cerebral oxygen supply, decreasing

excitotoxicity, and increasing blood-flow in the ischemic penumbra. It lowers glutamate concentrations, which are linked to cellular brain injury, especially in cases of subarachnoid hemorrhage. Dexmedetomidine reduces morphologic and functional consequences in the nervous system following ischemia (focal and global) and traumatic injury (Bekker & Sturaitis, 2005).

Respiratory system: Dexmedetomidine affects the patient so that it seems that the patient has entered a deep sleep (R. M. Venn, Hell, & Michael Grounds, 2000), On the other hand, it does not inhibit the human respiratory system even during high doses of it (Hsu et al., 2004), and it does not affect the respiratory rate or the oxygen saturation of the blood for patients who are not on mechanical ventilator (R. M. Venn et al., 2000). It maintains a degree of hypnosis and sedation without affecting the stability of the respiratory and circulatory system, so that it can be used as an option to calm patients in intensive care before removing the air intubation, due to the withdrawal symptoms that accompany this stage such as acute nervousness of patients, pain and instability in vital signs (Siobal, Kallet, Kivett, & Tang, 2006)

Endocrine and renal system: Dexmedetomidine inhibits the sympathetic reaction during a medical or surgical procedure by decreasing catecholamine secretion by peripherally acting on alpha 2 adrenergic receptors in peripheral presynaptic (Ebert, Hall, Barney, Uhrich, & Colinco, 2000). When using Dexmedetomidine for a short period, it was found that it is similar to Midazolam, but it differs from Etomidate in that it does not inhibit steroid-genesis (R. Venn, Bryant, Hall, & Grounds, 2001).

1.2.3.3 Indications

Dexmedetomidine can be used, as reported by the Food and Drug Organization, in many medical applications, as it can be used for sedation during the patient's stay in the intensive care departments, and it can be used during surgical and non-surgical procedures such as endoscopy.

It can also be used as a drug for patients who are not on mechanical ventilator and without advance air way like endotracheal tube, and its use has expanded to a large extent, as it has become used as a prevention and treatment for delirium, as it is used as analgesic and sleep aid in intensive care, and it can also be used to treat cases of alcohol withdrawal, all of that, because it is a safe medication on the respiratory and circulatory system.

In addition to being a sedative and analgesic at the same time, this is what specialists do not find in other sedative drugs (McLaughlin & Marik, 2016). Observing intensive care patients who were sedated with Dexmedetomidine, it was found that this drug delays the occurrence of delirium and reduces the incidence of its occurrence, as well as shortening its duration if it occurs compared to its counterparts of anesthesia drugs (Djaiani et al., 2016),

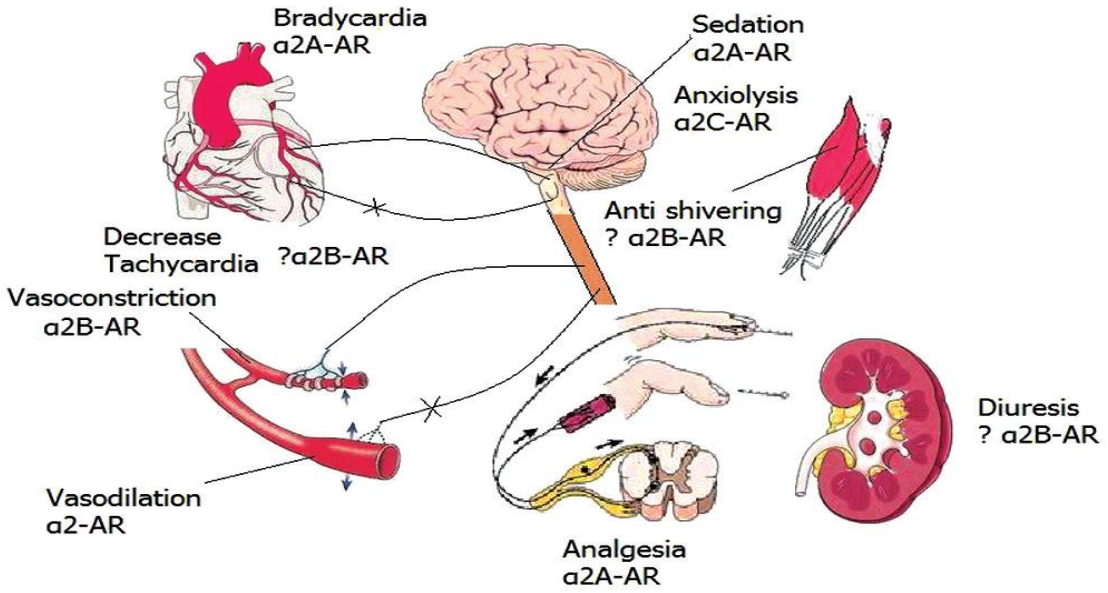
Research has also shown that this medication decrease the time of extubation process and reduces the patient's stay on the mechanical ventilator (Reade et al., 2016). Because of the effectiveness of this drug in terms of sedation and analgesia, it reduced the need for patients in intensive care for many drugs that either cover the analgesia part or sedation part.

In addition to the complications associated with the large number of drugs provided to patients, the Dexmedetomidine has proven its effectiveness in elderly patients after operations of open heart (D.-F. Zhang et al., 2019) Also, this drug has proven its effectiveness as a hypnotic and sleep aid in many cases that suffer from sleep disturbances (Alexopoulou et al., 2014) (Goucher Miranda, Krystal, & Fierro, 2017). It also proved highly effective in analgesia and in reducing the need for analgesics after surgical operations, and it was also noted that it masked the nausea reaction after operations anesthetize via general or spinal anesthesia (Blaudszun, Lysakowski, Elia, & Tramèr, 2011) (Chan, Maslany, Gorman, O'Brien, & McKay, 2016). In addition, the drug has been shown to hide the emergence of agitation (S. Kim, Kim, Lee, Song, & Koo, 2013) (Patel et al., 2010) (Dunn, Naik, Nemergut, & Durieux, 2016).

After the results have shown the effect of Dexmedetomidine in the prevention and treatment of delirium in intensive care patients, it was expected to see the same effect for delirium after surgical operations, but this was not observed. (Deiner et al., 2017)/ Finally, it has been has been found that Dexmedetomidine significantly prolong the duration of peripheral nerve blocks, with minimal systemic side effects and it has proven highly effective in this application (Kirksey, Haskins, Cheng, & Liu, 2015).

Figure 1:2

Physiology of various α2-adrenergic receptors



(Kaur & Singh, 2011)

1.2.3.4 Adverse reaction

One of the side effects of Dexmedetomidine is hypertension due to its effect on subtype B of alpha receptors when given in high concentration at a rate of less than ten minutes. Also, this drug causes hypotension due to its effect on subtype A of alpha receptors and reduce the secretion of noradrenaline from the sympathetic nervous system (Afshani, 2010). Long-term use of this drug leads to withdrawal symptoms accompanied by a sharp rise in blood pressure, headache and agitation (Morgan, Mikhail, & Murray, 2006), and other side effects have been reported, such as low calcium blood level and high blood sugar level, and it increases the acidity of the blood, causes a slowing of the heart rate, nausea and vomiting, and it has been classified as category C. for the expected risks during pregnancy (Afshani, 2010).

1.2.4 Midazolam

1.2.4.1 Mechanism of Action

Midazolam really does have a weak oral bioavailability and a 1.5 to 2.5 hour elimination half-life. Midazolam is converted to its active metabolite alpha-1 hydroxy Midazolam, which provides approximately 10% of the drug's effect. Liver CYP450 enzymes and glucuronide conjugation are involved in Midazolam metabolism. Midazolam's

mechanism of action is secondary or in-direct and is linked to GABA synthesis and benzodiazepine receptor affinity. A shared chloride channel couples two distinct GABA and benzodiazepine receptors. It increases the frequency in chloride channels openining. Membrane hyperpolarization and neural inhibition occur when both receptors are occupied. Midazolam's anticonvulsant properties are linked to the brain's motor pathways becoming overloaded with GABA. Midazolam relaxes the muscles via acting on the glycine receptors. anticonvulsant, anterograde amnesia, anxiolysis, and Sedation effects can all be explained by its impact on GABA receptors. The pharmacokinetics of Midazolam are also affected by age-related, hepatic, and renal impairment. Depending on the pH, Midazolam possesses both hydrophilic and lipophilic characteristics (Richter, 1981) (Spina & Ensom, 2007) (Olkkola & Ahonen, 2008) (Riss, Cloyd, Gates, & Collins, 2008).

1.2.4.2 Indications

There are many uses and justifications for the use of Midazolam In preference to other drugs, it is possible to give it intravenously in order to manage acute cases of seizures, induction of anesthesia and status epilepticus, As it can be given through intranasal and buccal routes which gives the possibility of many applications, especially for children even in adult cases, such as cases of seizures and sedation management during various surgical procedures and non-surgical procedures. This gives it superiority over many of its counterparts of drugs such as thiopental, where it achieves the desired degree of calmness and management of reactions, so its use has expanded in many diagnostic and therapeutic procedures (Reves, Fragen, Vinik, & Greenblatt, 1985) (McTague, Martland, & Appleton, 2018) (Walker, 2005).

1.2.4.3 Pharmacokinetic

Absorption: Midazolam can be absorbed through the gastrointestinal tract by giving it orally (Reves et al., 1985), as the patient begins to feel dizzy within fifteen minutes of oral administration, and its peak effect is thirty to ninety minutes after administration. (J. H. Kanto, 1985), Forty to fifty percent of the drug is absorbed during oral administration and its delivery to the circulatory system is due to its first-pass metabolism. Also, the results were similar during the administration of the drug through the nose, but the speed of response was greater during the nasal administration (Nordt & Clark, 1997)

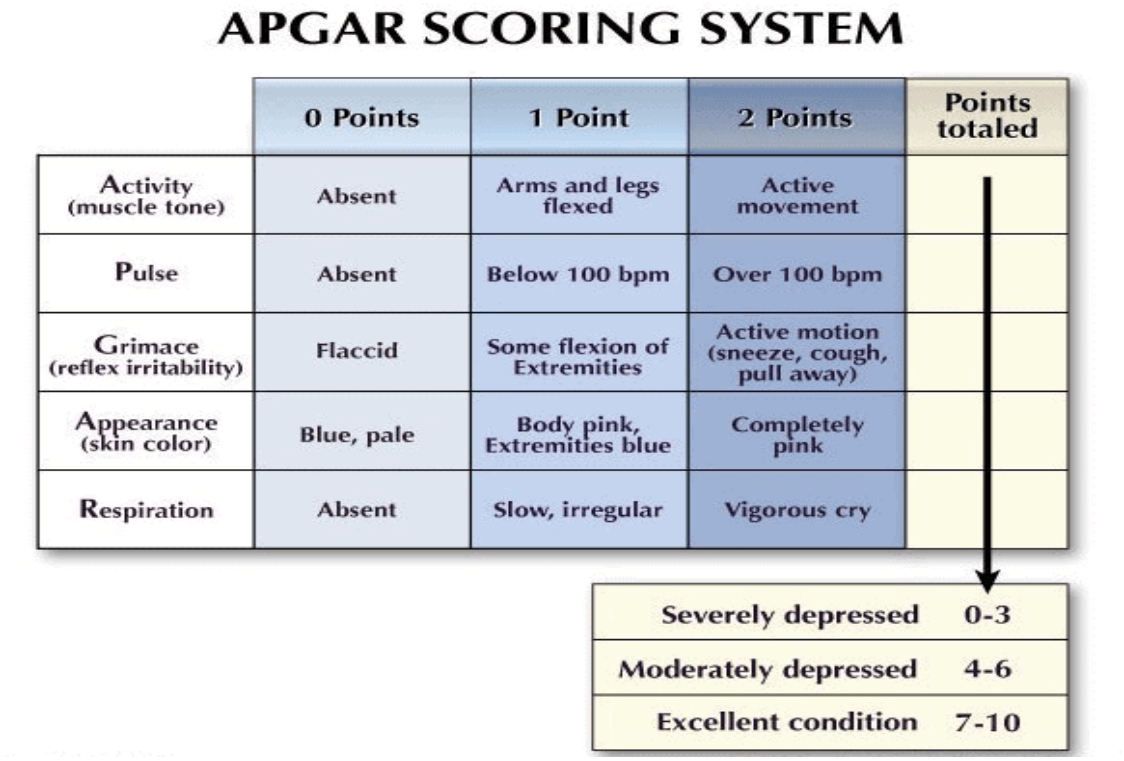
(Hartgraves & Primosch, 1994). Also, rectal administration of Midazolam has proven to be safe and effective, as the peak concentration in the blood plasma is reached within 9-20 minutes after administration (Hartgraves & Primosch, 1994). Whereas, Midazolam showed high efficacy during intramuscular administration, as the rate of its arrival in the blood plasma exceeds 90%, where its effect begins within five minutes and reaches its peak effect within 15-30 minutes (Taylor & Simon, 1990). Whereas, direct intravenous administration showed high efficacy, reaching its peak effect within three minutes (J. H. Kanto, 1985).

Distribution: The distribution volume of Midazolam is one to two and a half kilograms per liter in healthy people (Greenblatt & Abernethy, 1985) (Reves et al., 1985), and this number increases in people who suffer from obesity, due to its distribution in fatty tissues (Greenblatt & Abernethy, 1985) (Reves et al., 1985). It was also noted that this number increased in the elderly and during pregnancy (Dundee, Halliday, Harper, & Brogden, 1984). In an experiment on ewes, it was found that the Midazolam drug in the blood of ewes while giving the drug to mothers (Vree, Reekers-Ketting, Fragen, & Arts, 1984).

There is no information about the use of the drug in the first and second trimesters of pregnancy, and research about the last trimester is very limited, so that the Food and Drug Administration classified this drug as a pregnancy category D which means that it is only used in the absence of safe alternatives (Nordt & Clark, 1997). The drug was detected in the blood of newborns eleven hours after giving the drug to the mother before the caesarean section, and the Apgar scores (Figure 1:3) in the first and fifth minutes was normal 7-10 (J. Kanto, Sjövall, Erkkola, Himberg, & Kangas, 1983).

Figure 1:3

APGAR scoring system



(J. Kanto, Sjövall, Erkkola, Himberg, & Kangas, 1983).

Midazolam binds significantly with proteins in the blood plasma, especially albumin, with a free fraction representing four percent of the dose administered to the patient. (Reves et al., 1985). While this percentage increases to 6.5% in patients with chronic renal failure (Dundee et al., 1984). Midazolam affects the central and peripheral nervous system (J. H. Kanto, 1985), and it has a short half-life due to rapid tissue absorption. (Greenblatt & Abernethy, 1985).

It has not been proven that Midazolam penetrates the blood-cerebrospinal fluid (CSF) barrier (J. H. Kanto, 1985), and that brain baseline functions return to normal after an hour and a half of intravenous administration and after two hours of oral administration (Dundee et al., 1984). Midazolam is bio-transformed through hepatic microsomal oxidation followed by glucuronide conjugation, just like other benzodiazepines (Greenblatt & Abernethy, 1985), Midazolam is hydroxylated by cytochrome P450-3A4 to its primary metabolite, alpha-hydroxy-Midazolam, and inactive metabolites to a less level. These metabolites are then eliminated as glucuronide conjugates in the urine (Bauer et al., 1995).

Alpha-hydroxy-Midazolam is a pharmacologically active derivative of Midazolam with sedative characteristics similar to Midazolam. As a result of first-pass metabolism, this main metabolite is created in higher concentrations after oral treatment (J. H. Kanto, 1985), Midazolam's pharmacological activity may be enhanced by alpha-hydroxy-Midazolam (Dundee et al., 1984). Due to a 40-60% increase in hepatic blood flow after supination, plasma clearance of Midazolam is higher in supine patients. Midazolam metabolism may be accelerated during pregnancy (J. H. Kanto, 1985),Cimetidine and other cytochrome P450 inhibitors may significantly impair first-pass metabolism (Klotz, Arvela, & Rosenkranz, 1985) (Fee, Collier, Howard, & Dundee, 1987). Hepatic impairment may impair Midazolam elimination, leading in buildup, although this has never been confirmed (Dundee et al., 1984).

Elimination: From one and a half to three hours, the half-life of Midazolam is relatively short compared to diazepam, which extends for more than twenty hours (D. Stanski & Hudson, 1985). The pharmacological effect of Midazolam is prolonged from one to two hours (Wright et al., 1993). The half-life of Midazolam is reduced to 30 -120 minutes. In humans, the alpha-hydroxy-Midazolam metabolite has a half-life of 1 hour (J. H. Kanto, 1985), Midazolam plasma clearance is 5.8-9 ml/mm/kg in healthy people, however it is lower in the elderly (Dundee et al., 1984). Within 24 hours, over 90% of a radiolabeled Midazolam dosage taken orally is eliminated. The kidney is the primary route of elimination, with less than 10% eliminated in the stool within 5 days (Reves et al., 1985). In patients with renal impairment, Midazolam has been linked to accumulation and prolonged sedation (Bauer et al., 1995) (Vree et al., 1989).

1.2.4.4 Adverse Effects

There are many side effects associated with the use of Midazolam, such as nausea, vomiting, hiccups, and pain during administration at the site of intravenous administration. It also causes advanced memory loss, falls, dizziness and irritability in the elderly, so caution should be exercised while giving it at night or before driving a car to avoid the risk of falling or traffic accidents. In terms of vital signs, this drug may cause a drop in blood pressure and an irregular heartbeat, and in high doses it may cause respiratory failure, which may force the patient to be placed on a mechanical respirator extreme caution should be exercised while administering the drug to patients who drink alcohol or people who have aggressive behavior, which makes them more likely to

develop paradoxical effects such as intense crying, involuntary movements, incomprehensible words, and aggressive behavior, therefore, giving Midazolam with any other drug that depresses the nervous system such as Fentanyl increases the possibility of respiratory failure and may reach death. Long-term use of Midazolam leads to memory problems, so that this effect can only be partially reversed when the drug is discontinued (Korttila & Aromaa, 1980). As for pregnant women, this drug when used in the last trimester of pregnancy will cause withdrawal symptoms for the newborn and may also lead to many undesirable symptoms for the newborn, such as apnoeic spells, cyanosis, hypo-tonia, hyper-excitability, tremors and diarrhea (McElhatton, 1994). A third of people who use Midazolam for longer than four weeks experience a tolerance. In addition, when abruptly discontinuing the drug or rapidly reducing the dose of the drug, it will cause withdrawal symptoms. Among the withdrawal symptoms associated with benzodiazepines are the following: hypertension, tachycardia, diarrhea, nausea, vomiting, irritability, hypertonicity andclonus. Abruptly discontinuing the drug can cause status epilepticus. (Bartolomé, Cid, & Freddi, 2007; Vermeeren, 2004).

1.2.4.5 Contraindications

There are many contraindications to the use of Midazolam, including the following cases: hypotension, acute case of angle-closure glaucoma and patients in shock (Suri, 2000). Caution should be exercised when adjusting the dosage of the drug in the following cases: liver and kidney diseases, drug-dependent patients and alcohol patients, pregnant woman, comorbid psychiatric conditions and children. Administration in critically ill and elderly patients needs caution to avoid the accumulation of Midazolam active metabolites (Verbeeck, 2008). Caution should be exercised while administering the drug to patients with renal failure and people who use the following medication opioids, clarithromycin, erythromycin, sertraline, diltiazem, alcohol, protease inhibitors, antipsychotics, phenobarbital, rifampin, phenytoin and carbamazepine. In addition, grapefruit juice increases the activity of the drug due to its inhibition of the CYP450 enzyme, while on the other hand, St. plant reduces the effect of the drug by activating CYP450 (Bushra, Aslam, & Khan, 2011).

1.2.5 Fentanyl

1.2.5.1 Mechanism of Action

Fentanyl is a medication that is similar to other opioids. Fentanyl molecules contact with subclass of opioid receptor in the human body, concentrated in the brain inside specific neuroanatomical areas, and are particularly associated with emotion control, pain, and reward path way of addiction. It's a Mu-agonist biochemically. It can, however, activate additional opioid system receptors, including the delta and possibly the kappa-receptors. Analgesia is produced as a result of the activation of these receptors, mainly the Mu-receptors. In addition, the neurotransmitter dopamine (Da) is elevated in the reward centers of the brain, eliciting the traditional exhilaration and relaxing effects, and is typically linked to drug addiction (Comer & Cahill, 2019).

1.2.5.2 Pharmacokinetics

Fentanyl spreads quickly from plasma to highly vascular tissues after an intravenous bolus (brain, lung and heart). More 80% of the injected dose departs bloodstream within five minutes (Glass & Shafer, 2001), and more than 98% leaves after one hour (McClain & Hug Jr, 1980). Fentanyl redistributes to other areas, such as muscle and fat, and is rapidly eliminated from vascular tissue (Hug Jr & Murphy, 1981).

In a test of Fentanyl on rats, it was found that the drug's exit speed is less than the speed it enters the muscles due to its mass and fat and due to the fact that Fentanyl is highly lipid soluble, add that both are storage centers for this drug (Peng & Sandler, 1999). Due to redistribution rather than elimination, Fentanyl is short-lived following a single dose, Since Fentanyl has a long half-life, after large or multiple smaller shots of drug, accumulation occurs and redistribution has less efficiency in removing Fentanyl from the brain (D. R. Stanski & Hug, 1982). Norfentanyl and hydroxy-proprionyl-Fentanyl are the principal metabolites of Fentanyl in the liver (Mather, 1983).

Fentanyl metabolites have unknown pharmacologic activity, but they are believed to be very minimal (Mather, 1983). Less than ten percent of Fentanyl is excreted unchanged in the urine via kidney (McClain & Hug Jr, 1980).

1.2.5.3 Indications

Fentanyl is a drug similar to morphine, as it is considered one of the synthetic opioid drugs, but it is more effective than morphine, as it provides an ability to relieve pain fifty to one hundred times than that of morphine, giving the effect of one hundred micrograms of Fentanyl an effect similar to ten milligrams of morphine. Despite the similar effect, the mechanism of action of each is different. There are many medical applications in which Fentanyl is used, from pain relief to its use during anesthesia, where this drug is used as a pain reliever, especially for patients with kidney failure, as the metabolism of this drug is in the liver. It is also used as a pain reliever in cases of tolerance andit is used by cancer patients as a strong option for pain relief. In addition, it is usually used in the form of a patch and is also used as an adjunct treatment in cases of epilepsy, as for its use during anesthesia. There are also other uses of Fentanyl including using it for intensive care patients who are connected to the artificial respirator, and it is also used during surgeries in order to perform the operation without pain. (Glick et al., 2019; Hagedorn et al., 2018; Wakeman et al., 2019).

1.2.5.4 Adverse Effects

Fentanyl 's side effects are similar to other opioids, which produce addiction, respiratory depression. It may also lead to arrest, hypotension, constipation, confusion, euphoria, drowsiness, visual disturbances, nausea, dyskinesia, delirium, hallucinations, muscle rigidity, decrease level of consciousness, coma, and even death.

Drugslike cocaine or heroin and alcohol drink can increase the severity of these complications which put the patient in dangerous scenarios that may lead to death (Gallagher, 2018; Mars, Rosenblum, & Ciccarone, 2019; Ochalek, Parker, Higgins, & Sigmon, 2019).

1.2.5.5 Contraindications

Fentanyl is contraindicated in the following situations, : Biliary tract operations (it slows hepatic elimination of the Fentanyl), liver failure, intolerance to opioids, known allergy of Fentanyl , respiratory depression, Chronic obstructive pulmonary disease, asthma, obstructive sleep apnea,

Fentanyl is also contraindicated in pickwickian syndrome (hypoventilation related to obesity), contraindicated with CYP3A4 inhibitors like macrolide antibiotics erythromycin, roxithromycin, azithromycin and clarithromycin macrolide antibiotics or antifungal drugs especially azole group, and anti-viral like protease inhibitors, and abrupt discontinuation of a CYP3A4 inducer drug such as phenytoin which leads to an increase in concentrations of Fentanyl in blood plasma which prolongs the effects of opioids (Ramos-Matos, Bistas, & Lopez-Ojeda, 2021).

1.3 Problem statement

The optimum technique to reduce pain and provide an adequate amount of sedation via endoscopy is still being debated and researched (Triantafillidis et al., 2013), There has been no similar or relevant research in Palestine, but there has been little research on the same topic globally, and research on the use of Dexmedetomidine during endoscopy is still rare, despite the drug's usefulness, efficacy, and safety in many applications (Samson, George, Vinoth, Khan, & Akila, 2014),

There are numerous side effects related with the usage of Midazolam, including nausea, vomiting, hiccups, and pain at the site of intravenous delivery. It also causes advanced memory loss, falls, dizziness, and irritability in the elderly. Therefore, use caution when administering it at night or before driving a car is necessary to prevent the chance of falling or being involved in a traffic accident. This medication may induce a reduction in blood pressure and an irregular heartbeat, as well as respiratory failure in excessive doses, which may force the patient to be placed on a mechanical respirator.

Extreme caution should be exercised when administering the drug to patients who drink alcohol or have aggressive behavior, as they are more likely to develop paradoxical effects such as intense crying, involuntary movements, incomprehensible words, and aggressive behavior. therefore, giving Midazolam with any other drug that depresses the nervous system, such as Fentanyl , increases the possibility of developing paradoxical effects. Long-term use of Midazolam causes loss of memory, which can only be partially reversed when the medicine is stopped (Korttila & Aromaa, 1980). When used in the last trimester of pregnancy, this drug will create withdrawal symptoms for the infant as well as several negative symptoms for the newborn, such as apneic episodes, cyanosis, hypotonia, hyper-excitability, tremors, and diarrhea (McElhatton, 1994).

One-third of patients who use Midazolam for more than four weeks develop tolerance. Furthermore, abruptly quitting the medicine or rapidly reducing the dose of the drug will result in withdrawal symptoms. Benzodiazepine withdrawal symptoms include: hypertension, tachycardia, diarrhea, nausea, vomiting, irritability, hypertonicity, and clonus. Sudden discontinuation of the medication can result in status epilepticus (Bartolomé et al., 2007; Vermeeren, 2004),.

There are numerous contraindications to using Midazolam, such as hypotension, acute angle-closure glaucoma, and deffrent types shocks (Suri, 2000). Adjusting the dosage of the medication should be done with caution in the patients with liver and kidney disease, drug-dependent and alcohol-dependent individuals, pregnant women, comorbid psychiatric problems, and children.

To avoid the accumulation of Midazolam active metabolites in severely ill and elderly patients, administration should be done with caution (Verbeeck, 2008). Patients with renal failure and those using opioids, clarithromycin, erythromycin, sertraline, diltiazem, alcohol, protease inhibitors, antipsychotics, phenobarbital, rifampin, phenytoin, and carbamazepine should be administered with caution. Furthermore, grapefruit juice boosts drug activity by inhibiting the CYP450 enzyme, but St. plant lowers drug impact by activating the CYP450 enzyme (Bushra et al., 2011).

Finally, Midazolam toxicity is uncommon but can occur when combined with central nervous system depressants such as tricyclic antidepressants, opioids, and alcohol. In elderly patients, intravenous administration increased the risk, particularly in patients with chronic obstructive pulmonary disease. Flumazenil is the antidote for Midazolam poisoning, but one of the side effects of large dosages of Flumazenil is seizures. Furthermore, administering it via rapid intravenous infusion to older individuals with chronic obstructive pulmonary disease may result in significant adverse effects such as convulsions (Nordt & Clark, 1997). Furthermore, the role of sedation in endoscopy is important to promote patient's participation throughout the process; however, there is less evidence on the effects of Dexmedetomidine in upper endoscopy (K. H. Kim, 2014; Moon, 2014; Schweickert & Kress, 2008),

It is crucial to seek for alternative sedative medications that provide analgesia, amnesia, rapid patient recovery to the same level of consciousness as before the treatment, and have fewer adverse effects.

1.4 Aims of the study

The current study compares and investigates the efficacy and safety of Midazolam versus Dexmedetomidine in patients undergoing upper endoscopy at An-Najah National University Hospital in terms of respiratory, hemodynamic, analgesia, sedation, patient satisfaction, endoscopist satisfaction, and adverse effects.

primary outcomes: vital signs changes, including mean arterial pressure (MAP),oxygen saturation (SpO2),respiration rate and heart rate. Other primary outcomes include Ramsay sedation scale (RSS), time to full sedation, time to full recovery, additive dose of any sedative or analgesic drug when using of any drug to treat any side effect during procedure.

Secondary outcomes: patient and endoscopy specialist satisfaction and adverse effects regarding to patient: anxiety, gagging, discomfort and satisfaction, regarding to endoscopy specialist, secondary outcomes included: technical difficulty, satisfaction to the patient's sedation level, patient discomfort, patient retching and patient gagging.

1.5 Significance of study

Many factors contribute to patient's suffering when performing an endoscopy, including the dangers of anesthetic drugs, such as side effects, and complications associated with the endoscopy, as well as feelings of discomfort for patients and health care providers during the endoscopy due to not achieving the required depth of sedation, and many limitations that prevent the use of many options in anesthesia. Even when it requires the use of more than one medication to provide analgesia and sedation, it is necessary to look for a safe and effective option that has fewer side effects and increases patient and health care provider satisfaction. This is what Dexmedetomidine demonstrated during its widespread use in many medical, anesthetic, and therapeutic applications, as well as during endoscopy in countries other than Palestine. Endoscopy operations are one of the most significant procedures for the treatment, diagnosis, and evaluation of many illnesses. Patients under conscious sedation can maintain their responsiveness to pain and verbal

stimuli without compromising respiratory or cardiovascular function (Waring et al., 2003). In this type of sedation merges a benzodiazepine and opioid and is commonly used in minor surgeries and endoscopy (Huang et al., 2012) (Ozel et al., 2008). During the procedure pain, anxiety, fear and retching may let patients to be uncooperative, and it can induce harmful respiratory and cardiovascular effects (Eger et al., 2000). Endoscope is an irritating and painful procedure when performed without analgesia and sedation (Riphaus et al., 2005). To avoid mobility, pain, coughing, gagging and nausea, patients should be anesthetized while endoscopy. So, a sufficient analgesia and sedation agents should be given and monitored (Demiraran et al., 2007). It is critical to ensure that the client's protective reflexes are intact . The patient can recover from this type of anesthesia, regain his reactions, and return home on the same day, which benefits both the patient and the hospital, as the occupancy rate in hospitals is lowered and more cases can be received per day. Among the benefits of this sort of sedation over general anesthetic is the patient's faster recovery and ease of response to care providers when he awakens, as well as an improvement in his level of satisfaction and comfort (K. H. Kim, 2014; Moon, 2014; Schweickert & Kress, 2008). Sedative drugs are used to achieve analgesia, amnesia, and rapid patient recovery to the same level of consciousness as before the treatment (Wang et al., 2013). Despite the use of many sedatives, the "optimal" common method of endoscopic sedation has yet to be found. The most widely used sedative was Midazolam, however, in recent years, Dexmedetomidine has received increased attention. Dexmedetomidine is an adreno-receptor agonist that inhibits catecholamine responses and minimizes dose-dependence on heart rate and blood pressure. It is utilized as a sedative, anti-anxiety, pre-medication, and anesthetic adjuvant with little harmful effect on the respiratory system. (Lawrence & De Lange, 1997; Talke et al., 2000). A good sedation in gastrointestinal endoscopy helps health care providers and patients at the same time (Cohen et al., 2006; McQuaid & Laine, 2008), The purpose of this study was to compare the safety and efficacy of Midazolam versus Dexmedetomidine in sedation for upper gastrointestinal endoscopy in terms of respiratory, hemodynamic, analgesia, sedation, patient and endoscopy specialist satisfaction, and adverse effects for patients undergoing upper endoscopy at An-Najah National University Hospital.

1.6 Null Hypothesis

1. There are no significant differences (at P <0.05) related to the use of Dexmedetomidine versus Midazolam in respiration (respiratory rate, SPO2) in patients undergoing upper endoscopy at An-Najah National University Hospital.
2. There are no significant differences (at P <0.05) related to the use of Dexmedetomidine versus Midazolam in hemodynamic (systolic, diastolic blood pressure, MAP, heart rate) in patients undergoing upper endoscopy at An-Najah National University Hospital.
3. There are no significant differences (at P <0.05) related to the use of Dexmedetomidine versus Midazolam in sedation presented respectively by the Ramsay Sedation Scale (RSS; 1-6), in patients undergoing upper endoscopy at An-Najah National University Hospital.
4. There are no significant differences (at P< 0.05) related to use of Dexmedetomidine versus Midazolam in patient satisfaction in patients undergoing upper endoscopy at An-Najah National University Hospital.
5. There are no significant differences (at P< 0.05) related to use of Dexmedetomidine versus Midazolam in endoscopy specialist satisfaction in patients undergoing upper endoscopy at An-Najah National University Hospital.
6. There are no significant differences (at P< 0.05) related to use of Dexmedetomidine versus Midazolam in recovery time, in patients undergoing upper endoscopy at An-Najah National University Hospital.
7. There are no significant differences (at P< 0.05) related to use of Dexmedetomidine versus Midazolam in side effects, in patients undergoing upper endoscopy at An-Najah National University Hospital.

Chapter two
Literature Review

In order to acquire the required knowledge about comparison between Midazolam and Dexmedetomidine for patients undergoing upper endoscopy, the researcher collected the required information from the academic databases such as google scholar, scopus and pubmed by using several keywords: (Dexmedetomidine, Midazolam, sedation and upper endoscopy).

During a systematic review of twelve comparative studies between Midazolam and Dexmedetomidine during procedural sedation, it was discovered that Dexmedetomidine outperformed Midazolam in several axes, including analgesia, reliability, health care provider satisfaction, and patient satisfaction, while both showed a similar degree of safety on the respiratory and circulatory systems when administered in correct and accurate dose.

The findings revealed that combining local anesthetics with Dexmedetomidine is a viable option to Midazolam during procedural sedation (Barends, Absalom, van Minnen, Vissink, & Visser, 2017).

Through a meta-analysis in review of nine experimental studies on 657 patients to compare the drug Midazolam and Dexmedetomidine during the endoscopy procedure, five studies found that there is no difference between the two drugs in the effect on the concentration of oxygen in the blood. The results of six studies showed that there was no difference in the effect between the two drugs on the mean arterial pressure. As for the side effects, only four studies dealt with this matter, and they looked at the following side effects, which are: nausea and vomiting, respiratory depression, dysphoria, dizziness, reflux, pain and abdominal distention, It was found that the occurrence of side effects in the Dexmedetomidine group was less than in the Midazolam group (F. Zhang et al., 2016).

Another study compared the two drugs through the upper endoscopy using the following protocol retrospectively and randomized. The Dexmedetomidine group was given 0.3 mcg/kg of Dexmedetomidine and 1 mcg/kg Fentanyl intravenously ten minutes before

the procedure and followed directly by 0.2-0.3 mcg/kg/hr of Dexmedetomidine continuously until the acceptable degree of sedation was reached.

In the Midazolam group 0.05 mg/kg and 1 mcg/kg intravenous Fentanyl were used for ten minutes before the endoscopy, followed by 0.01 mg/kg intravenously every 2-5 minutes until the patient reached the desired degree of sedation, in addition to 1mcg/kg Fentanyl in case of need and pain control in both groups. The preference for the Dexmedetomidine group in terms of the MAP reading was lower in the Midazolam group and the blood oxygen concentration was more high in the Dexmedetomidine group. The satisfaction in the Dexmedetomidine group was higher. The results showed that there are no clinically significant complications in the two groups, and that the use of Dexmedetomidine is safe and effective in upper endoscopy (Wu, Chen, Zhang, & Chen, 2014).

In a comparative research between the two drugs during upper endoscopy, it was found that the safety and effectiveness of using Dexmedetomidine as an alternative to Midazolam in these cases. Results showed that the results of blood oxygen saturation, MAP, heart rate and respiratory rate were similar in the two groups while both showed satisfactory and similar results in terms of anxiety, discomfort and gagging, as well as patient satisfaction. The preferential results of Dexmedetomidine were shown in several aspects, namely, fewer side effects compared to Midazolam, less retching, and a significant increase in specialist satisfaction. The following protocol was used in sedation. In the Dexmedetomidine group 1 mcg/kg is started at ten minutes before the procedure, followed by 0.2 mcg/kg/hr until the end of the procedure while in the Midazolam group, 0.07 mg/kg is given, with a maximum of 5 mg immediately before the procedure. Add to this the use of a local anesthetic in both groups, using a throat spray of lidocaine by spraying four sprays (Demiraran et al., 2007).

Another study compared between Midazolam and Dexmedetomidine with the help of the drug Remifentanil as a pain reliever in both groups during the ERCP procedure.The efficacy and superiority of Dexmedetomidine was shown in several axes, where the following protocol was used: In the Midazolam group 0.05 mg/kg of Midazolam was given, and in the Dexmedetomidine group 1 mcg/kg was given over a period of ten minutes, followed in both groups by 0.05-0.2 mcg/kg/min of Remifentanil.

The results in terms of patient satisfaction were in favor of the Dexmedetomidine group, while the Midazolam group showed a higher incidence of decreased blood oxygen concentration than the other group, the period of recovery from sedation was longer in the Midazolam group than in the Dexmedetomidine group, while Dexmedetomidine showed less nausea reaction than in the Midazolam group during endoscopy (Lu, Li, Chen, & Qian, 2018).

Another study was conducted on elderly people over the age of eighty during an ERCP procedure in which the results supported the use of Dexmedetomidine. During a comparative study with Midazolam, the following protocol was used: In the group of Dexmedetomidine, the patients were given a dose of Dexmedetomidine 3 mcg/kg/hr intravenously for ten minutes then followed by 0.4 mcg/kg/hr intravenously until the end of the procedure. In addition to the dose of Midazolam given immediately before the procedure which is 2.5 mg intravenously, 2 mg Midazolam intravenously is given if the desired degree of sedation is not reached. until Ramsay 3-4. The second group took 2.5 mg Midazolam intravenously, followed by 2 mg Midazolam intravenously at the time of need to reach the desired degree of hypnosis, which is Ramsey 3-4.

The results showed the following: there were low incidence of cases of low blood oxygen concentration in the Dexmedetomidine group, and the median of the Midazolam dose used was lower. In addition to this, the systolic blood pressure reading and heart rate decreased in the Dexmedetomidine group, but no complications that led to heart failure or irregular heartbeats occured (Inatomi et al., 2018).

A study that included the age range (18-60) showed positive results for Dexmedetomidine through a comparative research between Midazolam and Dexmedetomidine during the ERCP procedure. In this study, the following protocol was used: In the Midazolam group 0.04 mg/kg of Midazolam was given intravenously in addition to 0.5 mg intravenously when needed to reach Ramsey 3-4. While in the Dexmedetomidine group, 1 mcg/kg intravenously was administered within ten minutes, then 0.5 mcg/kg/h intravenously were given to reach Ramsey 3-4. Each group was given 1 mcg/kg intravenously Fentanyl at the beginning of the procedure.

The results showed the following: In the Dexmedetomidine group, there was a decrease in heart rate, while there was no significant difference in the reading of blood pressure

and respiratory rate. The appearance of the gag reaction was more obvious in the Midazolam group than in the Dexmedetomidine group. The Dexmedetomidine group showed faster recovery than the Midazolam group. Finally, the satisfaction of patients and the endoscopy specialist was the higher in the Dexmedetomidine group (Sethi, Mohammed, Bhatia, & Gupta, 2014).

Another study compared between Midazolam and Dexmedetomidine during the ERCP procedure for age group 18-80. The following Protocol was used:In the Dexmedetomidine group 1 mcg/kg/hr intravenously was started at ten minutes before the procedure, followed directly by 0.2-0.7 mcg/kg/hr to achieve the desired sedation, which is Ramsey 3-4. In the Midazolam group 0.04 mg/kg intravenously were administered, followed by 0.5 mg intravenously as needed to achieve the required degree of sedation, which is Ramsey 3-4.

The results showed a lower heart rate in the Dexmedetomidine group, in terms of respiratory rate, but MAP results were similar, Whereas, regarding to side effects, nausea, vomiting, and coughing were observed in the Midazolam group, with none in the Dexmedetomidine group. As for the gagging, it was more observed in the Midazolam group than in the Dexmedetomidine group. The results also showed more satisfaction among the endoscopy specialists in the Dexmedetomidine group than in the Midazolam group (Kilic et al., 2011).

In the table 2:1 -Appendice D-, the previous studies that were explained in this chapter have been summarized.

Chapter Three
Methodology

3.1 Study design

This is a prospective and observational study.The diagrammatic representation of the design is outlined

Table 3:2

Study design: Prospective and observational *study.*

Number of group	Pre-test	Intervention	Post-test
One	O1	(Dexmedetomidine)	02
Two	O1	(Midazolam)	02

3.2 Study site and setting

Endoscopic department at An-Najah National University Hospital, Nablus, Palestine.

3.3 Population

Elective upper endoscopy outpatients, with American society of anesthesiologist grade one and two at An-Najah National University Hospital, Nablus-Palestine, between October 2021 and January 2022. The study has received approval from the Institutional Review Board (IRB) at An-Najah National University and the committee of Ethics at An-Najah National University Hospital whilst being conducted in line with the Declaration of Helsinki. All participants involved have received information about the purpose of the study and the study protocol alongside a written consent form which has been completed by every participant.

3.4 Sample and Sampling

With type one error alpha 0.05, type two error beta 20 %, and eighty percent power, the sample size to identify statistical significance was computed as 34 subjects for each group.

3.5 Sample size

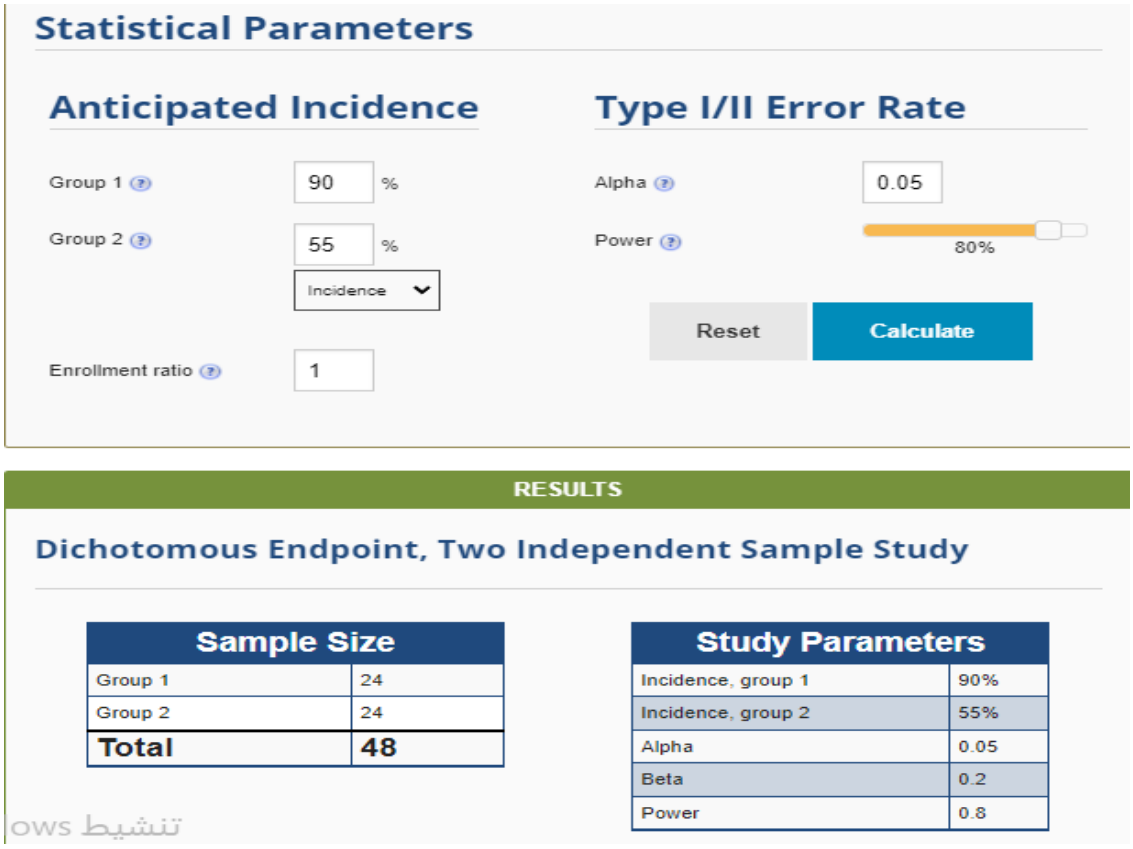
Using the online evidence-based clinical decision support computerized tool https://clincalc.com/stats/samplesize.aspx, inferences were used to calculate the sample size: type one error alpha is 5% and type two error beta is 20%. The anticipated incidence

and overall satisfaction with the procedure meant that results were higher than that of the patients in the midazolam group 90% versus 55%, P < 0.05.

Sample calculation based on previous studies that were performed and according to data obtained in these studies show that the patients in the Dexmedetomidine group had a higher anticipated incidence and overall satisfaction with the procedure result higher than that of the patients in the midazolam group (90% versus 55%, P < 0.05). The result of measuring the effect on 48 patients added to the 10% drop out. The sample size was calculated using benchmark 6ix sigma. According to this calculation, the sample size is 48 patients with an added 10% to cover the dropout. From 53 patients, the sample increased to 68. This means that there are 34 in every group. Bellow is the sample Size Calculator for 2 Proportion Test:

Figure 3:4

Sample size calculation



3.6 Inclusion criteria

Patients who met all of the following inclusion criteria were included:

1. American society of anesthesiologist grade one and tw

2. Elective upper endoscop
3. Aged 18 years to 60 years

3.7 Exclusion criteria

Participants who met one of the following exclusion criteria were excluded:

1. Inability to give consent
2. Allergy to any study drugs
3. Psychiatric disorder or using psychiatric drugs,
4. Addiction to opiates or sedatives
5. Alcoholism or history of it
6. Liver or renal disease
7. Uncooperative
8. Hypertension
9. A baseline systolic blood pressure less than 90 mmHg
10. Gastrectomy
11. Oncology or hematology disorders
12. Patients with cardiac anomalies
13. Pregnant

3.8 Tools

Tool 1: socio demographic data sheet

1. Initial letters of patient's name,
2. Case number,
3. Age in years,
4. Gender, male or female,
5. Height in cm,
6. Weight in kg,
7. BMI,
8. Ethanol use,
9. Tobacco use,

10. The highest completed level of education,
11. Indications for gastrointestinal endoscopy:
12. Dysphagia,
13. Esophageal reflux symptoms,
14. Dyspepsi,
15. Another

Tool 2: Time to full sedation and recovery

1. The time from the moment the medication is given to full sedation per min, RSS ≤4 (Time to full sedation)
2. Time from discontinuation of medication to full recovery per min, RSS = 2 (Time to full recovery)
3. Fully recovered after 15 min, 30 min, 45 min
4. Duration of endoscopy

Tool 3: follow up sheet Appendice (B)

Time-points:

1. Point 1: Before sedation.
2. Point 2: Before endoscopy and RSS 3-4.
3. Point 3: Significant value after the beginning of endoscopy or 5 min after the beginning of endoscopy if there is no significant value*.
4. Point 4. After endoscopy, (During one hour after endoscopy to take significant value*)

- significant value: bradycardia, tachycardia, hypotension, hypertension, desaturation, bradypnea, tachypnea, apnea, pain, gagging, anxiety, allergies, nausea, vomiting, retching, coughing and abnormal body movements.

3.9 The data sheet's validity

The researchers created the datasheet, which was then examined by the expert panel, including two anesthesiologists and an academic doctor, who specializes in nurse anesthetics, as well as one anesthesia nurse and one statistician. Their feedback was taken into consideration throughout the development of the data collection tool. This resulted

in data being collected in the most efficient manner possible which, in turn, led us to obtain the best possible data.

3.10 Data collection procedure

The data collection procedure follows the policy that has been used in the hospital.

Pre procedure

1. Explain procedure and the purpose of the study to the patient. Ensure that the consent form is obtained from the patient.
2. The endoscopist and staff in the procedure room were not aware of the sedation type. Upon a patients arrival, to the procedure room, envelopes were opened by the anesthesiologist only. The anesthesiologist was not involved in the research.
3. Review the patient's chart, nursing history and complete an assessment of illnesses including allergies and consent form.
4. Demographic data was obtained.
5. Be aware if the patient currently on anticoagulation therapy and if lab results are abnormal (PT, PTT, platelets).
6. Obtain baseline vital signs (Blood pressure, oximetry, pulse) and ASA level.
7. An emergency resuscitation cart should be available in the procedure room.
8. Inform the patient of restrictions related to driving a car, operating machinery, or making important decisions because sedation impairs patient reflexes and judgment so responsible adults must be available to accompany the patient home.
9. The nurse would connect the appropriate endoscope as ordered by the physician.
10. The nurse would look for suction, air, water, and white balance.
11. The nurse would set up the procedure area and equipment, ensuring that all necessary equipment, supplies, and drugs are on hand.

During procedure:

1. Wash hands.
2. Identify the patient.
3. Check the written doctors' orders.
4. Check the completeness of consent.

5. Check the patient is fasting.
6. Remove dentures if present.
7. Type patients' data in the computer.
8. Position the patient on their left lateral side.
9. Continues Cardiac monitoring with Pulse Oximeter and blood pressure
10. The doctor explains the procedure to the patient.
11. As a follow-up sheet, Readings should be taken and recorded, and follow up sheet should be filled. (point 1)
12. When patients arrive in a procedure room, envelopes are opened by the anesthesiologist only.
13. Anesthesia: When patients arrive at the procedure room, envelopes were opened by the anesthesiologist only and he did not involve in the research. patient admitted to the operating room without any pre-medication. Patients in the Dexmedetomidine group were given 0.3 mcg/kg of Dexmedetomidine and 1 mcg/kg Fentanyl intravenously ten minutes before the procedure and followed directly by 0.2-0.3 mcg/kg/hr of Dexmedetomidine continuously until the acceptable degree of sedation was reached, in the Midazolam group 0.05 mg/kg and 1 mcg/kg intravenous Fentanyl were used for ten minutes before the endoscopy, followed by 0.01 mg/kg of Midazolam intravenously every 2-5 minutes until the patient reached the desired degree of sedation, in addition to 1mcg/kg Fentanyl in case of need and pain control in both groups (Wu et al., 2014).
14. Standard monitoring (non-invasive blood pressure, respiratory rate, oxygen saturation, and Cardiac monitoring) performed and intravenous cannula G 20in antecubital ordered medication or fluid, prophylactic oxygen supply via a nasal cannula (1-2 L / min) or more during the endoscopy if desaturation occurs, Ramsay sedation scale (RSS) (Hayashi, et al 1991)maintained at 3–4 during endoscopy, all endoscopies performed with same techniques and performed by the same specialist (Waring et al., 2003; Wong, 2001).
15. Time to full sedation, min, recorded.
16. As a follow-up sheet, Readings should be taken and recorded, and a follow-up sheet should be filled. (point 2)

17. Put the mouthpiece inside the patient's mouth and ask him/her to gently bite down The mouthpiece.
18. While the doctor is slowly inserting the scope into the patient's mouth reassure the patient that everything, will be fine.
19. After 5 min as a follow-up sheet, Readings should be taken and recorded, and a follow-up sheet should be filled. (point 3)
20. If the doctor requires a biopsy, provide him the biopsy forceps and have him inspect the jaws by opening and shutting them
21. Off sedation.
22. After discontinuance of drugs and end of endoscopy a follow-up sheet within one hour after endoscopy to take significant value, Readings should be taken and recorded, and follow up sheet should be filled. (point 4)

Post procedure:

1. Close observation of vital signs, oxygen saturation, and consciousness.
2. Keep the patient on his or her left side until starting to wake up or keep him/her on his or her back with his head at 45 degrees if blood pressure is acceptable until the patient is awake and alert.
3. Time to full recovery, min, recorded.
4. The patient must remain fast till the gag reflex returns (at least 2 hours).
5. Reassure the patients that it's common to have mild soreness in their throat after the gastroscopy.
6. The Gastroscopy lasts for 10 to 15 minutes. When it is finished, patients either return to their room if they are an inpatient or stay in the unit until they are ready to go home.
7. A staff nurse may discharge the patient to the care of a family member after he/she met discharge criteria Post-Anesthesia Recovering Scoring System (PARS) for discharge criteria.
8. If a patient does not meet the discharge criteria then he can only be discharged by the physician.
9. Reinforce pre-procedure instructions regarding driving, operating machinery, and making decisions because of the effect of the medication.

10. Instruct the patient to notify the doctor of any sudden chest pain, abdominal pain, vomiting with blood, black stool, or fever.

Endpoints and evaluation

1. The main endpoint of efficiency quantity of Midazolam and Dexmedetomidine to reach satisfied sedation and pain managing with minimal or without complication.
2. The occurrence of any respiratory, circulatory or cardiac complications was monitored before, during and after the procedure for an hour to examine and document the effect of each of the two drugs on these systems in the body, oxygen desaturation considered if the oxygen saturation below ninety two percent for more than ten seconds, bradycardia is a heart rate less than fifty beats per minute or a twenty percent decrease from baseline and treated with 0.05 mg atropine intravenously, while tachycardia is a heart rate above 110 or an increase in baseline level of more than twenty percent, hypotension occurs while mean arterial pressure levels below 60 mmHg or twenty percent below baseline and treated with 5 mg ephedrine intravenously, andhypertension occurs if systolic blood pressure above 150 mmHg or twenty percent increase from baseline.
3. The quantity of anesthetics used, in addition to the analgesia, was also monitored
4. The quantity of medications supporting the circulatory system and heart was monitored and documented
5. Monitor and document all expected side effects during the session for both groups, such as retching, allergies, gagging, cough, nausea, vomiting and respiratory depression are recorded
6. Monitoring and documenting patient satisfaction before and after the procedure through these axes: Gagging, anxiety, discomforted and satisfaction.
7. Monitoring and documenting the specialist's satisfaction after the procedure through four axes: Satisfaction of patient’s sedation level, technical difficulty, gagging and retching
8. Monitor and document the time taken to access RSS 3 or 4
9. Monitoring and documenting the duration of the procedure

10. Monitoring and documenting the time taken from the end of the endoscopy or stopping the anesthesia medication, whichever is the latter, until full recovery is achieved
11. The patient is not considered full recovery until after achieving RSS2 and achieving PARS 10.

3.11 Ethical considerations

study get approval from the Institutional Review Board (IRB) at An-Najah National University and conducted in line with the Declaration of Helsinki (Shrestha & Dunn, 2019) and get approval from the Committee of Ethics at An-Najah National University Hospital. All subjects received information about the purpose of the study and the study protocol, written consent form which obtained from each subject, and has have right to withdraw or to refuse. Integrity, dignity, self-determination, confidentiality, voluntary and privacy of personal information of research patients were considered.

Information for the patient: A specialist physician performed an upper endoscopy in the hospital, An intravenous cannula applied in the arm to provide a drugs. Sedative drugs use to keep patient cooperative, relaxed and comfortable during endoscopy. The healthcare professional measure vital signs and ask some questions regarding the event before and after the procedure till the patient's discharge.Lie on your side on the operating table. The specialist physician gently insert the endoscope into the gasto intestinal tract, the endoscope is connected to a small camera in order to deliver the image to the digestive system, troubleshoot problems and increase safety during insertion, the procedure may take from fifteen to thirty minutes, the patient may fall asleep during the procedure, patient expected to stay in the hospital for an hour or two until the effect of the anesthetic drug leaves the body, finally, nausea or vomiting, stomach bloating, sore throat, and difficulty swallowing are expected post-endoscopy complications.

3.12 Project Time

October 2021 -January 2022

3.13 Data analysis plan

This study included 68 patients who underwent upper endoscopy under sedation of Midazolam or Dexmedetomidine, data were analyzed using SPSS software version 20

(Statistical Package for Social Sciences Inc, Chicago, IL). Using t-tes the continuous variables were expressed as mean ± standard deviation or number (%). The categorical variables were expressed as numbers and percentages (%). The normality of the data was tested using Kolmogorov-Smirnov. In the absence of normal distribution, the continuous variables were analyzed using the Mann Whitney U test. Intergroup comparison and analysis of categorical variables were performed using the chi-square test. A p value of ≤ 0.05 was considered statistically significant.

Chapter Four

Result

This study aimed to compare the Midazolam and Dexmedetomidine used for upper endoscopy performed under sedation, The primary outcome: vital signs changes, including mean arterial pressure, oxygen saturation , respiration rate, and heart rate of the patients and Ramsay sedation scale (RSS), time to full sedation, time to full recovery, an additive dose of any sedative or analgesic drug and if using of any drug to treat any side effect during the procedure. Secondary outcomes included: patient and endoscopy specialist satisfaction and adverse effects, regarding patient: anxiety, gagging, discomfort, and satisfaction, regarding endoscopy specialist: technical difficulty, satisfaction with the patient's sedation level, patient discomfort, patient retching, and patient gagging.

1**. Demographic Data of patients in Midazolam and Dexmedetomidine group**s

The study recruited 68 patients, who were randomly assigned to receive either Midazolam or Dexmedetomidine (n=34/group). Demographic and clinical data of the patients are shown in Table 4:3. There were no statistically significant differences between groups in sex distribution, age, BMI, smoking distribution and education level. While there was a significant difference in endoscopy duration between the two groups, Dexmedetomidine required 11.0 ± 1.9 minutes and Midazolam required 9.9 ± 1.5 minutes, p=0.008.

Table 4:3

Demographic Data of patients in Midazolam group and Dexmedetomidine group. Data is reported as Mean Standard deviation (SD) unless otherwise stated.

Variable	Midazolam group (n=34)	Dexmedetomidine group (n=34)	p
Age, year*	39.8 ± 13.0	40.8 ± 11.4	0.744
Sex, Male%/Female%	47.05%/52.95%	52.95% /47.05%/	0.809
Body mass index, kg/m2*	28.1 ± 6.0	28.4 ± 4.8	0.429
Duration of endoscopy, min*	9.9 ± 1.5	11.0 ± 1.9	0.008
Smoking%	35.29%	20.58%	0.280
Education level, n			
grammar school%	2.94%	0%	0.543
high school%	29.4%	20.59%	0.475
College%	38.23%	35.29%	0.841
graduate school%	29.4%	41.17%	0.542
*Mean ± SD			

2. Indications for endoscopy in Midazolam and Dexmedetomidine groups

When it came to endoscopic indications, there was a significant difference between the groups. When it came to dysphagia: 12/34 (35.3%) patients in the Midazolam group and 17/34 (50%) patients in the Dexmedetomidine group, p=0.032. There were also significant differences between the groups in terms of esophageal reflux, with 17/34 (50%) patients in the Midazolam group and 7/34 (20.5) patients in the Dexmedetomidine group, respectively, p=0.035. As well as significant differences in Dyspepsia across the groups 5/34 (14.7%) patients in the Midazolam group and 10/34 (29.4%) patients in the Dexmedetomidine group, p=0.031.(Table 4:4).

Table 4:4

Indications for endoscopy in Midazolam and Dexmedetomidine groups. Data presented as n(%)

Variable	Midazolam group (n=34)	Dexmedetomidine group (n=34)	p
Dysphagia%	35.29%	50%	0.032
Esophageal reflux symptoms%	50%	20.59%	0.035
Dyspepsia%	14.70%	29.41%	0.031

3. Pre-procedural expected patient satisfaction

Expected patient satisfaction before receiving Midazolam or Dexmedetomidine is not significantly different between the two groups for Satisfaction and discomfort (p >.05), but there is a significant difference between groups for gagging and anxiety. Mean gagging for Midazolam is lower than Dexmedetomidine 1.0± 1.1versus 1.6 ±1.1, p=0.020), and mean anxiety for Midazolam is higher than Dexmedetomidine, 2.6 ± 0.9 versus 2.1 ± 1.4, p=0.018 (Table 4:5).

Table 4:5

Pre-procedural expected patient satisfaction, discomfort, gagging and anxiety score. Data presents as mean (± SD)

Variable	Midazolam group (n=34)	Dexmedetomidine group (n=34)	p
Expected Satisfaction	7.7 ± 1.2	7.1 ± 1.9	0.228
Expected Discomfort	1.7 ± 1.6	2.1 ± 1.8	0.515
Expected gagging	1.0 ± 1.1	1.6 ± 1.1	0.020
Anxiety Score	2.6 ± 0.9	2.1 ± 1.4	0.018

4**. Post-procedural patient satisfaction**

Table 6 shows the patient satisfaction after receiving Midazolam or Dexmedetomidine. Except for the gagging score, there are significant variations between the two groups in terms of satisfaction, discomfort, and anxiety. (Table 4:6) There was a significant difference in satisfaction between the Dexmedetomidine group (9.1 ± 1.0) and the Midazolam group (8.06 ± 0.9), p=0.001. There was a significant difference in discomfort between the Dexmedetomidine group (0.7 ± 0.9) and the Midazolam group (1.7 ± 1.1), p=0.001. There was a substantial difference in anxiety between the Dexmedetomidine group 0.5 ± 0.8 and the Midazolam group 1.8 ± 1.4, p=0.001. When compared to the Midazolam group, the Dexmedetomidine group demonstrated much higher satisfaction, less discomfort, and less anxiety.

Table 4:6

Post-procedural patient satisfaction, discomfort, gagging and anxiety score. Data presents as mean (± SD)

Variable	Midazolam group (n=34)	Dexmedetomidine group (n=34)	p
Satisfaction (0-10 score)	8.06 ± 0.9	9.1 ± 1.0	0.001
Discomfort (0-10 score)	1.7 ± 1.1	0.7 ± 0.9	0.001
Gagging (0-10 score)	0.7 ± 0.9	0.6 ± 1.5	0.077
Anxiety (0-10 score)	1.8 ± 1.4	0.5 ± 0.8	0.001

5**. Endoscopy specialist satisfaction**

Patients receiving Dexmedetomidine had significantly better endoscopic specialist satisfaction than those receiving Midazolam (8.7±1.6 versus 8.2±1.0); P=0.001. Respectively. Patients taking Dexmedetomidine had significantly less discomfort than those receiving Midazolam (1.0 ± 1.4versus 1.8 ± 0.9); p=0.037. Patients taking Dexmedetomidine had considerably less gagging than those receiving Midazolam (0.8 ± 1.3 versus 1.0 ± 0.8; p=0.036).

Also Patients taking Dexmedetomidine had considerably less retching than those receiving Midazolam (0.5±1.1 versus 0.6±0.6; P0.013) (Table 7). There was a significant difference in technical difficulty between the Dexmedetomidine and Midazolam groups, with the Dexmedetomidine group scoring 1.1 ± 1.1vs the Midazolam group scoring 1.6 ±

0.8, p=0.035. In all facets of endoscopic specialist, the Dexmedetomidine group outperformed the Midazolam group (Table 4:7).

Table 4:7

Endoscopy specialist satisfaction, discomfort, gagging, retching, and technical difficulty. Data reported as Mean (± SD)

Variable	Midazolam group (n=34)	Dexmedetomidine group (n=34)	p
Satisfaction	8.2 ± 1.0	8.7 ± 1.6	0.001
Discomfort	1.8 ± 0.9	1.0 ± 1.4	0.037
gagging	1.0 ± 0.8	0.8 ± 1.3	0.036
Retching	0.6 ± 0.6	0.5 ± 1.1	0.013
Technical difficulty	1.6 ± 0.8	1.1 ± 1.1	0.035

6**. Recovery data in Midazolam and Dexmedetomidine groups**

For average recovery, Dexmedetomidine patients were recovered faster than Midazolam patients, Midazolam patients need 48.8 ± 6.0 min to recover while the Dexmedetomidine patients need 18.0 ± 5.2 min and this difference significant since the p <.05, Midazolam need 2.4 ± 7.7 min to sedate while the Dexmedetomidine need 9.5 ± 1.1 min and this difference significant since the p <.05 (Table 4:8).

Table 4:8

Recovery data in Midazolam and Dexmedetomidine groups. Data presented as Mean (±SD) and as n(%)

Variable	Midazolam group (n=34)	Dexmedetomidine group (n=34)	p
Time min RSS 3-4	2.4 ± 7.7	9.5 ± 1.1	0.001
Time min RSS =2	48.8 ± 6.0	18.0 ± 5.2	0.001
	Patients fully recovered, n (%)		
15 Min	0	17 (50%)	0.001
30 Min	0	17 (50%)	0.001
45 Min	34 (100%)	0	0.001

7**. Adverse effect**

Regarding side effect, table 4:9 represent the most side effect after receiving Midazolam or Dexmedetomidine, While assessing the following side effects, which are: hypertension, hypotension, tachycardia, bradycardia, hypoxia, tachypnea, bradypnea, apnea, coughing, vomiting, retching, nausea, allergies, and abnormal body movements.

The most frequent side effect was hypertension for both groups. It was found that the occurrence of side effects in the Dexmedetomidine group was less than in the Midazolam group but it was not significant.

Table 4:9

Adverse effects in Midazolam and Dexmedetomidine groups

Variable	Midazolam group (n=34)	Dexmedetomidine group (n=34)	p-value
Bradycardia%	8.82%	0%	0.076
Hypertension%	17.64%	17.64%	0.493
Coughing%	8.82%	2.94%	0.303
Tachycardia%	5.88%	0%	0.151
Nausea%	2.94%	0%	0.314

8**. Vital signs of the patients in both Midazolam and Dexmedetomidine groups**

Regarding vital signs, there is no significant difference between the Midazolam group and the Dexmedetomidine group, except for respiratory rate, Dexmedetomidine group has less rate compared to the Midazolam group 16.7 ± 1.9, 18.6 ± 4.7 respectively, p=0.028 (Table 4:10), And (Table 4:11) -Appendice (D)- showed the measurement for all vital signs at four points for two groups Midazolam and Dexmedetomidine, as a result, there are no significant differences for all points (MAP, HR, and SpO2), while there significant difference at point 3 and 4 in respiratory rate sign. Dexmedetomidine group has less rate compared to the Midazolam group.

Table 4:10

Vital signs of the patients in both Midazolam and Dexmedetomidine groups data displayed as Mean (± SD)

Variable	Midazolam group (n=34)	Dexmedetomidine group (n=34)	p
Mean Arterial Pressure	90.7 ± 6.3	91.4 ± 8.5	0.713
Heart Rate	80.7 ± 11.5	77.4 ± 11.6	0.238
oxygen saturation	97.7 ± 1.3	97.8 ± 2.5	0.861
Respiratory Rate	18.6 ± 4.7	16.7 ± 1.9	0.028

Chapter five
Discussion

5.1 Discussion

The result of the current study proved the efficacy and safety of using Dexmedetomidine and its superiority to Midazolam in many aspects, such as patient satisfaction, endoscopy specialists' satisfaction, stability of vital signs, and the lack of side effects, as well as the speed of recovery after procedure, which reduces the patient's stay in the hospital and increases the occupancy rate of the department to provide places for patients in a way faster. The importance of this research stems from the large number of side effects expected from the drug Midazolam, these findings are consistent with those of other research that have been published which were shown that the concomitant use of Midazolam with analgesia drugs increases the risk of respiratory and circulatory failure in patients (Vermeeren, 2004) Bartolomé et al., 2007) (Korttila & Aromaa, 1980; McElhatton, 1994), its toxicity, its conflict with many drugs, and the many caveats with many pathological conditions (Bushra et al., 2011; Verbeeck, 2008) Add to that the length of the patient's stay in recovery departments, which reduces the possibility of receiving other cases (Lu et al., 2018; Sethi et al., 2014). As a result, there was a need to look for a safe and effective alternative to meet the endoscopic anesthetic need.

During this research, Midazolam and Dexmedetomidine were compared in upper endoscopy only, and the drug Fentanyl was used as analgesia, as many researches (Sethi et al., 2014; Wu et al., 2014). But in other research, Remifentanil was used as an analgesia (Lu et al., 2018), another used topical lidocaine (Demiraran et al., 2007), Others, on the other hand, did not utilize analgesics and instead focused on treating pain with the effects that each of the two medications has on patients (Inatomi et al., 2018; Kilic et al., 2011).

The ratio of males to females in this study was randomly 1:1, While in other studies, the percentage of males was more than female, percentage was as follows 62% (Kilic et al., 2011), 55% (Wu et al., 2014) and 52% (Lu et al., 2018). On the contrary, the percentage of males was lower in other studies, and their percentage was as follows 44% (Demiraran et al., 2007), 46% (Inatomi et al., 2018) and 45% (Sethi et al., 2014).

There are significant difference between two groups for all binoculars of patient satisfactions except gagging score, Dexmedetomidine group showed higher satisfaction, less discomfort and less anxiety compared to Midazolam group.In Demiraran and his colleges research, both gropes showed satisfactory and similar results in terms of anxiety, discomfort and gagging, as well as patient satisfaction (Demiraran et al., 2007). In another study for the gagging assessment, more occurrence were observed in the Midazolam group than in the Dexmedetomidine group (Kilic et al., 2011). And in a systematic review study for 12articles including 883 patients, the superiority and merit of Dexmedetomidine over Midazolam was shown in patient satisfaction (Barends et al., 2017). Also in a meta-analysis for 9 eligible randomized controlled trials included 657 patients, the superiority of Dexmedetomidine was shown in patient satisfaction aspect over Midazolam (F. Zhang et al., 2016). In a retrospective randomized study for 60 adult patients, the satisfaction in the Dexmedetomidine group was higher, (Wu et al., 2014). The results in terms of patient satisfaction were preferable to the Dexmedetomidine group in a Prospective, randomized, single-blinded preliminary trial including 198 patients (Lu et al., 2018).Finally, the satisfaction of patients was the highest in the Dexmedetomidine group in a randomized controlled trial for 60 patients (Sethi et al., 2014).

The endoscopy specialist rating for all satisfaction aspects was significant difference between two groups, for patient satisfaction significantly higher in the patients receiving Dexmedetomidine than those receiving Midazolam (87.8±1.6 versus 8.2±1.0; P=0.001). Retching was significantly lower in patients receiving Dexmedetomidine compared with those receiving Midazolam (0.5±1.1 versus 0.6±0.6; P<0.001). Dexmedetomidine group showed better than Midazolam group in all Visual analog scale (VAS) score. This was in line with many studies that support the superiority of Dexmedetmomidine over Midazolam in the context of specialist satisfaction, and this was demonstrated by Barends and colleagues in the Systemic Review Study, which was conducted in 2017 (Barends et al., 2017). In another study, the endoscopy was performed by the same specialist, and the scale was weighed in favor of Dexmedetomidine in the context of the specialists' satisfaction, where several criteria were considered, which are the patient's discomfort from the specialist's point of view, satisfaction with the patient's sedation, technical problems, gagging and retching (Demiraran et al., 2007). In another study, to examine the specialists' satisfaction with using criteria from one to four, where one is poor, followed

by Fair, then Good, and then Excellent, the superiority of Dexmedetemomidine over the other drug was shown through this scope (Sethi et al., 2014). In another study, a tool with two options, either satisfied or very satisfied, was used to assess the specialist's satisfaction, and the results showed similar results to the previous one with the superiority of Dexmedetomidine (Kilic et al., 2011). In the research conducted by Zhiqiang Lu and his colleagues in a study that included 198 patients, it was found that the specialist's satisfaction in the Dexmedetomidine group is not different from his satisfaction in the Midazolam group. A scale of one to six was used to assess their satisfaction, with six being very satisfactory (Lu et al., 2018).

For average recovery, Dexmedetomidine patients were recovered faster than Midazolam patients, Midazolam patients need 48.8 ± 6.0 min to recover while the Dexmedetomidine patients need 18.0 ± 5.2 min and this difference significant since the $p < .05$, Midazolam need 2.4 ± 7.7 min to sedate while the Dexmedetomidine need 9.5 ± 1.1 min and this difference significant since the $p < .05$. One of the studies that used a mechanism to assess the time required to recover from sedation, as the time was calculated from the moment the procedure ended until reaching modified ramsay sedation score 2, it showed that the duration of recovery in the Dexmedetomidine group is shorter than in the Midzolam group, but the difference does not constitute a statistical difference (Lu et al., 2018). Further research showed that ninety percent of the Dexmedetomidine group achieved a Modified Aldrete score of nine or more within five minutes of completing the procedure, while seventeen percent of the Midazolam group showed the same result after the same period and the difference was statistically different (Sethi et al., 2014).

Regarding to vital signs, there are no significant difference between Midazolam group and Dexmedetomidine group, except respiratory rate, Dexmedetomidine group has less rate compared to Midazolam group 16.7 ± 1.9, 18.6 ± 4.7 respectively. In a review of a group of studies examining the safety of Dexmedetomidine on the respiratory system compared to Midazolam, it was found that twenty cases of hypoxemia occurred in the Dexmedetomidine group compared to twenty-four cases. So that this research included an analysis of evidence for seven hundred and sixty-seven cases, and this difference was not statistically significant, while both showed safety in terms of affecting the circulatory system in the same research, so that during the analysis of the data, the striking results were those that were mentioned in eight studies, where there was a drop in blood pressure

for ten patients in the Dexmedetomidine group compared to seven patients in the Midazolam group and this difference is not statistically different, and two of the studies that were analyzed showed the emergence of some cases of high blood pressure in the Midazolam group (Barends et al., 2017).In analyzing the results of five studies with no significant heterogeneity in data, it was found that there is no difference between the two drugs in the effect on the concentration of oxygen in the blood, the results of six studies with no significant heterogeneity in datashowed that there was no difference in the effect between the two drugs on the mean arterial pressure (F. Zhang et al., 2016). In the research conducted by Wei Wu and his colleagues the preference for the Dexmedetomidine group in terms of the mean arterial pressure reading was lower in the Midazolam group, the blood oxygen concentration was more high in the Dexmedetomidine group (Wu et al., 2014). In another study the results showed the following that blood oxygen saturation, mean arterial pressure, heart rate and respiratory rate were similar in the two groups (Demiraran et al., 2007). While the Midazolam group showed a higher incidence of decreased blood oxygen concentration than the other group (Lu et al., 2018). The results in terms of safety, there were low incidence of cases of low blood oxygen concentration in the Dexmedetomidine group, and also in the Dexmedetomidine group the median of the Midazolam dose used was lower; In addition to this, the systolic blood pressure reading and heart rate decreased in the Dexmedetomidine group, but no complications that led to heart failure or irregular heartbeats (Inatomi et al., 2018). Further research showed that in the Dexmedetomidine group, there was a decrease in heart rate, while there was no significant difference in the reading of blood pressure and respiratory rate (Sethi et al., 2014). In the research conducted by Kilic and his colleagues the results showed a lower heart rate in the Dexmedetomidine group, in terms of respiratory rate and MAP the results were similar (Kilic et al., 2011).

While assessing the following side effects, which are: hypertension, hypotension, tachycardia, bradycardia, hypoxia, tachypnea, bradypnea, apnea, coughing, vomiting, retching, nausea, allergies and abnormal body movements. The most important and most frequent side effect was hypertension for both groups.Eighteen times side effects occurred in the Midazolam group, and they were in the following numbers in each symptom: three in bradycardia, six in hypertension, three in coughing, three in hypoxia, two in

tachycardia, one in nausea. Compared to the Dexmedetomidine group, in which five times side effects occurred, four of which were in hypertension and one in coughing. It was found that the occurrence of side effects in the Dexmedetomidine group was less than in the Midazolamgroup.In another study, as for the side effects, only four studies dealt with this matter, and they looked at the following side effects, which are: nausea and vomiting, respiratory depression, dysphoria, dizziness, reflux, pain and abdominal distention, It was found that the occurrence of side effects in the Dexmedetomidine group was less than in the Midazolam group (F. Zhang et al., 2016). But in another study the results showed that there are no clinically significant complications in the two groups, and that the use of Dexmedetomidine is safe and effective in upper endoscopy (Wu et al., 2014). While the preferential results of Dexmedetomidine were shown in several aspects, namely, fewer side effects compared to Midazolam, less retching, and a significant increase in specialist satisfaction (Demiraran et al., 2007). In another study Dexmedetomidine showed less nausea reaction than in the Midazolam group during endoscopy (Lu et al., 2018). Inatomi and his colleagues conclude that, it is no complications that led to heart failure or irregular heartbeats (Inatomi et al., 2018). In gaging assessment Sethi conclude that the appearance of the gag reaction was more in the Midazolam group than in the Dexmedetomidine group (Sethi et al., 2014). Finally Killic and his colleagues conclude that regarding to side effects, nausea, vomiting, and coughing were observed in the Midazolam group, with none in the Dexmedetomidine group (Kilic et al., 2011).

5.2 Conclusion

Dexmedetomidine outperformed Midazolam in terms of recovery time, patient satisfaction, endoscopy specialist satisfaction, discomfort, anxiety and retching, Dexmedetomidine appears to be a useful alternative to Midazolam for sedating patients during upper endoscopy because it is both safe and effective.

5.3 Recommendations

1. The use of Dexmedetomidine in the sedation of patients during upper endoscopy is considered a superior option over Midazolam.
2. Dexmedetomidine is a safe and effective option with very satisfactory results after anesthesia, in terms of complications and rapid recovery.

3. The lack of research on the same subject and its support for the superiority of Dexmedetomidine prompts more research to be conducted on the enhancement of its use in more than one field.
4. The need for more research to support the result of my research and similar research that supports the majority of my research results.

5.4 Limitations

1. The lack of published research on the same topic, made it more difficult to obtain more comparisons.
2. Fear of new anesthetic options, such as the use of Dexmedetomidine, as it is a new option within the hospital.

List of Abbreviations

ASA	American Society of Anesthesiologists
CYP	Cytochromes P
ERCP	Endoscopic retrograde cholangiopancreatography
G	Gauge
GABA	Gamma aminobutyric acid
hr	Hour
ICP	intracranial pressure
ICU	intensive care unit
IRB	institutional review board
IV	Intravenous
kg	kilogram
L	Litter
MAP	Mean arterial pressure
MAS	Modified Aldrete Score
mcg	Microgramme
min	Minute
PT	Prothrombin time
PTT	Partial thromboplastin time
RSS	Ramsay Sedation Scale
SD	Standard deviation
SPO2	Oxygen saturation
VAS	Visual analog scale

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Appendices

Appendice (A)

consent to participate in a scientific research

نموذج طلب موافقة على المشاركة في بحث علمي

عنوان الدراسة: مقارنة بين دوائي Dexmedetomidine و Midazolam للمرضى الذين يخضعون لتنظير الجهاز الهضمي العلوي في مستشفى جامعة النجاح الوطني. دراسة كمية، مستقبلية، عشوائية.

اسم الباحث الرئيسي: إبراهيم محمد غول

المشرفين على البحث: د. عائدة ابو السعود القيسي (مشرفاً اكاديمياً) د. وائل صدقة (مشرفا اكلينيكيا)

ملخص البحث: نقوم بهذه الدراسة استيفاء لمتطلبات التخرج من برنامج ماجستير تمريض التخدير في جامعة النجاح الوطنية وهي دراسة سريرية لمقارنة دواء Dexmedetomidine و Midazolam للمرضى الذين يخضعون لتنظير الجهاز الهضمي العلوي وبحث افضلية الدوائين في الكفائة والأمان من خلال مراقبة العلامات الحيوية وعمق التخدير والجرعة المستهلكة وادارة الالم ومراقبة المضاعفات والاعراض الجانبية الناجمة عن كل منهما وتقييم رضاء المريض واخصائي المناظير لكل دواء منهما.

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

تم اختيار فئة المرضى الذين تنطبق عليهم المعايير التالية: بأن تكون حالتهم المرضية من الدرجة الاولى والثانية حسب تقييم جمعية التخدير الامريكية وأن يكون عمر المريض من 18 الى 60 عام وستبدأ الدراسة من لحظة دخول المشارك الى المستشفى وصولا الى خروجه من المستشفى.

المخاطر المتوقعة والخصوصية:

ليست هنالك اي مخاطر للدراسة سواء نفسية او جسدية، سيتم حفظ خصوصيتك كمشارك بالدراسة وسوف يتم التكتم على هويتك وسيبقى اسمك طي الكتمان والمكان الوحيد الذي سيتم ذكر اسمك فيه هو نموذج الموافقة على المشاركة

في الدراسة. سوف يتم التعامل مع العينة والمعلومات الخاصة بك بطريقة الترميز حماية لخصوصيتك، ويحق لك الانسحاب من البحث متى شئت من دون أن يأثر ذلك عليك او على الرعاية الطبية التي سوف تتلقاها.

المنافع المتوقعة:

استخدام دواء ال Dexmedetomidine من المتوقع ان يكون ذو كفاءة وأمان اعلى من دواء ال Midazolam من حيث ثباتية العلامات الحيوية وعمق التخدير وكمية الجرعة المستخدمة بافضل نتيجة واقل اعراض جانبية ومن جهة ادارة الالم ورضاء المريض ورضاء اخصائي المناظير.

طريقة التواصل مع الباحث:

إذا كانت لديك اي سؤال او استسفار عن الدراسة يمكنك التواصل مع الباحث (ابراهيم محمد غول) بكل رحابة وفي اي وقت عن طريق (الهاتف: 0597651580) أو البريدالإلكتروني Ibrahim.sgs96@gmail.com

توقيع المشاركة في البحث:

لقد حصلت على شرح مفصل عن الدراسة وأهدافها وإجراءاتها، ومنافعها، والمخاطر المحتملة. ولقد فهمت كافة المعلومات التي قدمت لي وتمت الإجابة كل أسئلتي. لذا فأنني أوافق وبمحض ارادتي على المشاركة في هذه الدراسة.

الاسم:..... التوقيع:.....

التاريخ:.....

Appendice (B)

Tool

Tool 1: Demographic data:

Demographic data
Initial letters of patient's name
Case number
Sex, male/female
Age/years
Weight/kg
Height/cm
BMI
Ethanol use
Tobacco use
The highest completed level of education
Indications for gastrointestinal endoscopy
* Dysphagia
* Esophageal reflux symptoms
* Dyspepsi
* Another

Tool 2: Time to full sedation and recovery:

Time to full sedation and recovery
The time from the moment the medication is given to full sedation per min, RSS3−4 (Time to full sedation)
Time from discontinue of medication to full recovery per min, RSS = 2 (Time to full recovery)
Patients fully recovered: 15 min, 30 min, 45 min
Duration of endoscopy

Tool 3: follow up sheet

Item:	Point1	Point2	Point3	Poin4
Patient follow up:				
Heart rate, beats/min				
Mean arterial pressure, mmHg				
Systolic, mmHg				
Diastolic, mmHg				
Pulse oximetry, SpO2				
Respiratory rate				
Total dose of Midazolam/mg (at the end of research written by anesthasoligist)	*	*	*	
Total dose of Dexmedetomidin / µg (at the end of research written by anesthasoligist)	*	*	*	
Total dose of Fentanyl / µg	*	*	*	

(at the end of research written by anesthasoligist)				
Total dose of Atropine/mg	*	*	*	
(at the end of research written by anesthasoligist)				
Total dose of Ephedrine/mg	*	*	*	
(at the end of research written by anesthasoligist)				
PARS 0-10	*	*	*	
Patient satisfaction:				
Satisfaction (0 = none, 10 = intolerable) Visual analog scale VAS		*	*	
Discomfort (0 = none, 10 = intolerable) VAS		*	*	
Anxiety (0 = none, 10 = severe) VAS		*	*	
Gagging (0 = none, 10 = severe) VAS		*	*	
Item:	Point1	Point2	Point3	Poin4
Adverse effects:				
Hypertension				
Hypotension				
Tachycardia				
Bradycardia				
Hypoxia				
Tachypnea				
Bradypnea				
Apnea				
Coughing				
Vomiting/retching				
Nausea				
Allergies				
Abnormal body movements				
Endoscopist follow up (satisfaction):				
Patient discomfort (0 = none, 10 = severe) VAS	*	*	*	
Gagging (0 = none, 10 = severe) VAS	*	*	*	
Retching (0 = none, 10 = severe) VAS	*	*	*	
Satisfaction of patient's sedation level (0 = very dissatisfied, 10 = very satisfied) VAS	*	*	*	
Technical difficulty (0 = easy, 10 = very demanding) VAS	*	*	*	

- **There is no need for documentation**

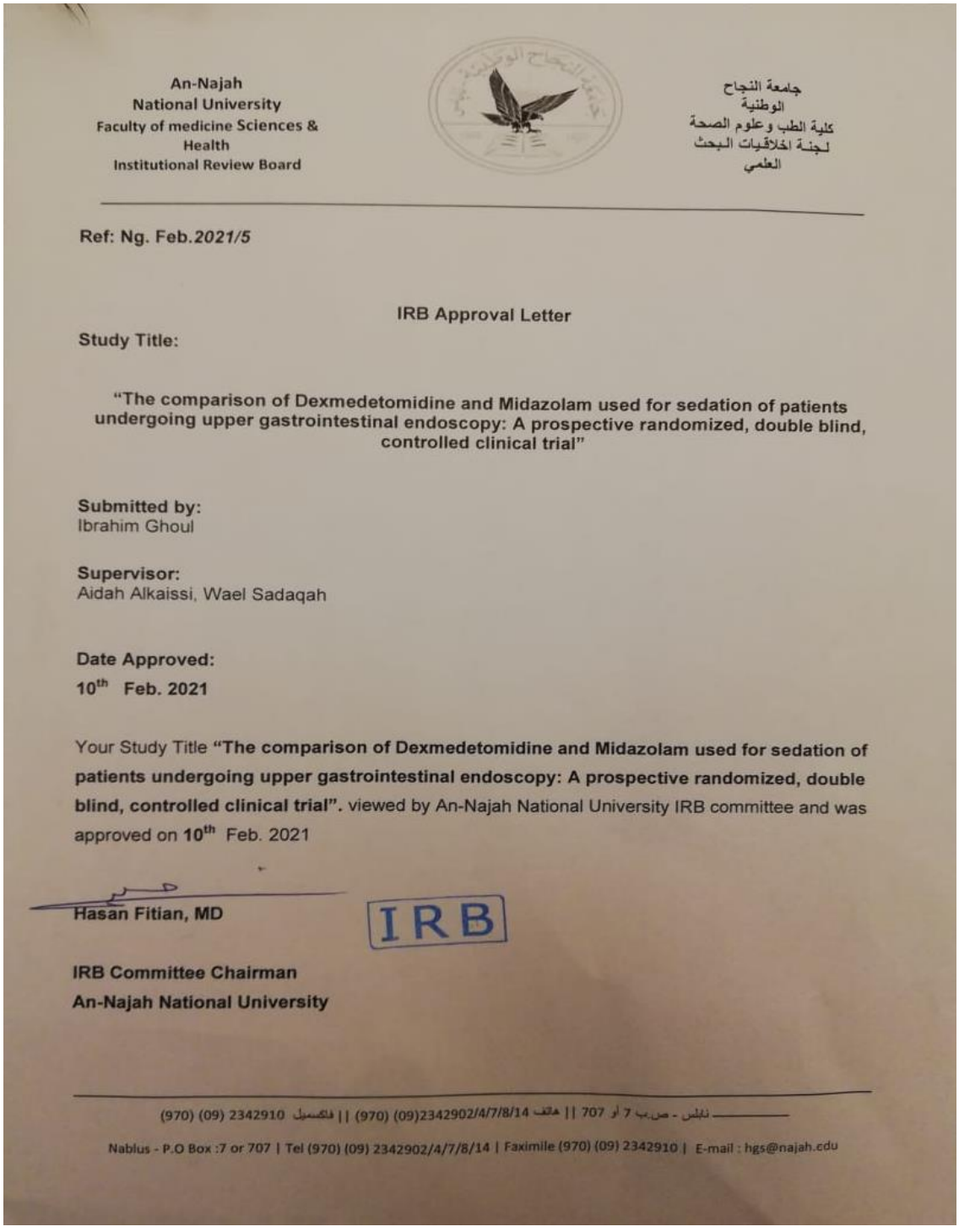
Time-points:

- Point 1. Before sedation.
- Point 2. Full sedation before endoscopy.
- Point 3. Significant value after beginning of endoscopy or 5 min afterbeginning of endoscopy if no significant value*.
- Point 4. After completion of endoscopy and discontinuance of drugs, (During one hour after examination in 15 minutes interval to take significant value*)

- significant value: bradycardia, tachycardia, hypotension, hypertension, desaturation, bradypnea, tachypnea, apnea, pain, gagging, anxiety, allergies, nausea, vomiting/retching, coughing and abnormal body movements.

Appendice (C)

IRB



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

جامعة النجاح
الوطنية
كلية الطب وعلوم الصحة
لـجنـة اخلاقيات البحث
العلمي

Ref: Ng. Feb.*2021/5*

IRB Approval Letter

Study Title:

"The comparison of Dexmedetomidine and Midazolam used for sedation of patients undergoing upper gastrointestinal endoscopy: A prospective randomized, double blind, controlled clinical trial"

Submitted by:
Ibrahim Ghoul

Supervisor:
Aidah Alkaissi, Wael Sadaqah

Date Approved:
10th Feb. 2021

Your Study Title **"The comparison of Dexmedetomidine and Midazolam used for sedation of patients undergoing upper gastrointestinal endoscopy: A prospective randomized, double blind, controlled clinical trial".** viewed by An-Najah National University IRB committee and was approved on **10th** Feb. 2021

Hasan Fitian, MD

IRB

IRB Committee Chairman
An-Najah National University

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Appendice (D)

Tables

Table 2:1

Summary of literatures in literature review.

Author, Study Design, Size	Topic	Protocol	Conclusion
(Barends et al., 2017) A Systematic Review study 12 articles 883 patients	”Dexmedetomidine versus Midazolam in Procedural Sedation. A Systematic Review of Efficacy and Safety”	A Systematic Review study including adult, human, age over eighteen and clinical trial	Superiority of Dexmedetomidine was shown in several axes analgesia, reliability, health care provider satisfaction and patient satisfaction, while both showed a similar degree of safety on the respiratory and circulatory systems during their administration in correct and accurate doses. The results showed that the combined use of local anesthetics with Dexmedetomidine constitutes a suitable alternative to Midazolam during procedural sedation
(F. Zhang et al., 2016) meta-analysis 9 eligible Randomized controlled trials 657 patients	”Dexmedetomidine versus Midazolam for sedation during endoscopy: A meta-analysis”	Randomized controlled trials compared between Midazolam and Dexmedetomidine conscious sedation for outpatients undergoing endoscopy procedures and American Society of Anesthesiologists grade one to three	In analyzing the results of five studies, it was found that there is no difference between the two drugs in the effect on the concentration of oxygen in the blood. The results of six studies showed that there was no difference in the effect between the two drugs on the mean arterial pressure, as for the side effects. Only four studies dealt with this matter, and they looked at the following side effects, which are: nausea and vomiting, respiratory depression, dysphoria, dizziness, reflux, pain and abdominal distention, It was found that the occurrence of side effects in the Dexmedetomidine group was less than in the Midazolam group

(Wu et al., 2014) retrospective randomized study 60 adult patients	”Dexmedetomidine versus Midazolam for sedation in upper gastrointestinal endoscopy”	Dexmedetomidine group was given 0.3 mcg/kg of Dexmedetomidine and 1 mcg/kg Fentanyl intravenously ten minutes before the procedure and followed directly by 0.2-0.3 mcg/kg/hr of Dexmedetomidine continuously until the acceptable degree of sedation was reached, in the Midazolam group 0.05 mg/kg and 1 mcg/kg intravenous Fentanyl were used for ten minutes before the endoscopy, followed by 0.01 mg/kg intravenously every 2-5 minutes until the patient reached the desired degree of sedation, in addition to 1mcg/kg Fentanyl in case of need and pain control in both groups	preference for the Dexmedetomidine group in terms of the MAP reading was lower in the Midazolam group, the blood oxygen concentration was more high in the Dexmedetomidine group, and the satisfaction in the Dexmedetomidine group was higher, the results showed that there are no clinically significant complications in the two groups, and that the use of Dexmedetomidine is safe and effective in upper endoscopy
(Demiraran et al., 2007) prospective, randomized study 50 adult patients	” The comparison of Dexmedetomidine and Midazolam used for sedation of patients during upper endoscopy”	In the Dexmedetomidine group 1 mcg/kg is started at ten minutes before the procedure, followed by 0.2 mcg/kg/hr until the end of the procedure, in the Midazolam group 0.07 mg/kg is given,	The results of blood oxygen saturation, MAP, heart rate and respiratory rate were similar in the two groups. While both showed satisfactory and similar results in terms of anxiety, discomfort and gagging, as well as patient satisfaction. While the preferential results of Dexmedetomidine were shown in several aspects, namely, fewer side effects compared to Midazolam,

		with a maximum of 5 mg immediately before the procedure. Add to this the use of a local anesthetic in both groups, using a throat spray of lidocaine by spraying four sprays	less retching, and a significant increase in specialist satisfaction
(Lu et al., 2018) A Prospective, Randomized, Single-Blinded Preliminary Trial 198 patients	”Efficacy of a Dexmedetomidine-Remifentanil Combination Compared with a Midazolam-Remifentanil Combination for Conscious Sedation during Therapeutic ERCP”	In the Midazolam group 0.05 mg/kg of Midazolam was given, and in the Dexmedetomidine group 1 mcg/kg was given over a period of ten minutes, followed in both groups by 0.05-0.2 mcg/kg/min of remifentanil	patient satisfaction was in favor of the Dexmedetomidine group, while the Midazolam group showed a higher incidence of decreased blood oxygen concentration than the other group. The period of recovery from sedation was longer in the Midazolam group than in the Dexmedetomidine group, while Dexmedetomidine showed less nausea reaction than in the Midazolam group during endoscopy
(Inatomi et al., 2018) retrospective randomized study 62 aged over 80 years	”Dexmedetomidine is safe and reduces the additional dose of Midazolam for sedation during ERCP in very elderly patients”	In the Dexmedetomidine group, the patient is given a dose of Dexmedetomidine 3 mcg/kg/hr intravenously for ten minutes then followed 0.4 mcg/kg/hr intravenously until the end of the procedure, in addition to the dose of Midazolam given immediately before the procedure which is 2.5 mg intravenously and if the	There were low incidence of cases of low blood oxygen concentration in the Dexmedetomidine group, and also in the Dexmedetomidine group the median of the Midazolam dose used was lower. In addition to this, the systolic blood pressure reading and heart rate decreased in the Dexmedetomidine group, but no complications that led to heart failure or irregular heartbeats

		desired degree of sedation is not reached, 2 mg Midazolam intravenously is given until Ramsay 3-4, while the second group takes 2.5 mg Midazolam intravenously, followed by 2 mg Midazolam intravenously at the time of need to reach the desired degree of hypnosis, which is Ramsey 3-4.	
(Sethi et al., 2014) An open-label randomised controlled trial 60 patients	”Dexmedetomidine versus Midazolam for conscious sedation in ERCP”	In the Midazolam group 0.04 mg/kg of Midazolam was given intravenously in addition to 0.5 mg intravenously when needed to reach Ramsey 3-4. While in the Dexmedetomidine group 1 mcg/kg intravenously was administered within ten minutes, then 0.5 mcg/kg/h intravenously were given to reach Ramsey 3-4. Each group of the two groups is given 1 mcg/kg intravenously Fentanyl at the beginning of the procedure.	In the Dexmedetomidine group, there was a decrease in heart rate, while there was no significant difference in the reading of blood pressure and respiratory rate, the appearance of the gag reaction was more in the Midazolam group than in the Dexmedetomidine group, the Dexmedetomidine group showed faster recovery than the Midazolam group. Finally, the satisfaction of patients and the endoscopy specialist was the highest in the Dexmedetomidine group.
(Kilic et al., 2011) prospective, randomized, double-blind study 50 adult patients	”Conscious sedation for ERCP: Dexmedetomidine versus Midazolam”	In the Dexmedetomidine group 1 mcg/kg/hr intravenously was started at ten minutes before the procedure, followed directly by	Lower heart rate in the Dexmedetomidine group, in terms of respiratory rate and MAP the results were similar, Whereas, regard to side effects, nausea, vomiting, and coughing were observed in the

		0.2-0.7 mcg/kg/hr to achieve the desired sedation, which is Ramsey 3-4. In the Midazolam group 0.04 mg/kg intravenously were administered, followed by 0.5 mg intravenously as needed to achieve the required degree of sedation, which is Ramsey 3-4.	Midazolam group, with none in the Dexmedetomidine group. As for the gagging, more observations were observed in the Midazolam group than in the Dexmedetomidine group. While the results showed more satisfaction among the endoscopy specialists in the Dexmedetomidine group than in the Midazolam group.

all vital signs at four points for two groups Midazolam and Dexmedetomidine

Table 4:11

Vital signs of the patients in both Midazolam and Dexmedetomidine groups data displayed as Mean (± SD)

A

MAP in both Midazolam and Dexmedetomidine groups data displayed as Mean (± SD)

Variable	Midazolam group (n=34)	Dexmedetomidine group (n=34)	p
Point 1	92.7 ± 11.4	92.7 ± 10.5	0.896
Point 2	91.3 ± 7.8	95.9 ± 13.8	0.311
Point 3	89.7 ± 10.2	90.2 ± 8.7	0.777
Point 4	88.7 ± 9.6	88.4 ± 11.3	0.658

B

HR in both Midazolam and Dexmedetomidine groups , data displayed as Mean (± SD)

Variable	Midazolam group (n=34)	Dexmedetomidine group (n=34)	p
Point 1	80.91 ± 16.58	80.18 ± 13.52	0.654
Point 2	81.03 ± 13.20	77.977± 15.64	0.353
Point 3	80.82 ± 14.24	75.74± 13.75	0.049
Point 4	78.8 ± 12.13	74.79 ± 11.41	0.163

C

SpO2 in both Midazolam and Dexmedetomidine groups, data displayed as Mean (±SD)

Variable	Midazolam group (n=34)	Dexmedetomidine group (n=34)	p
Point 1	97.65 ± 1.64	98.65 ± 2.56	0.063
Point 2	97.59 ± 1.74	97.50 ± 2.50	0.970
Point 3	97.24 ± 1.89	97.09 ± 2.77	0.975
Point 4	97.29 ± 1.60	96.97 ± 3.43	0.797

D

SpO2 in both Midazolam and Dexmedetomidine groups, data displayed as Mean (±SD)

Variable	Midazolam group (n=34)	Dexmedetomidine group (n=34)	p
Point 1	17.74 ± 0.71	16.53 ± 2.56	0.063
Point 2	17.59 ± 0.92	17.00 ± 2.53	0.970
Point 3	17.38 ± 0.98	15.82 ± 2.40	0.004
Point 4	20.38 ± 0.84	16.06 ± 2.55	0.001

جـامعـــة النجاح الوطنية

كليـــة الدراســـات العليـــا

مقارنة بين Dexmedetomidine و Midazolam للمرضى الذين يخضعون لتنظير الجهاز الهضمي العلوي في مستشفى جامعة النجاح الوطني

دراسة مقارنة، كمية، مستقبلية، قائمة على الملاحظة

إعداد

إبراهيم محمد غول

إشراف

د. عائدة أبو السعود القيسي

د. وائل صدقة

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

2022

مقارنة بين Dexmedetomidine و Midazolam للمرضى الذين يخضعون لتنظير الجهاز الهضمي العلوي في مستشفى جامعة النجاح الوطني
دراسة مقارنة، كمية، مستقبلية، قائمة على الملاحظة

إعداد
إبراهيم محمد غول
إشراف
د. عائدة ابو السعود القيسي
د. وائل صدقة

الملخص

الخلفية: إجراءات التنظير للجهاز الهضمي هي من أهم الإجراءات التشخيصية والعلاجية لمجموعة واسعة من المشاكل الطبية مثل فقدان الدم في القناة الهضمية، وإزالة الأجسام الغريبة، والإجراءات الأكثر تعقيدًا مثل التنظير الداخلي للقنوات الصفراوية والبنكرياس. التنظير الداخلي هو إجراء مزعج ومؤلم. لتجنب الحركة والألم والسعال والتقيؤ والغثيان، يجب أن يتم تخدير المرضى أثناء التنظير الداخلي. لذلك، يجب إعطاء مسكنات وعوامل مهدئة كافية ومراقبتها بأقل قدر من الآثار الجانبية أو المضاعفات بحيث يمكن للمرضى الحفاظ على استجابتهم للألم والتنبيهات اللفظية دون فشل في وظائف الجهاز التنفسي أو القلب والأوعية الدموية.

الأهداف: الهدف من الدراسة الحالية هو المقارنة والتحقيق في فعالية وسلامة Midazolam مقابل Dexmedetomidine من حيث الجهاز التنفسي، وديناميكية الدورة الدموية، والتسكين، والتنويم، ورضا المريض، ورضا أخصائي التنظير الداخلي، والأعراض الجانبية في المرضى الذين يخضعون للتنظير العلوي

المنهجية: دراسة عشوائية مستقبلية، مزدوجة التعمية، مضبوطة، أجريت على 68 مريضًا يخضعون للتنظير العلوي بين سن 18 و60 عامًا، من تصنيف الجمعية الأمريكية لطبيب التخدير للوضع الصحي للمرضى من النوع الأول والثاني في مستشفى جامعة النجاح الوطني، نابلس –فلسطين، بين أكتوبر 2021 ويناير

2022. بحيث تلقى جميع الأشخاص معلومات حول الغرض من الدراسة ومنهجية الدراسة، استمارة موافقة خطية تم الحصول عليها من كل شخص.

النتائج: فيما يتعلق برضا المريض، أظهر Dexmedetomidine رضاءًا أعلى بكثير، وأقل إزعاجًا، وقلقًا أقل منه في دواء Midazolam مع .P <0.05 فيما يتعلق بأخصائي التنظير الداخلي، أظهر الرضا، وعدم الراحة، والتقيؤ، وحركة الجهاز الهضمي، والصعوبة الفنية أن Dexmedetomidine تفوق على Midazolam مع.P <0.05 وكانت افاقة المرضى من دواء Dexmedetomidine بشكل أسرع من مرضى Midazolam مع p <.05 ، واحتاجت مجموعة Midazolam إلى 2.4 ± 7.7 دقيقة للتخدير بينما احتاجت مجموعة Dexmedetomidine إلى 9.5 ± 1.1 دقيقة وهذا الاختلاف مع .p <.05اما فيما يتعلق بظهور الآثار الجانبية كان Dexmedetomidine أقل مما كان عليه في Midazolam ولكن لم يكن هناك فرق ذو قيمة احصائية. اما فيما يتعلق بالعلامات الحيوية، لا يوجد فرق احصائي بين Midazolam و .Dexmedetomidine

الاستنتاجات: يعتبر Dexmedetomidine آمنًا وفعالًا ومتفوقًا على Midazolam فيما يتعلق برضا المريض ورضا أخصائي التنظير الداخلي وسرعة الافاقة، ولكن فيما يتعلق بالآثار الجانبية والعلامات الحيوية، لا يوجد فرق ذو قيمة احصائية فارقة.

الكلمات المفتاحية: ديكسميديفتوميدين، ميدازولام، التخدير، التنظير العلوي