An-Najah National University

Faculty of Graduate Student

Dexamethasone and Metoclopramide, and their Combination for the Prevention of Postoperative Nausea and Vomiting in Female Patients Undergoing Laparoscopic Surgery

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This Thesis is Submitted in Partial Fulfillment of the Requirements for the Master's Degree in Nurse Anesthesia, Faculty of Graduate Studies, An-Najah National University, Nablus-Palestine.
2017

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Dedication

I dedicated this thesis to the sake of Allah, and my great teacher and messenger, Mohammed (May Allah bless and grant him), who taught us the purpose of life.

To my homeland Palestine, the intimate womb, and to the great martyrs and prisoners, the symbol of sacrifice.

My great parents, who have always loved me unconditionally and whose have taught me to work hard for the things that I aspire to achieve, My dearest wife, who leads me through the valley of darkness with light of hope and support, My beloved brother and sisters, My beloved kids: Hasan, and Laila, whom I can't force myself to stop loving. To all my family, and my friends who encourage and support me, all the people in my life who touch my heart, I dedicate this research.

Acknowledgements

First, I give all the glory to **God**, the source of my strength, for granting me both the mental and physical endurance to complete this monumental task.

I would like to extend a very special thanks to my advisors **Dr. Aidah Alkaissi** and **Dr. Nouraldin Almasri** for believing in me and for theirdiligent supervision, clear guidance, continued support and encouragement throughout this process.

To **Dr. Wael Sadaqa, and Dr. Abd-Elbaset Nazzal**, my teachers, I extend special thanks and gratitude to you for your assistance, encouragement, and support.

Then, I would like to thank my entire family, especially my loving parents, for their love, understanding, and support, and to my dedicated wife who has been a constant source of support and encouragement during the challenges of graduate school and life.

To everyone who gave me the moral support for the completion of this task, Thank you.

الاقرار

انا الموقع ادناه مقدم الرسالة التي تحمل العنوان

Dexamethasone and Metoclopramide, and their Combination for the Prevention of Postoperative Nausea and Vomiting in Female Patients Undergoing Laparoscopic Surgery

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Declaration

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

Student Name: **الاسم:**

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List of Abbreviations

ASA	American Society of Anesthesiologists
BMI	Body Mass Index
CO_2	Carbon Dioxide
CNS	Central Nervous System
CSF	Cerebrospinal fluid
GA	General Anesthesia
Hrs	Hours
5-HT	5-HydroxyTryptamine (serotonin)
5HT3	5-HydroxyTryptamine receptor-subtype-3
IV	Intravenous
Kg	Kilogram(s)
LC	Laparoscopic Cholecystectomy
LMP	Last Menstrual Period
Lt	Liters
Ml	Milliliter(s)
µg	Microgram (s)
O_2	Oxygen
PACU	Post Anesthetic Care Unit
PONV	Postoperative Nausea and Vomiting
VAS	Visual Analog Scale

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Abstract

Introduction: No single antiemetic drug has proven to be a universal solution to postoperative nausea and vomiting. There is evidence however, that in patients with a high risk of developing PONV, combination antiemetic therapy is considered to be a viable assistive practise. The aim of this study is to evaluate the effect of prophylactic dexamethasone and metoclopramide as monotherapies and in combination for female patients with moderate to high risk for PONV related to laparoscopic surgery under general anesthesia.

Methods:A multicenter, prospective, randomized, double-blind, placebo controlled trial was used in this study.One hundred twenty female patientswere allocated randomly to one of the four groups, with thirty patients in each: (D) group received 8 mg dexamethasone one minute immediately before induction of anesthesia and 10 ml saline before end of anesthesia, (M) group received 10 ml saline one minute immediately before induction of anesthesia and metoclopramide 20 mg before end of anesthesia, (C) group received dexamethasone (8 mg) one minute

immediately before induction of anesthesia and metoclopramide (20 mg) before end of anesthesia, and (P) group received 10 ml saline one minute immediately before induction of anesthesia and 10 ml normal saline before end of anesthesia. Postoperative symptoms were assessed postoperatively.

Results: Significant differences in **the incidence of vomiting**within 24 hrs postoperatively between placebo group17 (56.7%) and combination group 6 (20%), P = 0.0037, and dexamethasone group 6 (20%), P = 0.0037 were demonstrated. The results show that the incidence of vomiting was reduced significantly by use of dexamethasone as amonotherapy or in combination with metoclopramide.

Significance differences were also noted **in the incidence of nausea** 24 hrspostoperatively between the treatment groups (D, M, and C) when compared with placebo group $p< 0.05$. There were no statistical significance differences between the three treatment groups, $p>0.05$. Results can be interpreted as evidence that using metoclopramide and dexamethasone alone or in combination in this sample decreased the incidence of nausea during the 24 hours after recovery as compared with a non-active placebo.

Significant differences were exhibited in **the intensity of nausea** 24 hours postoperative between the combination group 1.05 (± 0.90) compared with dexamethasone 1.78 (± 1.14), P = 0.008, Metoclopramide 2.43 (± 1.03), P = 0.000 and the placebo group 3.07 (± 1.34), P=0.000. These results

demonstrate that using a combination of dexamethasone and metoclopramide canreducs significantly the intensity of nausea in the critical 24 hour postoperative period.

There were noted significant differences in need to administer **antiemetic**in the 24 hour postoperative period.The total number of patients who received the combination therapy 6(20%)and dexamethasone 7(23.3%) required antiemeticat a lower rate than those who received placebo 19(63.3%), $p < 0.05$. There was no significant difference evidenced between placebo and metoclopramide 13 (43%) $p= 0.1237$. The results show that use of either dexamethasone or combination reduced significantly the need for additional analgesic medication 24 hours post-operation.

Reported incidence of pain24 postoperativein combination therapy was 22 (77.3%) and in the dexamethasone group 21 (70%) compared to the placebo group 29 (96.7%), $p< 0.05$ and the metoclopramide group 28 (93.3%), $p< 0.05$. The results indicate that the incidence of pain was reduced significantly in the combination and dexamethasone groups.

Conclusion: The combination of dexamethasone plus metoclopramide appears to be a more effective prophylactic in reducing the intensity of nausea than dexamethasone, metoclopramide alone or a placebo. Dexamethasone and the combination of dexamethasone plus metoclopramide were more effective in preventing PONV and decreasing the severity of postoperative pain than metoclopramide alone and placebo.

Patients who are at high risk for PONV may demonstrate positive results when using a combination therapy. In addition no adverse events related to use were found.

Keywords: PONV, Dexamethasone, Metoclopramide, Postoperative symptoms.

Chapter One

Introduction

Introduction

Patients who submit to surgery are exposed to risks and complications that originate from both their initial diagnosis and the surgery itself (Doubravska, Dostalova et al. 2010). Postoperative nausea and vomiting (PONV) are two of the most prevalent and disturbing side effects subsequent to anesthesia and surgery (Chatterjee, Rudra et al. 2011). PONV is defined as any nausea, retching, or vomiting developing through the first 24 – 48 hours postoperatively in patients after surgery (Pierre and Whelan 2013).

The incidence of PONV ranges generally between 20% and 30% after using volatile anesthetics in general anesthesia (GA).(Watcha and White 1992). Many factors can aggravate the condition including movement such as transport on the trolley, changing position in bed, being released from the medical setting or activity at home(Alkaissi, Ledin et al. 2005).

PONV is a multifactorial problem; These factors can be divided into pharmacological factors, patient factors, and surgical factors(Rother 2012). PONV is known to be affected by gender, age, history of motion sickness or PONV, the type of surgical procedure, smoking, duration of anesthesia , etc. (Ku and Ong 2003).

PONV is a source of persistent concern in surgical patients (Gan, Meyer et al. 2007). To minimize the occurrence and severity of PONV, anesthetists may use single or combinations of antiemetic drugs to patients. (Karanicolas, Smith et al. 2008).

No antiemetic drug has proven to be a comprehensive solution to PONV when used as a monotherapy, in addition using these drugs in high doses is not recommended due to the effects of saturation and safety; therefor combinations of antiemetic drugs have been proposed as a logical choice (Wallenborn, Gelbrich et al. 2006). There is evidence that, in patients with a high risk for PONV, combination antiemetic therapy should be considered as a viable option (McCracken, Houston et al. 2008).

The aim of this study is to evaluate the effect of prophylactic dexamethasone and metoclopramide as monotherapies and in combination for female patients with moderate to high risk for PONV undergoing laparoscopic surgery under GA.

1.1 Background

1.1.1 Definition of Terms

Nausea and vomiting are the most common side-effects appearing in patients having surgery under GA. ***Nausea*** is defined as a personal unpleasant sensation, assessed only by the individual, not by the observer. The best description of sensation is the propensity to vomit without eject gastric muscular movement. (Knapp and Beecher 1956).

Vomiting is the vigorous ejection of stomach contents through the mouth which is result of a strong contraction of the abdominal muscles and diaphragm combined with the opening of the gastric cardia (the orifice of the stomach).(Watcha and White 1992).

Retchingis a labored intermittent and rhythmic contraction of the respiratory muscles including the diaphragm, chest wall and abdominal wall muscles without the ejection of stomach contents or mouth opening.(Watcha and White 1992). Retching is usually distinguished from vomiting by the production of stomach contents. When gastric contents are not driven out, the expulsive efforts are classified as retching. Retching is commonly a signal of an empty stomach and is perceived as distressing for the patient as vomiting (Knapp and Beecher 1956). Retching and vomiting may also be gathered under the term "emetic episode" (Knapp and Beecher 1956).

Fatigue is generally defined as a feeling of lack of energy and motivation that can be physical, mental or both. Fatigue is not the same as drowsiness, but the desire to sleep may accompany fatigue. Apathy is a feeling of indifference that may accompany fatigue or exist independently. Fatigue is physical and/or mental exhaustion that can be triggered by stress, medication, overwork, or mental and physical illness or disease (Miller-Keane and O'Toole 2003).

Tiredness defined asbecome, physically or mentally in want of rest, because of lack of strength, patience, interest(Heritage 2016).

Headache is a pain in the head, one of the most common ailments of humans, it is a symptom rather than a disorder in itself; it accompanies many diseases and conditions, including emotional distress. Although recurring headache may be an early sign of serious organic disease, relatively few headaches are caused by disease induced structural changes. Most result from vasodilation of blood vessels in tissues surrounding the brain, or from tension in the neck and scalp muscles (Miller-Keane and O'Toole 2003).

Drowsiness is a sensation of faintness and whirling or an inability to maintain normal balance in a standing or seated position, sometimes associated with giddiness, mental confusion, nausea, and weakness (Mosby 2012).

1.1.2 Pathophysiology of PONV

The pathophysiology of nausea and vomiting is complex. The neuroanatomical site regulatingnausea and vomiting is an ill-definedarealocated in the lateral reticular formation in the brainstem known as “vomiting center” (Chatterjee, Rudra et al. 2011). The vomiting center receives afferent inputs from different sources, including the chemoreceptor trigger zone (CTZ), the vestibular system and the cerebral cortex, and enteric vagal nerve afferents. (Hamilton, Ravikumar et al. 2013).

The CTZ is situated within the area postrema (located outside the blood–brain barrier) and includes several varied receptors that modify its activity(Chandrakantan and Glass 2011). Immunochemical studies conducted in this anatomical zonereveal that these areas contain serotonin, histamine, neurokinin-1, cholinergic, and D2 dopamine receptors and that the contact of CTZ with cerebrospinal fluid (CSF) allows for substances in the blood to interact with CSF. (Chatterjee, Rudra et al. 2011).

Additional interactions take place within the nucleus tractussolitarius (NTS) which is found in the floor of the fourth ventricle (Chatterjee, Rudra et al. 2011). The NTS contains high concentrations of histamine, enkephaline,muscarinic, and cholinergic receptors (Watcha and White 1992).

The multifactorial mechanisms leading to PONV are comprised ofnoxious substances stimulatingthe dopamine and 5-hydroxytryptamine type 3 receptors in the CTZ such as opiates and anesthetic agents, and the stimulation of gut chemoreceptors and stretch receptors (Hamilton, Ravikumar et al. 2013). Most antiemetic drugs work by directly or indirectly antagonizing emetogenic substances on receptors in the CTZ which reduce PONV(Chandrakantan and Glass 2011).

Intra-abdominal and laparoscopic surgery has high risk of PONV (Hamilton, Ravikumar et al. 2013). The mechanoreceptors may be affected by the surgical manipulation of the gut which can also irritate the mucosa of the small intestine(Hammas 2001). The vagus nerve is considered the

main nerve for revealing and mediating emetic stimuli from the gastrointestinal tract (Andrews and Wood 1988).

While there are various receptor systems affecting the occurrence and management of PONV, it seems clear that using a combination of drugs workingon the different receptors would decrease the incidence of PONVmore than that of a single drug (Chandrakantan and Glass 2011).

1.1.3 Risk Factors for PONV

To achieve the optimal use of prophylactic antiemetic and multimodal management strategies, awarenessof independent risk factors for PONV is crucial.There are manystudies including multivariable, meta-analyses, and systematic reviews that have greatly increased such knowledge (Apfel, Laara et al. 1999, Habib and Gan 2001, Gan 2006, Chatterjee, Rudra et al. 2011, Gan, Diemunsch et al. 2014). Several risk factors have been identified that trigger PONV in three main categories: patient, surgical and anesthesia-related factors (Hambridge 2013).

PONV has been described in the literature since the late 1800s (Gan 2006). Research on the risk factors of PONV began in the early 1990s, with publication of initial studies which attempted to identify multiple risk factors(Chatterjee, Rudra et al. 2011). A simplified risk scale for predicting PONV devised byApfel et al., concluded that there are 4 main risk factors including gender (female) , prior history of motion sickness or PONV, non-smoker, and the use of postoperative opioids.Risk factors should be

evaluated to identify patients who may benefit from prophylactic antiemetic(Apfel, Laara et al. 1999).

❖ **Anesthesia-Related Risk Factors**

Characteristics of the anesthetic regimen may be considered as risk factors dependent uponthe type of intravenous and volatile anesthetic agents used, the use of nitrous oxide, the reversal of neuromuscular blockadewith higher doses of neostigmine, the use of opioids and the experience of the anesthesiologist (Habib and Gan 2001).

When inhalational anesthetics are used the incidence of PONV may be increased and inversely decreased when Propofol is used; additionally PONV occurance may depend on the amount of opioids used (Chatterjee, Rudra et al. 2011). The risk for PONV does not appear to be affected by choice of volatile anesthetic,, such as isoflurane versus sevoflurane versus enflurane, (Gan 2006).

Use of larger doses intraoperative or postoperative opioids and larger postoperative doses have also been associated with PONV(Gan 2006). The strongest predictor of PONV avoidance is the administration of a long-acting rather than a short-acting opioids(Gan 2006).

Duration of surgery is considered to be an independent risk factor for PONV as shown in a few studies with both adults and children (Gan 2006). Incidence of PONV has been found to increase as the duration of surgery increases (Habib, White et al. 2004). Chatterjee*et al*, reported that,

the risk of PONV may increase by 60% when increasing the operative duration by 30 minutes (Chatterjee, Rudra et al. 2011).

❖ **Age**

In adults, higher incidences of PONV are shown in intra-abdominal surgery (70%), major gynecological surgery (58%), laparoscopic surgery (40–77%), breast surgery (50–65%), eye and ENT surgery (71%) (Kenny 1994). However, high incidence of postoperative vomiting in children is associated with operations including strabismus, adenotonsillectomy, hernia repair, orchidopexy, and penile surgery (Chatterjee, Rudra et al. 2011).

Among pediatric patients the age group between 6-10 years has the high incidence of PONV (up to 34%) However rates of PONV decrease in younger patients, and the incidence reduces with the onset of puberty(Chatterjee, Rudra et al. 2011).

❖ **Gender**

The greater incidence of PONV in women may be linked to female hormones, as it has been found that most PONV occurs in the luteal phase of the menstrual cycle(Kenny 1994). Chatterjee*et al.*reported that the incidence in high-risk groups may be as high as 70%, when considering females, having a previous history of PONV and being a non-smoker. He added also that the releaseof follicle-stimulating hormone and estrogen

during the pre-ovulatory phase of the menstrual cycle and during menstruationmay be linked toPONV (Chatterjee, Rudra et al. 2011).

❖ **Smoking**

Cohen *et al*. determined that occurrences of PONV in non-smokers were twice aslikely as in smokers(Cohen, Duncan et al. 1994). Chatterjee et al.proposed that alterations in liver microsomal enzymes resulting from chronic exposure to smoke, chiefly polycyclic aromatic hydrocarbons, may affect the metabolism of drugs used during the perioperative period and the ability of these drugs to produce PONV(Chatterjee, Rudra et al. 2011).

❖ **History of PONV**

Patients who have a history of PONV are more likely to have a higher risk of future episodes of the condition (Hambridge 2013). PONV is up to three times more likely to occur in patients who have experienced emesis after a previous operation**.** Susceptibility to motion sickness has also been linked to an increased risk of PONV (Purkis 1964)**.**Chatterjee*et al*. reported that the individuals who have a history of motion sickness are more susceptible to emetogenicstimuli (Chatterjee, Rudra et al. 2011).

❖ **Weight**

Several studies have reportedthat body weight is a factor in the incidence of PONV, with incidence increasing in obese patients (Watcha and White 1992). Increased intra-abdominal pressure in patients with a body mass index of more than 30 make them more susceptible to have an increased

risk for PONV(Chatterjee, Rudra et al. 2011). Chatterjee*et al*.suggested that the anesthetic gases are excreted more quickly in patients with a lower weightbecause anesthetic agents have prolonged half-lives in obese patients due to the pharmacokinetic effects of lipophilic properties in these agents.(Chatterjee, Rudra et al. 2011).

- **Laparoscopic Surgeries**

The gas used to "inflate" the abdomen in laparoscopic surgeries puts pressure on the vagus nerve, which has a connection to the vomiting center which may lead to the high incidence of PONV in laparoscopy (Chatterjee, Rudra et al. 2011). Moreover, increased incidence of PONV may result from high levels of anxiety and postoperative pain, especially of pelvic or visceral origin (Chatterjee, Rudra et al. 2011).

1.1.4 Risk Assessment Tool

The pre-anesthetic interview should cover questions designed to determine the patient's risk for developing PONV, and anesthesiologists should consider the many variables in formulating a perioperative plan for PONV (Bryson, Frost et al. 2007). The overall risk that a particular patient will develop PONV depends upon factors unique to the patient, the surgical procedure, and the anesthetic technique (Bryson, Frost et al. 2007).

Many risk assessment tools have been developed to assist healthcareproviders to identify patients who may experience PONV and to detect who is most likely to benefit from prophylactic anti-emetic therapy.

However,Hambridge reported that, there is no risk assessment tool can accurately predict the likelihood of apatient to have PONV (Hambridge 2013).

Applying PONV risk analysis in order to improve patient outcomes by employing, anti-emetics prophylactically with patients with a high probability of emesis could prevent or at least reduce theses adverse symptoms (Koivuranta, Laara et al. 1997). Apfel*et al.*suggested that risk assessment scores can be helpful in assessingpatients and directing prophylactic therapybyproviding an objective measure of PONV risk inindividual patients (Apfel, Laara et al. 1999).

Logistic regression analysis was used to determine the association of independent fixed patient factors in the incidence of PONV (Toner, Broomhead et al. 1996). The fixed patient factors of gender, history of previous emesis, postoperative opioids and an interaction between gender and previous emetic history were identified as the most significant independent variables (Toner, Broomhead et al. 1996). Motion sickness had a weak association which did not reach statistical significance but was retained in the model on the basis that the weak finding was probably a result of the small number of patients (Toner, Broomhead et al. 1996). These factors were expressed in a logistic regression equation from which the risk of postoperative emesis for an individual patient could be calculated before operation (Toner, Broomhead et al. 1996).

Apfel et al. developed a simplified risk score incorporating of four predictors: gender, history of motion sickness or PONV, nonsmoker and the use of postoperative opioids. If none, one, two, three, or four of these risk factors were present, the incidences of PONV were 10, 21, 39, 61 and 79% respectively(Apfel, Laara et al. 1999). There is evidence that, patients with moderate to high risk score for having PONV, prophylactic antiemetic should be considered as high risk patients, and combination therapy should be considered (McCracken, Houston et al. 2008).

In another scoring system developed by Koivuranta M *et al*. the duration of surgery for more than 60 minutes was added as fifth risk factor to gender, history of motion sickness, history of PONV and non-smoking status(Koivuranta, Laara et al. 1997). Van den Bosch*Jet al*, compared this tool to the Apfel scoring system and found it equally adequate when used in a study including 1,388 patients underwent various surgeries (van den Bosch, Kalkman et al. 2005).

Despite the limitations in reliability of PONV risk scoring systems, their use to plan the antiemetic regimenfor patients has been shown to significantlydecrease the incidence of PONV, especially in high risk patients, while in lower risk patients it decreased the expense and potential side effects of prophylactic antiemetic(Gan 2006).

1.1.5 Pharmacological Management

Despite a variety of attempts in the last decades to establish an optimal antiemetic regimento decrease the incidence of PONV without increasing the risk of adverse effects for both adults and children, the prevention of PONVin the surgical setting is still challenging(Henzi, Walder et al. 2000).However, while there is no perfectantiemetic drug for the prevention of PONV, the potential adverse effects of these drugs must also be taken into account (Lee 2013). In spite of an abundance of available antiemetic drugs, there is none 100% effective in preventing PONV. This maybe because of the multifocal origin of PONV as there is no single motivator for PONV (Kumar, Patodia et al. 2013).As such the use of combination antiemetic drugs are a viable option when high doses of such drugs are unadvisable due to effects of saturation and safety(Wallenborn, Gelbrich et al. 2006).

Prophylaxis with antiemetic drugs is the current gold standard for managing PONV (Lee 2013). Antiemetic drugs used in combination havebeen found to have superior efficacy compared with drugs used aloneas prophylactic for PONV (Habib and Gan 2001). Prophylaxisantiemetics should be considered for patients at moderate to high riskfor PONV, with combination therapy or a multimodal approach recommended.(Gan, Meyer et al. 2007).

Pharmacologic prophylaxis of nausea and vomiting improves patient comfort and satisfaction, reduces time to discharge, and should be done selectively per the American Society of Anesthesiologists(ASA)standards, despite a lack of agreement related to the use of multiple pharmacologic agents for the prophylaxis of nausea and vomiting (Apfelbaum, Silverstein et al. 2013).

The costeffective way to prevent PONV is to use prophylactic medications for patients with a 40% or greater risk of PONV (Apfel, Korttila et al. 2004). The first and second-line prophylaxis antiemeticsrecommended for PONV in adults include the 5-hydroxytryptamine (5-HT3) receptor antagonists (ondansetron, dolasetron, granisetron, and tropisetron), steroid (dexamethasone), phenothiazines (promethazine and prochlorperazine), phenylethylamine (ephedrine), butyrophenones (droperidol, haloperidol), antihistamine (dimenhydrinate), anticholinergic (transdermal scopolamine)(Gan, Meyer et al. 2007), and NK_1 receptor antagonist (aprepitant).

None of the available antiemetics is absolutely effective for preventing PONV, especially in patients with high risk score. This is likely because most of these drugs act through blockade of mainly one receptor (Habib and Gan 2001). However, understanding the multifactorial etiology of PONV might be explainwhy using a combination of drugs acting at different receptor sites is more effective (Habib and Gan 2001). The first use of combination therapy was by Parikhto treat vomitinginduced by

chemotherapy (Parikh, Charak et al. 1988). The use of a combination of drugs from different classes can provide superior efficacy with a lowerunacceptable adverse-effect (Habib and Gan 2001).

❖ **Dexamethasone**

Dexamethasone is a corticosteroid with strong anti-inflammatory and prolonged antiemetic effect (Liu, Hsu et al. 1999). It was first used in 1981as an antiemetic therapy in cancer patients receiving chemotherapy (Aapro and Alberts 1981). Single dose dexamethasone given at induction of anesthesia is reported to reduce PONV and perioperative fatigue (Magill, Bahia et al. 2011).

Dexamethasone has been shown to minimize postoperative symptoms after a variety of surgical procedures (Gomez-Hernandez, Orozco-Alatorre et al. 2010). Recently, dexamethasone has been reported to be effective in reducing the incidence of postoperative nausea and vomiting in pediatric patients undergoing strabismus repair (Madan, Bhatia et al. 2005), tonsillectomy (Samarkandi, Shaikh et al. 2004), and in women undergoing Mastectomy (Gomez-Hernandez, Orozco-Alatorre et al. 2010)and major gynecological surgery (Liu, Hsu et al. 1999).

The antiemetic characteristics of dexamethasone are well defined. It reduce stimulation of the chemoreceptor trigger zone in the brain by reducing circulating inflammatory mediators (Djalali 2012). Also, the antiemetic capability of dexamethasone may be explained by its antagonistic effect on

5-HT receptors (Suzuki, Sugimoto et al. 2004). Furthermore, its mode of action is the inhibition of postoperative synthesis and decrease in 5HT3 levels in CNS and anti-inflammatory action at the operative site (Aziz, Naz et al. 2011).A previous study has indicated that dexamethasone may haveantagonize effects on prostaglandin receptors(Aapro, Plezia et al. 1984)or release endorphins (Golembiewski, Chernin et al. 2005)resulting in mood enhancement, a sense of well-being, and improvement in appetite.

Dexamethasone's antiemetic effect may begin approximately at two hours (Wang, Ho et al. 2000). 8–10 mg is the most commonly used dose is in adults and 1–1.5 mg/kg in children (Habib and Gan 2001). In previous studies, IV dexamethasone had an antiemetic effect persisting at least 24 hourspostoperatively in patients undergoing a variety of surgical procedures (Fujii, Tanaka et al. 1997) (Wang, Ho et al. 1999).

Dexamethasone's adverse effects depend on dosage and time of administration (Djalali 2012). The most common side effects are poor wound healing, wound infection, and adrenal suppression. However, these side effects occur most commonly with long-term usage (Buck, Mustoe et al. 2006).

Dexamethasone 4 mg IV has similar efficacy to ondansetron 4 mg IV and droperidol 1.25 mg IV for PONV prophylaxise(Eberhart, Geldner et al. 2004).In more recent studies dexamethasonewas used in higher doses than 8 mg rather than the minimum effective dose of 4 mg(Gan, Diemunsch et al. 2014). Prophylactic8 mg dexamethasone improved the quality of

recovery in addition to decreasing nausea, pain, and fatigue after discharge(Murphy, Szokol et al. 2011). Therefore, in our study, a dose of 8 mg of dexamethasone is utilized.

❖ **Metoclopramide**

The most commonly used antiemetic arein the Benzamides group. Metoclopramide is an antiemetic with multi modeleffects. (Aziz, Naz et al. 2011). It acts on both central dopamine and serotonin receptors, with both pro-kinetic and antiemetic effects (Bryson, Frost et al. 2007). Initially Metoclopramide was used for the treatment of nausea and vomiting in migraine headaches , radiotherapy and chemotherapy (Aziz, Naz et al. 2011). Currently Metoclopramide is used to reduce preoperative gastric contents and to treat, gastrointestinal reflux, heartburn, and gastroparesis(Norred 2003).

Metoclopramide decreases gastric emptying time by increasing smooth muscle tension of the lower esophagus and stomach andcausing relaxation of the pylorus and duodenum. Metoclopramide also minimizes the small intestinal transit time of ingested substances by cholinergic stimulation of the postganglionic nerves of the gastrointestinal tract. Furthermore, itincreases prolactin and aldosterone secretion but does not affect secretion of gastric hydrogen ion or pH (Norred 2003).

Metoclopramide may be usefulin cases of patients who have fasted for an insufficient time preoperative, have a full stomach, obese patients,

maternity patients, diabetic patients with autonomic neuropathy, after trauma, or are at risk for aspiration pneumonia (Norred 2003).

Metoclopramide dosage should be decreased in pediatric and geriatric patients and patients with renal failure or impairment who may be at higher risk for unacceptable side effects. Moreover in patients with breast cancer, intestinal obstruction, or pheochromocytoma, and for patients taking medication for Parkinson disease, seizure disorders, or depression, metoclopramide is contraindicated(Norred 2003).

Adverse effects such as restlessness, dry mouth, headache, dizziness and extrapyramidal symptoms may occur with high doses of metoclopramide(Aziz, Naz et al. 2011)and in patients with head trauma, metoclopramide may elevate intracranial pressure (Norred 2003).Furthermore cardiovascular side effects like hypotension, bradycardia or tachycardia may be associated with rapid IV administration (Habib and Gan 2001).

Metoclopramide is not associated with sedation, making it a more attractive therapy for outpatient or prophylaxis (Bryson, Frost et al. 2007). However, it may cause cramping, or prostaglandin-induced pregnancy termination(Norred 2003).

In various PONV prophylactic studies, metoclopramide has been used as an option, however due to it is a weak antiemetic effects paired with a half-life of only 30–45 min, its effectiveness for PONV was limited. However,

Metoclopramide is often given as adjunct therapy at a low dose (10 mg)with the time of administrationan area of contention (early, pre-op, or at induction versus late prior to emergence) (Kovac 2013).

In a study in volving more than 3000 patients, metoclopramide demonstrated an antiemetic effect when used in dosageshig her than 20 mg (Gan, Diemunsch et al. 2014). Due to the short duration of antiemetic effect, it has been confirmed that it is more efficacious when administered at the end of anesthesia than when given at its induction (Nesek-Adam, Grizelj-Stojcic et al. 2007).

❖ **Ondansetron**

Ondansetron is a carbazalone derivative that is structurally related to serotonin and has specific 5-HT3 subtype receptor antagonist characteristics, without affecting activity of dopamine, histamine, adrenergic, or cholinergic receptor (Ku and Ong 2003). Serotonin (5-HT3) receptor antagonists act at vagal afferents in the gastrointestinal tract and influence the chemoreceptor trigger zone (Kumar, Patodia et al. 2013). Ondansetron, is the most commonly used 5-HT3 receptor antagonist and is thefirst drug introduced in this class (Ku and Ong 2003).

Ondansetronis highly effective at reducing the emetic side-effects of chemotherapy or radiotherapy and is also effective at reducing postoperative nausea and vomiting (Tincello and Johnstone 1996). While thousands of studies have investigated anti-emetics for the prevention of

PONV, very few have studied the efficacy of rescue treatment (Apfel 2010). Anyway, Tramèr et al summarized that when used Ondansetron in doses 1, 4, or 8 mg, it has similarefficacy as rescue antiemetic for PONV in the PACU (Tramer, Moore et al. 1997).

The more common side effects of Ondansetron are headache, light-headedness, dizziness, flushing at the IV site, transient elevation in liver transaminase enzymes, a warm epigastric sensation, and constipation. Moreover, rare dangerous adverse effects of hypersensitivity are reported occasionally (Ku and Ong 2003).

1.1.6 Non-Pharmacological Treatment

As pharmacologic interventions have been unable to eliminate PONV, investigators have looked into the potential benefits of non-pharmacologic interventions (Bryson, Frost et al. 2007).Acupuncture, transcutaneous electrical stimulation, and acupressure have all been studied as non-pharmacological options in the treatment of PONV. Acupuncture is themost studied, and it has been shown that acupuncture of point pericardium 6 (P6) is effective in prevention of PONV with few side effects(Mann 2012).

- **P6-Acupressure**

A non-invasive analogue of acupuncture, has been submitted as prophylaxis against PONV (Alkaissi, Evertsson et al. 2002). However its mechanism of action is still unclear, possibly affecting neurotransmission

in the dorsal horn or higher centersbyreducerecurrent excitation of the skin activates A-b and A-d fibers(Rowbotham 2005).The anatomical location of P6 point presents2 Cun proximal from the distal palmcrease, precisely at the wrist between the tendons of palmarislongus and flexor carpi radials. One Cunis a measurement unit equalize the width of the patient's thumb across the interphalangeal joint (Schlager, Boehler et al. 2000).

Alkaissiand colleagues have conductedtwo studies in female patients undergoing minor gynecological procedures to examine acupressureusinga Sea-Band®. The first study conducted in 1999 included sixty women undergoing outpatient minor gynecological surgery. Patients were randomized into three groups, first group receivedan acupressure stimulation bandon bilateral P6 points (A), a second group received a bilateral placebo stimulation band (P) and a third control group received no acupressure wrist band (R). The results showed that; in the acupressure group no patient vomited, but in the placebo acupressure and in the reference group2 and 5 patients vomited respectively. None of patient in the acupressure group needed rescue drugs, but 5 patients in the placebo group and 4 in the reference group requestedanalgesic medication (Alkaissi, Stalnert et al. 1999).

A second studywas conducted in410female patients undergoing elective gynecological surgery under GA, the higher incidence of PONV was reported in the control group 46%, and 38% in the group with pressure on a non-acupoint and 33% in P6 acupressure group. The corresponding

decrease from 59% to 55% in the laparoscopic surgery group was statistically insignificant (Alkaissi, Evertsson et al. 2002).

In another randomized, double-blind study, sixty women with high and low tendency for motion sickness were randomized into three groups; with an active P6 acupressure, placebo acupressure, and a no band control group. Results indicated that, P6 acupressure enhanced tolerance to an experimental nauseogenic stimuli, and decreased the total number of symptoms reported in women with a history of motion sickness(Alkaissi, Ledin et al. 2005).

- **Korean Hand Acupuncture (**K-K9**)**

K-K9 acupunctureis a method that was first established and described by the Korean physician (T-W Yoo) related to pressure located on the middle phalanx of the fourth finger on both hands(Boehler, Mitterschiffthaler et al. 2002). However,few studiesexamining the efficacy of Korean hand acupuncture are available.

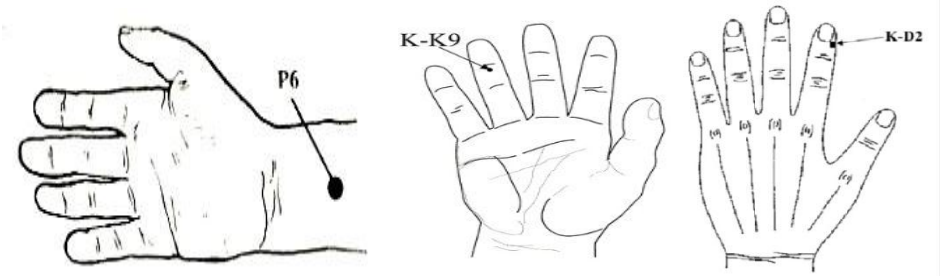
Schlager et al, conducted a double-blind, randomized, placebo-controlled study in children undergoing strabismus surgery to examine the effectiveness of K-K9 acupuncturein preventing POV. In the experimental group, patients received acupressure 30 minutes before induction anesthesia by applying an acupressure disc onto the K-K9 point; and the disc kept in place at least for 24 hours. The second group served as placebo group. The results showed that, the incidence of vomiting significantly

decrease in acupressure group (20%) compared with placebo group (68%) (Schlager, Boehler et al. 2000).

In another study, 80 women undergoing minor gynecological laparoscopic proceduresparticipated in double-blind, randomized, placebo-controlled study. The incidence of nausea was significantly decreasedin the acupressure group (40% compared with 70% in the placebo group) and the incidence of vomiting was significantly minimized(from 50% in the placebo group to 22.5% in the acupressure group)(Boehler, Mitterschiffthaler et al. 2002).

❖ **Korean Acupressure Point K-D2**

In a study conducted in 2002, the effect of capsicum plaster (PAS) applied at P6 and K-D2 acupressure points was administered to reduce the incidence of PONV. A randomized, double-blinded study involved one-hundred-sixty healthy patients scheduled for abdominal hysterectomy: the treatment groups involved 50 patients in the K-D2 group and 50 patients in the P6 group, whereas 60 patients were in the placebo group, The acupressure was performed by PAS before anesthesia induction and left in situfor 8 hourspostoperative. After 24 hours postoperative, the incidence of vomiting was significantly reduced from 56.7% in the placebo group to 22% for the K-D2 group and 26% for the P6 group. In addition patients in treatment groups requested lessrescueantiemetics compared with the placebo group(Kim, Koo et al. 2002).



(A) (B) (C)

Figure1. (A) Location of the point pericardium 6 (P6) (B) Korean Hand Acupuncture (K-K9) (C) Korean acupressure point K-D2

❖ Electro-Acupoint Stimulation

A study was conducted in patients undergoing GA for breast surgery to evaluatethe efficacy of electro-acupointstimulation, ondansetron versus placebo for the prevention of PONV. The patients were randomly allocated into three groups, one group receivedactive electro-acupoint stimulation (A), a second group received ondansetron4mg IV (O), and a third group received electrodes without electro-acupoint stimulation; placebo (P). The complete response was significantly more frequent in the treatment groups compared with placebo (77%, 64%, 42%, in A, O, P respectively) and patients in the treatment groups required less rescue antiemetic (19%, 28%, 54% in A, O, P groups respectively). Moreover, the patients in group Ahave lower incidence and intensity of nausea compared with the O groupand the P group (19%, 40%, 79%, respectively)(Gan, Jiao et al. 2004).

❖ Oxygen Therapy

The effect of oxygen therapy in preventing PONV is currently conflicting, Goll et al, reported positive results using oxygen therapy to reduce incidence of PONV compared with Ondansetron in patients undergoing gynecological laparoscopic surgery. During 24 hours postoperatively, the total incidence of nausea (and/or) vomiting was significantly reduced from 44% in the patients received 30% oxygen, and 30% in the patients received Ondansetron, to 22% in those given 80% oxygen(Goll, Akca et al. 2001).

In contrast to this study, Purhonen et al, in a study conducted on one hundred patients scheduled for ambulatory gynecologic laparoscopy, showed no differences between groups in the incidence of PONV and need for rescue antiemeticsafter oxygen therapy (Purhonen, Turunen et al. 2003).

❖ Intraoperative Hydration

In patients undergoing ambulatory surgery, high infusion intravenous fluids (20 ml/Kg)intraoperative have been associated with less incidence of nausea in the first day postoperative when compared with low infusion (2 ml/Kg)(Yogendran, Asokumar et al. 1995). More specifically, Moretti et al,completed an applied comparative study to examine the efficacy of colloid vs. crystalloid on PONV and postoperative recovery profile. Their results conclude that, intraoperative fluid resuscitation with predominantly colloids appears to improve postoperative recovery as compared with

crystalloids. Specifically, colloid administration significantly reduced the incidence and severity of nausea, vomiting, and need for rescue antiemetics (Moretti, Robertson et al. 2003).

1.2 Problem statement

Postoperative nausea and vomiting (PONV) are two of the most prevalent and disturbing side effects subsequent to anesthesia and surgery (Chatterjee, Rudra et al. 2011)and are considered a source of persistent concern in surgical patients(Gan, Meyer et al. 2007).

PONV can lead to complications such as wound dehiscence, bleeding, gastric contents aspiration, fluid and electrolyte imbalances, delayed discharge, hospital readmission, and low patient satisfaction (Ku and Ong 2003).

The source of PONV after laparoscopic surgery performed under GA is unclear, but it is presumably multifactorial (Watcha and White 1992). Habib and Gan revealed that, the incidence of PONV ranges between 40%-77% in patients undergoing laparoscopic surgery (Habib and Gan 2001).

Despite a multitude of attempts in the last decades driven to establish an optimal antiemetic regimen which would decrease the incidence of PONV without increasing the risk of adverse effects for both adults and children, the prevention of PONV in the surgical setting is still challenging (Henzi, Walder et al. 2000).

Prophylaxis with antiemetic drugs is the current gold standard for managing PONV (Lee 2013). When used antiemetic drugs in combination they have superior efficacy compared with drugs used alone as prophylactic for PONV (Habib and Gan 2001)

None of the available antiemetics is absolutely effective for preventing PONV, especially in patients with high risk. This is likely because most of these drugs act through a blockade of one receptor (Habib and Gan 2001). However, understanding the multifactorial etiology of PONV might be of use in understanding how using a combination of drugs acting at different receptor sites may be more effective in combating the complexity of PONV (Habib and Gan 2001).

Pharmacologic prophylaxis of nausea and vomiting improves patient comfort and satisfaction, reduces time to discharge, as recommended by the despite disagreement whether to use multiple pharmacologic agents for the prophylaxis of nausea and vomiting (Apfelbaum, Silverstein et al. 2013).

1.3 Significance of the Study

Although significant developments have been made in the field of PONV and the number of available antiemetic agents, the overall incidence of PONV is still estimated to be around 20%-30%(Cohen, Duncan et al. 1994) andin patients with highrisk factors, the incidence reaches 70% (Apfel, Laara et al. 1999). Postoperative nausea and vomiting (PONV) is one of the most commondistressing complaintsafter anesthesia, and can lead

tocomplicationsas wound dehiscence, bleeding, gastric contents aspiration, fluid and electrolyte imbalances, delayed discharge, hospital readmission, and low patient satisfaction (Ku and Ong 2003).Apfelet al. found that patients were more afraid of PONV than postoperative pain, which substantiated the importance of avoiding incidence of PONV (Apfel, Kranke et al. 2004). Apfel et al. created a simplified risk scalebased on four predictors: gender, history of motion sickness or PONV, nonsmoker and the use of opioids postoperatively. The predictive score calculated by presence none, one, two, three, or four of these risk factors, had incidents of PONV at 10, 21, 39, 61 and 79% respectively(Apfel, Laara et al. 1999). There is evidence that, patients with moderate to high risk scorefor having PONV, prophylactic antiemetic should be considered and in high risk patients, combination therapy should be counted(McCracken, Houston et al. 2008).

Dexamethasone has been given as antiemetic for patients during chemotherapyfor over 20 years (Italian Group for Antiemetic 1995), with limited side effects (Aapro and Alberts 1981), and has also shown to decrease the incidence of PONV when used as adjunct therapy in antiemetic regimen (Elhakim, Nafie et al. 2002).

In patients undergoing laparoscopic cholecystectomy (LC), a combination of ondansetron and dexamethasone was demonstrated to be a very effective prophylactic regimen(Elhakim, Nafie et al. 2002), but the use of ondansetron as routine prophylactic has been limited because of its high

cost (Subramaniam, Madan et al. 2001). Therefore, the current study used metoclopramide, the most common and inexpensive antiemetic agent instead of ondansetron.

The source of PONV after laparoscopic surgery performed under GA is unclear, but it is presumably multifactorial (Watcha and White 1992). Several factors including age, sex, smoking, history of motion sickness, intraoperative use of opioids and Isoflurane, peritoneum abdomen, irritation membranes, and manipulation of viscera (Kenny 1994) have been identified as influencing the occurrence of PONV.

In the current study the effect of administration of dexamethasone and metoclopramide as monotherapies and in combination for patients at moderate to high risk for PONV was tested.

1.4 Aim of the Study

The aim of this study was to evaluate the effect of prophylactic dexamethasone and metoclopramide as monotherapies and in combination for female patients with moderate to high risk for PONV undergoing laparoscopic surgeries under GA.

1.4.1 Objectives of the Study

- To assess the effect of perioperative administration of dexamethasone and metoclopramide as a single agent and in combination on PONV.
- To assess the effect of perioperative administration of dexamethasone and metoclopramide as a single agent and in combination on

postoperative symptoms (pain, headache, fatigue, tiredness and drowsiness).

1.4.2 Study Hypothesis

- There is a significant difference at a level of 0.05 related to the incidence of post-operative nausea and vomiting between groups of patients.
- There is a significant difference at a level of 0.05 related to the incidence of postoperative symptoms (pain, headache, fatigue, tiredness and drowsiness) between groups of patients

The primary endpoints of this study are the incidence and intensity of nausea, vomiting, use of rescue medication and analgesics.

The secondary outcomes are the incidence of postoperative symptoms (pain, drowsiness, headache, fatigue, and tiredness) as determined by interview or spontaneous patient report for 24 hours postoperative and satisfactory statement about the patient's health condition.

Chapter Two

Literature review

2. Literature Review

Postoperative nausea and vomiting (PONV) have been associated for many years with the use of general anesthetics for surgical procedures (Liu, Hsu et al. 1999). There is a fivefold increase in the risk of PONV among patients receiving GA compared with other types of anesthesia (Samarkandi, Shaikh et al. 2004).

While none of the currently available antiemetic drugs are fully effective in all patients, it has been reported that dexamethasone is effective against emesis in most patients undergoing GA(Khalaj, Miri et al. 2013).The incidence and severity of postoperative nausea and vomiting have been significantly decreased by the use of a preoperative single-dose steroid administration in several studies (Henzi, Walder et al. 2000).

Meta-analysis showed that a 4-mg to 5-mg dose of dexamethasone seems to have similar clinical effects in the reduction of PONV as the 8-mg to 10-mg dose when dexamethasone was used as a single drug or as a combination therapy (De Oliveira, Castro-Alves et al. 2013).

Coloma et al.demonstrated in 2001 that the administration of a single I.V. dose Dexamethasone (4 mg) shortened the time for home readiness without increasing the incidence of postoperative wound infections in a high risk

outpatient population undergoing anorectal surgery(Coloma, Duffy et al. 2001).

Hernández et al. conducted a prospective, double-blind, placebo-controlled study with 70 patients scheduled for mastectomy with axillary lymph node dissection who were randomized to single-dose preoperative I.V. Dexamethasone (8 mg) or a placebo. The incidence of PONV was lower in the dexamethasone group at the early postoperative evaluation (28.6% vs. 60%; p = 0.02) and at 6 hours post-op (17.2% vs. 45.8%; p = 0.03). More patients in the placebo group required additional antiemetic medication. Additionally there were no adverse events, morbidity or mortalityrelated to Dexamethasone use (Gomez-Hernandez, Orozco-Alatorre et al. 2010).

Dexamethasone at a dose of 8 mg was found to significantly decrease the incidence of nausea and vomiting after LC (Wang, Ho et al. 1999). In a study conducted in patients undergoing LC, the incidence of nausea decreased from 40% in placebo group to 18% in the Dexamethasone (8 mg) group, incidence of vomiting reduced from 18% in placebo group to 3% in the Dexamethasone (8 mg) group, and Dexamethasone was reported to decrease pain and fatigue after surgery (Fukami, Terasaki et al. 2009).

In a double-blind, placebo-controlled study Samarkand et al. demonstrated positive effects in children undergoing tonsillectomy. Children were randomized to I.V. Dexamethasone (0.5 mg/ kg) or equal volume of saline (placebo) after induction of anesthesia. Impressive positive effects on recovery were found. Preoperative Dexamethasone reduced pain, fatigue,

nausea and vomiting in children, when compared with placebo (Samarkandi, Shaikh et al. 2004).

Wang et al. reported the results from a randomized, double-blind, placebo-controlled study, examining 90 female patients scheduled for laparoscopic tubal ligation. Patients were randomized to I.V. Dexamethasone (10 mg) or placebo (2 ml) at the induction of anesthesia. The incidence of PONV was lower in the Dexamethasone group 4 hours after surgery (27% vs. 63%; $p < 0.01$) and during the 24-hour postoperative period (34% vs. 73%; $p < 0.001$). More patients in the placebo group received a rescueantiemetic medication ($p < 0.05$). In addition there were no adverse events, morbidity or mortality related to Dexamethasone use(Wang, Ho et al. 2000).

In a well-conducted meta-analysis examining LC, it was shown that prophylactic Dexamethasone decreases the incidence of nausea and vomiting after LC relative to placebo and may decrease the severity of postoperative pain. It was suggested that surgeons should consider administering prophylactic corticosteroids to patients undergoing LC, particularly those at high risk of postoperative nausea and vomiting (Karanicolas, Smith et al. 2008).

Liu K et al. studied 60 female patients undergoing GA for major gynecological surgery, randomized to receive a preoperative single-dose either Dexamethasone (10 mg I.V.), or placebo in a prospective, randomized, double-blind fashion. Six patients in dexamethasone group and 19 in control group experienced vomiting at least once within the 24-

hour postoperative period; Dexamethasone was effective in reducing the overall incidence of vomiting from 63.3% to 20.0% ($P < 0.01$)(Liu, Hsu et al. 1999).

Dexamethasone (8mg dose) was found superior to Metoclopramide as a prophylactic antiemetic in patients undergoing LCin a variety of studies (Aziz, Naz et al. 2011, Khalaj, Miri et al. 2013).

Dexamethasone and a Dexamethasone /Metoclopramide combination was found more effective in preventing PONV than Metoclopramide alone or no anti-emetic administration (Ivanov, Ignatov et al. 2008).

The prophylactic administration of 8 mg of IV Dexamethasone, one-minute prior induction of anesthesia, reduces the incidence of PONV during the first 24 hours postoperatively, with no increase in adverse side effects or delay in PACU discharge, when compared with the intravenous metoclopramide 10 mg, in patients undergoing orthognathic surgery according to a 2011 study (Gashi 2011).

Manaa and Seif found that, the combination of Dexamethasone with Metoclopramide was not significantly more effective than single administration of Dexamethasone in the prophylaxis of PONV in patients undergoing maxillofacial surgery(Manaa and Seif 2012).

The addition of high dose Metoclopramide (50 mg) to 8 mg Dexamethasone intra-operatively is an effective, safe, and cheap way to prevent postoperative nausea and vomiting. Whereas a reduced dose of 25

mg metoclopramide intra-operatively, with, additional postoperative prophylaxis in high risk patients, may be equally effective and cause fewer adverse drug reactions (Wallenborn, Gelbrich et al. 2006).

In 2005, Bedin et al., conducted a study in children scheduled for ambulatory surgical procedures. Their results showed that, Dexamethasone is better in reducing the incidence of postoperative vomiting in the first 4 hours after surgery as well as after discharge, and demonstrated that a higher number of children required treatment in Metoclopramide group (Bedin, Pinho Mde et al. 2005).

However, treatment with a combination of 20 mg Metoclopramide and 5 mg Dexamethasone is an effective, safe, and inexpensive way to prevent PONV when compared to treatment with 4 mg Ondansetron and 5 mg Dexamethasone (Jee, Yoon et al. 2010).

When comparingDexamethasone with Depridol, both Dexamethasone and Droperidolwere found to be effective as prophylactic antiemetics in women undergoing thyroidectomy, but with Droperidol producing more side effects (Wang, Ho et al. 1999).

Chapter Three

Methodology

3.1 Study Design

A multicenter, prospective, randomized, double-blind, placebo controlled trial was organized in favor of to evaluate the impact of Dexamethasone and Metoclopramide in reducing nausea and vomiting in female patients after elective laparoscopic surgery under GA. The study design was chosen because it is the most suitable for the study objectives as well as the intervention given related to the intervention outcomes measured.

3.2 Study Setting

The study was conducted in multi centers in Nablus, Palestine and included both governmental (Rafedia Hospital)and private(Al Enjeli hospital).

Inclusion criteria for participation include patients who were:

- Scheduled for elective laparoscopic surgery
- Age among 18-60 years
- Weight between 50-120 kg
- Planned for laparoscopic surgery under GA.
- Arisk scoreof ≥60% for PONV according to Apfelscore(Apfel, Laara et al. 1999).

❖ **Exclusion criteria:** Patients who had significant history of heart, respiratory, liver, kidney or blood disorders, discord to receive the drugs of

the trial, history of gastrointestinal hemorrhage, suspected pregnancy, smoker and alcoholism. Patients who had developed nausea and vomiting through the last day prior surgery, who had receive antiemetic drugs through the last 24 hours prior surgery, and conversion to open cholecystectomy.

3.3 Study Sample

120 female patients, scheduled for elective laparoscopic surgery, ASA physical status one or two, their age between 18-60 years, and their weight between 50-120 kg and with a risk of > 60% for PONV.

3.4 Study Variables

- **Dependent Variable:**

Nausea and vomiting after surgery is recognized as the incident of any nausea, retching, or vomiting in inpatients after surgery within the first 24 hours(Pierre and Whelan 2013). Dependent variables are summarized in Table 1.

Table1. Dependent variables of the study.

Total incidence of vomiting or retching
Incidence of nausea
Intensity of nausea (measured by likert type scale 0-6)
The frequency (percentage) of patients requesting rescue antiemetic
Incidence of Pain
Intensity of pain measured by VAS-scale
The frequency (percentage) of patients requesting rescue analgesic
Satisfactory statement about the patient's health condition
Incidence of drowsiness
Incidence of headache
Incidence of fatigue
Incidence of tiredness

- **Independent Variables:**

Demographic characteristics: The incidence of PONV studied regard to variable summarize in Table 2.

Table2. Independent variables of the study

Age/years
Height/cm
Weight/kg
BMI
LMP
Span of anesthesia (min)
Span of surgery (min)
Total doses of perioperative Fentanyl (µg)
Total doses of perioperative Propofol (mg)

3.5 Outcome Measurements

The main outcome was the occurrence of PONV. A patient was considered to be suffering from PONV if nausea or vomiting, retching was documented in any of the post-operative assessments.

A secondary outcome was the intensity of the nausea, assessed by aself-report lickertscale (Morrow 1984) ranging from 0 to 6 (0 for no nausea, 1 for very mild nausea,2 mild, 3moderate, 4 severe, 5very severe, 6 intolerable). In addition the study definednausea when requesting a single dose of an antiemetic medication as a rescue that isOndansetron 4mg. Other outcomes included the frequency and intensity of pain, measured with a VAS –score(McCormack, Horne et al. 1988)spans from 0-10 (0 for no pain and 10 the worst pain that may be possible) measured at postoperative hours immediately after surgery in PACU, 2, 4, 8, 16, 24 hours. A score of four and above on VAS-scale was defined as pain requiring administration of an analgesic drug (2 mg of IV of morphine) repeated as needed to achieve patient comfort.

Patient's satisfaction was measured by a scale of statements including: very unsatisfied, unsatisfied, neither satisfied nor unsatisfied, satisfied, and very satisfied.

3.6 Administration of Medications

Participants were allocated by random to one of the four study groups. In a double-blind fashion, study medications prepared and given by an

anesthesia nurse in similar 10 ml syringes. Two syringes were assigned to each patients, one minute prior the administration of anesthesia and the other one at the termination of anesthesia.

Group one received 8 mg Dexamethasone one minute before induction of anesthesia and 10 ml saline before termination of anesthesia (D).

Group Two received 10 ml saline one minute before administration and Metoclopramide 20 mg before termination of anesthesia (M).

Group Three received Dexamethasone (8 mg) one minute before administration and Metoclopramide (20 mg) before termination of anesthesia (C).

Group Four received 10 ml saline one minute before administration of anesthesia and before termination of anesthesia (P).

Table 3: Administration of perioperative medications summarized .

	Before induction of anesthesia	**After termination of anesthesia**
Dexamethasone group (D)	8 mg Dexamethasone	10 ml Slaine
Metoclopramide group (M)	10 ml Slaine	20 mg Metoclopramide
Combination group (C)	8 mg Dexamethasone	20 mg Metoclopramide
Placebo group (P)	10 ml Slaine	10 ml Slaine

Metoclopramide at dose of 10 mg is a weak antiemetic andisnotefficient in reducing the occurrence of nausea and vomiting (Henzi, Walder et al. 1999). Based on guidelines for the management of PONV(Gan, Diemunsch et al. 2014), and evidence-based practices of PONV management (Habib and Gan 2004), Metoclopramide hasan antiemetic effect when given in doses higher than 20 mg**.**

3.7 Blinding

The patients, all employees included in patient care, the person who was collected the data, and the outcome adjudicators were unaware of the treatment group allocation.

3.8 Intervention /Treatment

Study drugs were prepared by a nurse unrelated to the study. Medication was administered in a syringe containing either 10 ml saline, 10 ml saline with 8 mg dexamethasone, or 10 ml saline with 20 mg metoclopramide. Medication was indistinguishable by sight or smell.

Syringes were labeled with a study-specific identification that is the number for each patient. The anesthesiologist administered the study medication immediately before the induction of anesthesia and was totally unaware of the distribution of the treatment group. Following, all the participants underwent GA, laparoscopic procedures and routine postoperative care (which will be explained in detail later in study procedure).

3.9 Sample size calculation

Sample size was predefined by power analysis dependent on the probability that the decision rule would lead to conclusion that the total frequency of PONV in the placebo group and the frequency of PONV in the treatment groups would differ. The (a) error was set at 0.05 which is the risk of making type I error, and (b) Power(1-type II error) was set at 0.85 c. Minimum Standard Error=1(Kutner, Nachtsheim et al. 2004). According to the analysis of power, 27 patients were recommended. 30 were recruited to account for the possibility of dropout.

3.10 Randomization

Randomization of the participants into study groups was done through sealed envelopes; the sealed envelopes were opened only after patient had been found eligible for the trial and had signed the informed consent form.

3.11 Assessment of questionnaire

Each study subject was interviewed by a research blind observer following surgery.A specific questionnaire was developed for the study (Annex2). The questionnaire was evaluated by a group of relevant experts including2physicians, 3 anesthetic nurses, one PACU nurse and one statistician, who were requested to decide whether or not the questions were suitable and plausible. After a few alterations the questionnaire was considered valid. Reliability was investigated with a test-retest in a further

20 patients. The test-retest dichotomous correlation coefficients were between (0.56) and (0.90) with significant levels less than 0.05.The questionnaire was defined as suitable and gave a right picture of their experience by (97) % of the patients.

3.12 Anesthesia Protocol

Fifteen minutes before the administration of anesthesia, all the participants were pre-medicated with Dormicum 1 mg IV. Lactated Ringer s at a rate of 10 ml / kg was administered to all participants. Monitoring throughout anesthesiaachieved by electrocardiogram, noninvasive blood pressure, pulse oximetry and capnometry. The same consistent anesthetic approach was used in all participents. GA was induced with Fentanyl (2 μg / kg) and Propofol (2 mg / kg). In all groups, Atracurium was given (0.5 mg / kg) for ease of tracheal intubation. Anesthesia contained 1.2% Isoflurane, 50% air in O_2. Extra Fentanyl and Atracurium were used as required. The ventilation was mechanically controlled and modified to preserve end-times of Carbonic dioxide between 35 and 40 mmHg. At the end of the operation, Atropine was administered 0.01 mg / kg and Neostigmine 0.05 mg / kg IV for repeal of muscle relaxation and the endotracheal tube was removed.

3.13 Surgical Protocol

During the entire operation, patients were put in reverse Trendelenburg position and the abdominal cavity was inserted with CO_2 till make intra-

abdominal pressure between 13-15 mmHg. A temporal nasogastric tube was inserted to enhance gastric drainage. Before endotracheal extubation, the nasogastric tube was suctioned again and then pulled out. In PACU, all patients obtained oxygen, (5 Lt/min) by a face mask. All patients obtained intravenously Lactated Ringer solution at a rate of 2 ml / kg per hour until they tolerated oral fluids.

- **In the PACU**

After extubation, participants were relocated to the post anesthetic care unit (PACU). During their stay in the PACU (2 hours), O2 saturation was monitored constantly, while heart rate, blood pressure, and respiratory rate, were monitored each 15 min. Oxygen (5 Lt/min) was administered via face mask on admission and stopped before transferred to the ward. Patients were discharged to a ward for further observation 2 hours later.

- **In the Ward**

After patients reached the ward, a research blind nurse observed them postoperatively. The patients were evaluated at 30 minutes, 1st, 4th, 6th, 12th, and 24th hours after surgery by an individual unaware of which antiemetic the patients had received. Nausea scores ranged from 0 to 6 (0 for no nausea; 1 for very mild nausea, 2; mild, 3; moderate. 4; severe, 5: very severe, 6: intolerable). Vomiting was assessed by frequency. Participants were requested to report nausea, vomiting, or retching occurred throughout the study period.

Ondansetron 4 mg IV was administered when the nausea score was 3 and above and/or When the frequency of vomiting twice and higher. The occurrence of nausea or vomiting was recorded during the early period (0-2 hours) and delayed (2-24 hours) period of study, and the number of patients requiring antiemetic therapy also recorded.

Intensity of pain assessed subjectively by patients through the Visual Analog Scale (VAS; 0 = no pain, 10 = most severe pain) each 1 hour in PACU and at 4 hour periods in the ward. Morphine 2 mg IV was given to patient when pain score on VAS was 4 or above and when patient requested analgesia.

The occurrence of any side effects headache, drowsiness, fatigue, and tiredness during the study period was evaluated either by follow-up with blinded nurse or by spontaneous reports by the participants.

3.14 Data Analysis

❖ The data was analyzed using SPSS software statistical package version 20. Means, standard deviations, percentages and frequencies were used to describe data for each group, Chi Square test was utilized to examine differences between Percentages, Tukey HSD Post-Hoc test examined pairwise differences between means, and One Way Analysis of Variance (F-Test) was used to examine differences between means.

3.15 Ethical Consideration

Ethical principlesthat insure respect for all people and protection of their health and rights were strictly adhered to. The study followed the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research on Humans(World Medical 2013).

The dignity, integrity, right to self-determination, privacy, voluntary, and confidentiality of personal information of research participants considered.The patients were informed about their right to refuse participation or to withdraw from the study at any time without revenge.

Approval of the study has been taken from the Institutional Review Board (IRB) at An-Najah National University and from the Palestinian Ministry of Health.

Consent forms were obtained from patients after detailed explanation of the aim and objectives of the study.

Chapter Four

Results

The data was analyzed using the SPSS software statistical package version 20. I used Means, standard deviations, percentages and frequencies were conducted to describe data for each group, Chi Square test was used to examine differences between Percentages, Tukey HSD Post-Hoc test was analyzed to examine pairwise differences between means, and One Way Analysis of Variance (F-Test) was completed to examine differences between means.

4.1 Patient Characteristics and Operative Information.

Table 4: Patient Characteristics and Operative Information.

Variable		Dexamethasone N=30	Metoclopramide N=30	Combination N=30	Placebo N=30	P-value
Age		37.43±10.28	32.40±11.67	36.20±13.17	37.40±10.62	0.284
BMI	Normal	5(16.7%)	8(26.7%)	7(23.3%)	7(23.3%)	0.732
	Overweight	12(40%)	8(26.7%)	10(33.3%)	9(30%)	
	Obese	13(43.3%)	14(46.6%)	13(43.3%)	14(46.6%)	
LMP(Days)	0-8	8(26.7%)	7(23.3%)	12(40%)	6(20%)	0.149
	9-16	11(36.7%)	10(33.3%)	8(26.7%)	8(26.7%)	
	17-28	2(6.7%)	10(33.3%)	4(13.3%)	7(23.3%)	
	>28	9(30%)	3(10%)	6(20%)	9(30%)	
Duration of Anesthesia (min)		80.77±20.45	77.98±25.95	75.90±30.61	77.73±20.59	0.898
Duration of Surgery (min)		61.10±18.77	56.57±26.26	55.10±28.79	59.07±20.60	0.775
Total dose of Perioperative Fentanyl (µg):		162.33±68.25	168.17±88.89	144.33±62.54	172.33±79.82	0.496
Total dose of Perioperative Propofol (mg):		170.32±26.78	168.21±24.65	165.28±19.23	169.33±28.54	0.877

Significant at 0.05 level. Data are Mean ±SD with P-values derived from ANOVA test.

Data include Frequencies and Percentages (%) with P-values derived from Chi Square test.

According to the results in the table (3), All 120 patients recruited in the study had their laparoscopic surgery completed. There were no statistically significant differences among the 4 groups according to patient age, BMI, LMP, duration of anesthesia, surgery, and total dose of perioperative Fentanyl and Propofol.

4.2 Postoperative Nausea and Vomiting

Table5: The incidence of postoperative nausea and vomiting, intensity of nausea and complete response between study groups

Variable	Dexamethasone N=30	Metoclopramide N=30	Combination N=30	Placebo N=30	P-value
Vomiting (In PACU)	2(6.7%)	7(23.3%)	1(3.3%)	14(46.7%)	0.000*
Vomiting (In Ward)	6(20%)	8(26.7%)	5(16.7%)	14(46.7%)	0.043*
Vomiting (In Total 24 Hrs.)	6(20%)	10(33.3%)	6(20%)	17(56.7%)	0.006*
Frequency of Vomiting (In PACU)	1.5±0.71	1.25±0.5	1±0	1.45±0.52	0.788
Frequency of Vomiting (In Ward)	1.67±0.52	2.14±0.69	1.8±0.84	2.58±1.08	0.162
Frequency of Vomiting (In Total 24 Hrs.)	1.58±0.49	1.86±0.63	1.67±0.82	2.1±0.83	0.439
Incidence of Nausea (In PACU)	5(16.7%)	9(30%)	1(3.3%)	19(63.3%)	<0.001*

Incidence of Nausea (In Ward)	6(20%)	10(33.3%)	5(16.7%)	17(56.7%)	0.008*
Incidence of Nausea (In Total 24 Hrs.)	6(20%)	10(33.3%)	5(16.7%)	19(63.3%)	<0.001*
Intensity of Nausea (In PACU)	1.77±1.19	2.33±1.35	0.73±0.94	3.17±1.60	<0.01*
Intensity of Nausea (In Ward)	1.80±1.32	2.53±1.11	1.37±1.19	2.97±1.47	<0.01*
Intensity of Nausea (In Total 24 Hrs.)	1.78±1.14	2.43±1.03	1.05±0.90	3.07±1.34	<0.01*
Complete Response (In Total 24 Hrs.)	23 (76.6%)	17 (56.6%)	24(80%)	11 (36.6%)	

Significant at 0.05 level. Data are Mean ±SD with P-values derived from ANOVA test.

Data include Frequencies and Percentages (%) with P-values derived from Chi Square test.

4.2.1 Incidence of Vomiting

In the 0-2 hour period postoperatively, there were reported differences in the incidence of vomiting between groups of patients. The differences were in combination group 1 (3.3%) and Dexamethasone group 2(6.7%) compared with placebo group 14(46.7%), $P < 0.05$, and in combination group 1 (3.3%) compared with metoclopramide 7(23.3%), $P = 0.0237$. There is no significant difference between combination group 1(3.3%) and Dexamethasone group 2 (6.7%), $P = 0.5491$.Results indicate that Dexamethasone alone or in combination with Metoclopramide is more effective to reduce incidence of vomiting in PACU when compared with Metoclopramide alone or placebo (Table 4).

In the 2 -24 hours postoperatively, incidence of vomiting occurred in the combination group 5 (16.7%) and Dexamethasone group 6 (20%) significantly less than in the placebo group 14(46.7%), $p<0.05$. There were no significant differences between combination and Dexamethasone groups when compared with the Metoclopramide group 8 (26.7%), $p>0.05$, also there were no significant differences between placebo and Metoclopramide groups $p>0.05$.These results indicate that the effect of Metoclopramide is similar as to that of placebo (Table 4).

According to the results represented in table (4), during the 24 hour period after recovery from anesthesia, the incidence of postoperative vomiting in patients who received Dexamethasone alone 6(20%) or Dexamethasone plus Metoclopramide 6(20%) were lower than those who had received

placebo 14(46.7%),p = 0.0037. There is nosignificant difference between placebo 14(46.7%) and Metoclopramide group 10(33.3%) p = 0.0708**.** The results suggest that the incidence of vomiting was reduced significantly by use of Dexamethasone as a monotherapy or in combination with Metoclopramide (Figure 2).

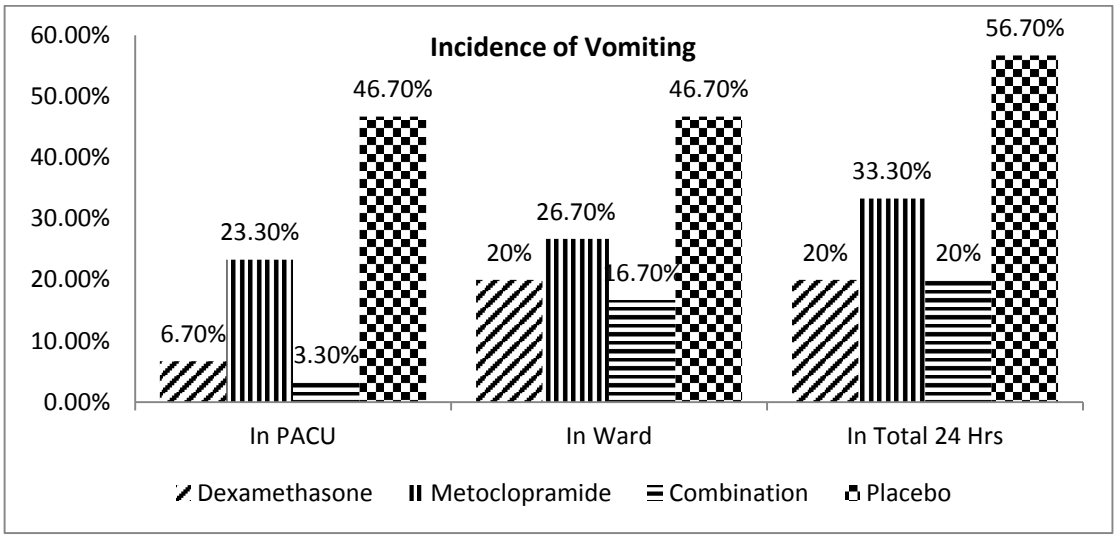


Figure 2: Incidence of Vomiting by Percentage in PACU, Ward and within a total of 24 hrs.

4.2.2 Incidence of Nausea

In table 4, with regard to incidence of nausea, during their stay in the PACU (2 hours postoperatively), there were statistical significance differences reported between study groups, Dexamethasone 5 (16.7%), Metoclopramide 9 (30%), combination therapy1(3.3%) and placebo 19(63.3%), p <0.001. In order to identify where is the statistical difference is located a Post Hoc test was used. The results indicated that, there was a statistical significance difference between the three treatment groups when compared with placebo group (p< 0.05). In addition there was a

significance difference between the combination group 1(3.3%) compared with the Metoclopramide group 9(30%) p=0.0059. There was no significant difference noted between Dexamethasone and Metoclopramide plus Dexamethasone. The author concludes that, nausea could be reduced by using a combination, Dexamethasone or Metoclopramide, howeverthe combination effect was clearly superior over Metoclopramide.

In the table 4, the number of patients of patients who reported nausea while inpatients reduced significantly in the combination group 5 (16.7%) and Dexamethasone group 6(20%) when compared with placebo group 17(56.7%), $p < 0.05$. There is no significant difference between Metoclopramide group 10(33.3%) and placebo group17 (56.7%), $p = 0.0708$. Results reflect that Dexamethasone alone and in combination is more effective to reduce incidence of nausea thanMetoclopramide and no active treatment (placebo group).

As represented in table 4, during the postoperative observation period of 24 hours, there was significance difference between the treatment groups (D, M, and C) when compared with the no active treatment placebo group $p< 0.05$. There were no statistical significance differences between the three treatment groups, $p>0.05$.Summarized the results demonstrate that, using Metoclopramide and Dexamethasone alone or in combination decreased the incidence of nauseain the 24 hours after recovery as compared with a non-active placebo. The results indicate that, the three treatments groups(D,

M, and C) have similar effect in reducing overall incidence of nausea (Figure 3).

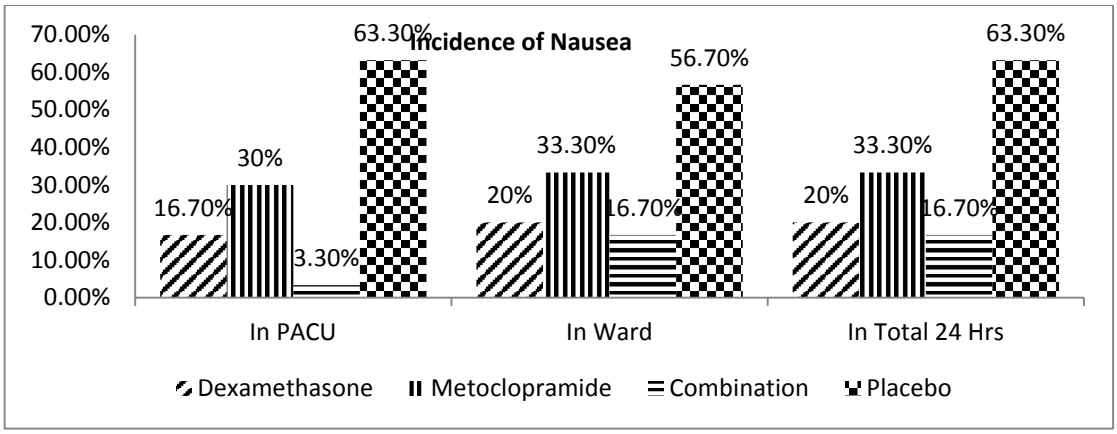


Figure 3: Incidence of nausea by percentage in PACU, Ward and during a total of 24 hours

4.2.3 Intensity of Nausea

As represented in table 4, while in PACU, the intensity of nausea reduced significantly for the combination group (0.73) and Dexamethasone group (1.77)as compared with placebo group (3.17), $p < 0.05$. There are statistical significance differences betweenthe combination group compared with Dexamethasone group $p = 0.013$, and Metoclopramide group at $p = 0.000$.There is no significant difference between the Metoclopramide group (2.33) and placebo group(3.17), $p = 0.066$. Results show that combination treatment is more effective in reducing intensity of nausea of patients while in PACU as compared withDexamethasone,Metoclopramide andplacebo. However it was noted that, the combination therapy was superior to Dexamethasone alone.

As presented in table 4, in an inpatient ward, the intensity of nausea in the combination group (1.37) and Dexamethasone group (1.80)was

significantly reduced when compared with the placebo group (2.97), at $p < 0.05$. There is a significance difference betweenthe combination group as compared with Metoclopramide group (2.53) at $p= 0.003$. There is no significant difference between the Metoclopramide group and the placebo group ($p = 0.558$). As a result, by using Dexamethasone alone or in combination the intensity of nausea was reduced in ward compared with the placebo group. In addition, combinationtherapy (1.37) was more effective than Metoclopramide (2.53), at $P <0.01$.

Table 4 shows that, during 24 hours postoperatively, the intensity of nausea in the combination group (1.05) was significantly less than in the Dexamethasone group (1.78), $P= 0.0079$. The cumulative score of nausea decreased in the Dexamethasone (1.78) and combination groups (1.05) as compared with a non-active placebo group (3.07), at $p = 0.000$ and the Metoclopramide group (2.43) at $p = 0.000$. There is no significant difference indicated between the Metoclopramide group and the placebo group, $p = 0.128$. The results demonstrate that combination treatment only reduces the cumulative score for intensity of nausea in the 24 hours postoperatively compared with the three treatment groups. However it was noted that, the combination therapy was superior to Dexamethasone alone (Figure 4).

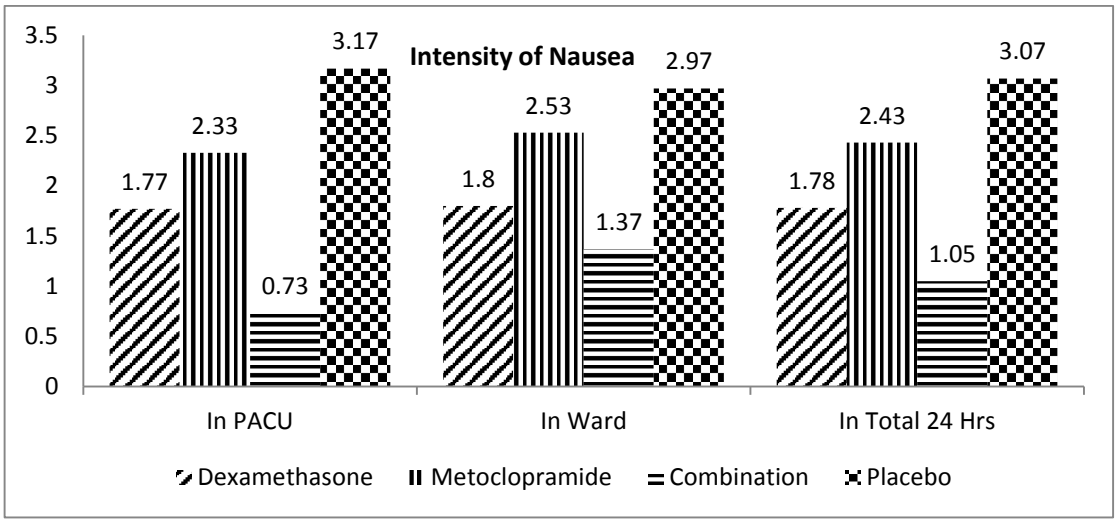


Figure 4: Intensity of nausea in PACU, Ward and in total 24 hr.

4.2.4 Complete Response

Table 4 shows the cumulative score for complete response in the 24 hours postoperatively there is a significant difference in the complete response between combination group 24 (80%), dexamethasone group 23 (76.6%) versus placebo group 11 (36.6%), P = 0.0007 and P = 0.0019 respectively . There is no significant difference between placebo group and metoclopramide group 17 (56.6%), P = 0.123. There is a significant difference between the combination group and metoclopramide group, P = 0.0534. There is no significant difference between dexamethasone and metoclopramide, P = 0.1034. The result clarifies that the number of patients with complete response in dexamethasone and combination groups is significantly greater than the placebo group. However it was noted that, the combination therapy was superior to metoclopramide alone and placebo.

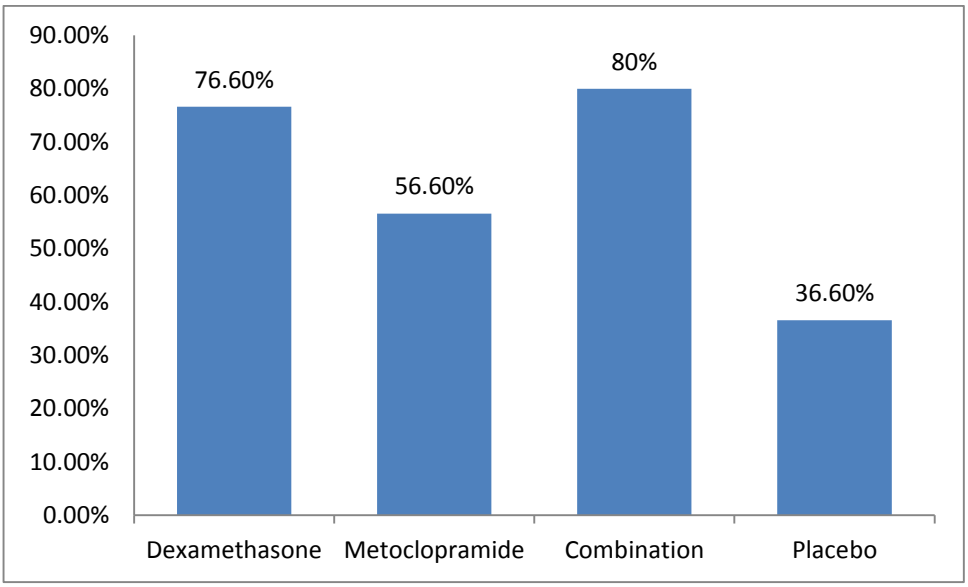


Figure 5: Complete Response (no nausea, no retching, no vomiting and no need for rescue medication) in the four study groups in total 24 hr.

4.3 Postoperative Symptoms

Table 5 represents the analysis results of differences in the incidence of postoperative symptoms between groups of patients in the total 24 hours postoperatively.

Table6: The numbers and percentage of episodes of postoperative symptoms in the four groups of patientsin the total 24 hours postoperatively.

Variable	Dexamethasone N=30	Metoclopramide N=30	Combination N=30	Placebo N=30	P-value
Headache	3(10%)	9(30%)	9(30%)	8(26.7%)	0.212
Tiredness	9(30%)	11(36.7%)	7(23.3%)	14(46.7%)	0.265
Drowsy	10(33.3%)	14(46.7%)	11(36.7%)	13(43.3%)	0.708
Fatigue	9(30%)	12(40%)	7(23.3%)	11(36.7%)	0.524
Incidence of Pain	21(70%)	28(93.3%)	22(73.3%)	29(96.7%)	0.004*
VAS for Pain	4.20±1.37	5.07±1.28	4.40±1.4	5.47±1.04	0.001*

Significant at 0.05 level. Data are Mean ±SD with P-values derived from ANOVA test.

Data include Frequencies and Percentages (%) with P-values derived from Chi Square test.

4.3.1 Post-operative Symptoms

According to the results in Table 5, there are no significant differences in postoperative symptoms (headache, tiredness, drowsy, and fatigue) between groups of patients in PACU, in ward, or in the total 24 hours of monitoring ($p > 0.05$). (Figure 6).

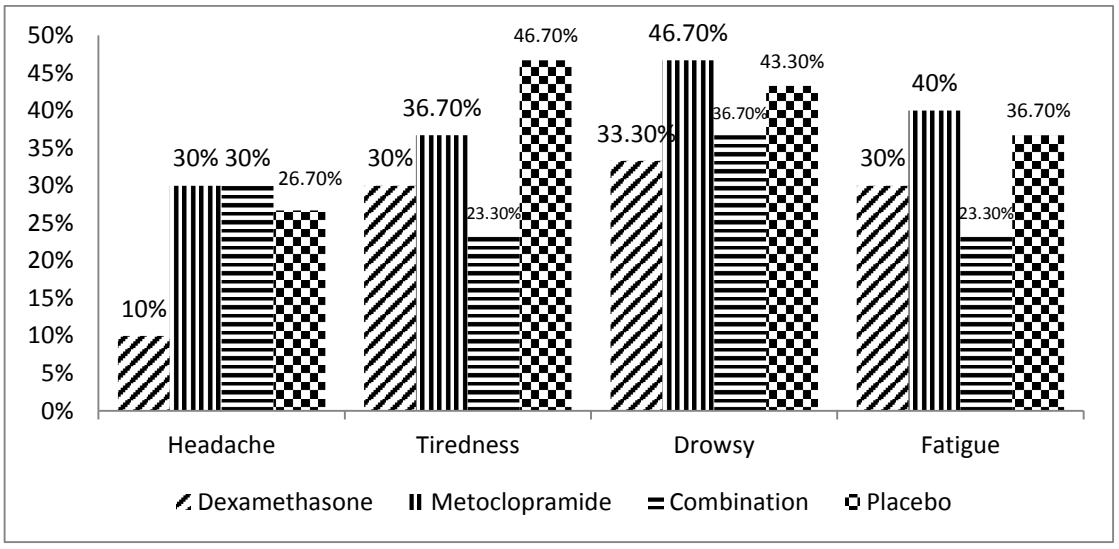


Figure 6: Overall Incidence of postoperative symptoms by percentage in total 24 hour period**.**

4.3.2 Incidence of Pain

According to the results in Table 5, during the 24 hour postoperative period, significantly fewer patients complained of pain in the Dexamethasone group 21(70%) and combination groups22(73.3%)as compared with the Metoclopramide group 28(93.3%) and placebo group 29 (96.7%), P=0.001. There was no significant difference reported between combination and Dexamethasone groups p=0.7786, also there was no significant difference between placebo and metoclopramide groups p=0.5491. The results demonstrate that the incidence of pain was decreased significantly by use of Dexamethasone alone or in combination with Metoclopramide during the 24 hour postoperative period.(Figure 7)

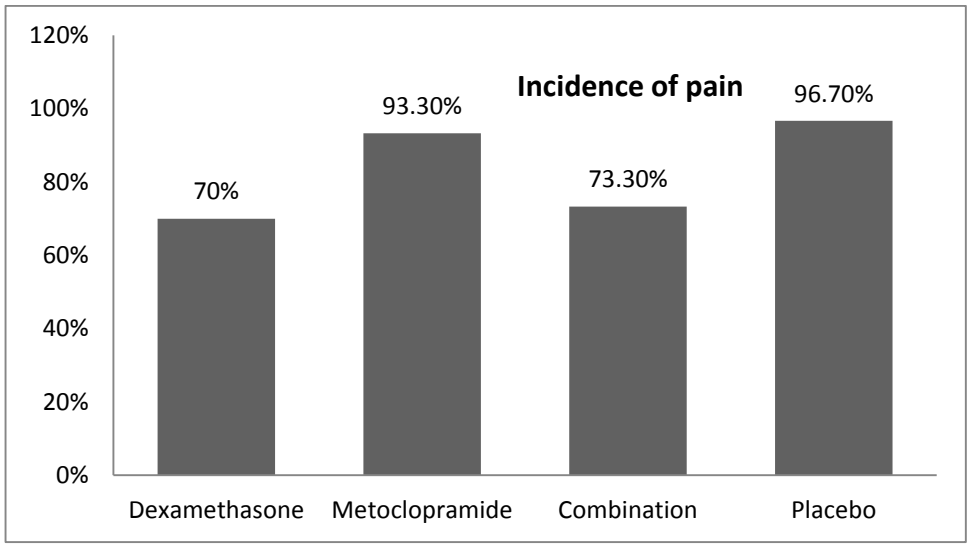


Figure 7: Overall incidence of pain by percentage in total 24 hour post operative period

4.3.3 Intensity of Pain

During the 24 hour postoperative period, the cumulative score of pain reduced significantly in the Dexamethasone group (4.20) and combination group (4.40) when compared to the placebo group (5.47), at $p < 0.05$. There is a significance difference noted between the Dexamethasone group and Metoclopramide group (5.07), $p = 0.049$ with Dexamethasone being more effective .There were no significant differences reported between the Metoclopramide group and combination group or the non-active placebo group, $p > 0.05$.The results can be interpreted that by using Dexamethasone alone or in combination the intensity of pain in the 24 hour period postoperative is reduced compared with placebo group (Figure 8).

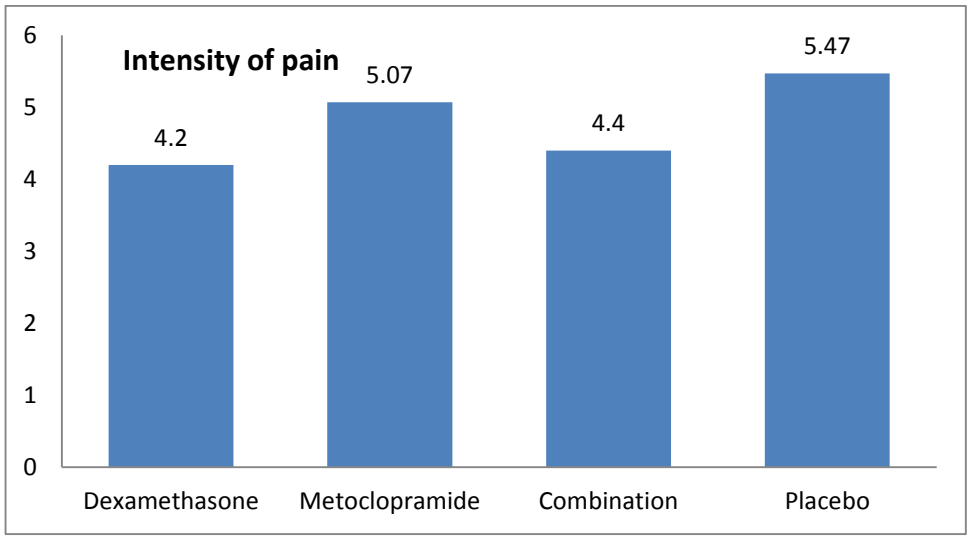


Figure 8: Intensity of pain in the total 24 hr. period

4.4 Rescue Medications

Table 6 shows the results of analysis of differences in both rescue antiemetic (Ondansetron) and rescue analgesic (Morphine) between treatment groups in the total 24-hour post-operative period

Table 7: The frequency and percentage of patientsrequireding rescue antiemetic and analgesic.

Variable	Dexamethasone N=30	Metoclopramide N=30	Combination N=30	Placebo N=30	P-value
Rescue Antiemetic (Ondansetron)	7(23.3%)	13(43.3%)	6(20%)	19(63.3%)	0.000
Rescue Analgesic (Morphine)	21(70%)	28(93.3%)	22(73.3%)	29(96.7%)	0.004*

Data include Frequencies and Percentages (%) with P-values derived from Chi Square test.

❖ Rescue Antiemetic (Ondansetron)

- Table 6 shows that in the 24 hour postoperative period, the total number of patients who received combination 6(20%) and Dexamethasone 7(23.3%)that required rescue antiemeticwas lower than those who received a non-active placebo 19(63.3%),$p < 0.05$. There was no significant difference between placebo and Metoclopramide groups 13(43.3%) $p = 0.1237$. There is a significant difference between the combination group and metoclopramide group, $P = 0.0544$. There is no significant difference between dexamethasone and metoclopramide, $P = 0.1031$.The results suggest that using Dexamethasone alone or in combination reduces the need for rescue antiemetic in 24 hourspostoperatively (Figure 9).

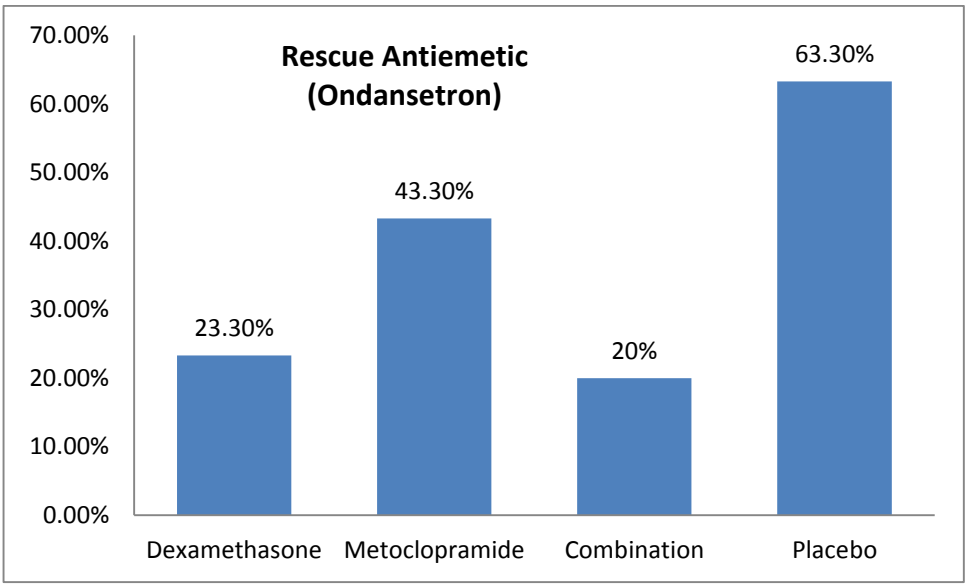


Figure 9: Percentages of patients requiring rescue antiemetic.

❖ Rescue Analgesic (Morphine)

Table 6 presents finding that show that, during the 24 hour postoperative period, the number of patients receiving Dexamethasone 21(70%) and combination 22 (73.3%)who required rescue analgesic was significantly less than those who in the Metoclopramide 28(93.3%) and placebo groups29 (96.7%), at $p < 0.05$. There were no significant differences between the combination and Dexamethasone groups $p = 0.7786$. No significant differences between the placebo and metoclopramide groupswere indicated $p = 0.5491$. The results show that the consumption of postoperative rescue analgesic was decreased significantly by use of dexamethasone alone or in combination with metoclopramide (Figure 10).

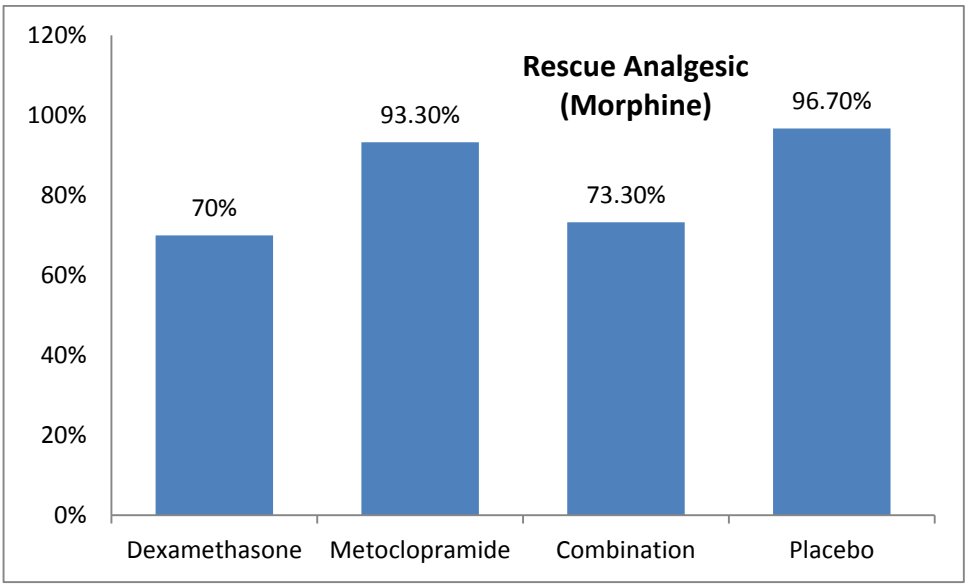


Figure 10: Percentages of patients required rescue analgesic.

4.5 Self-Report Satisfaction Survey

Table 8: The numbers and percentages of patient report regarding satisfaction

Variable	Dexamethasone N=30	Metoclopramide N=30	Combination N=30	Placebo N=30	P-value
Very Unsatisfied	2(6.7%)	7(23.3%)	0(0%)	9 (30%)	0.014*
Unsatisfied	5(16.7%)	4(13.3%)	4(13.3%)	7 (23.3%)	
Neither Satisfied nor Unsatisfied	1(3.3%)	0(0%)	0(0%)	0 (0%)	
Satisfied	21(70%)	17(56.7%)	22(73.3%)	13 (43.3%)	
Very Satisfied	1(3.3%)	2(6.7%)	4(13.3%)	1(3.3%)	

Data include Frequencies and Percentages (%) with P-values derived from Chi Square test.

The data in table 7demonstrate that, more patients in the Dexamethasone group reported satisfaction related to their health status 22(73.3%) versus 7 (23.3%) who stated they were unsatisfied.

In the Metoclopramide group, 19 patients (63.4%) reported they were satisfied with their health status while 11 patients (36.6%) reported they were unsatisfied.

The majority of patients 26(86.6%) in the combination group reported satisfaction with their health status as compared with 4(13.3%) who stated they were unsatisfied.

Finally, the largest proportion of patients in the placebo group 16 (53.3%) reported they were unsatisfied with their health status as compared to 14 (46.3%) who were satisfied.

The results show that, patients who received prophylactic antiemetic were more satisfied with their status as compared with those who received non-active placebo. The highest rate of satisfaction was noted in patients who received a combination of Dexamethasone and Metoclopramide (Figure 11).

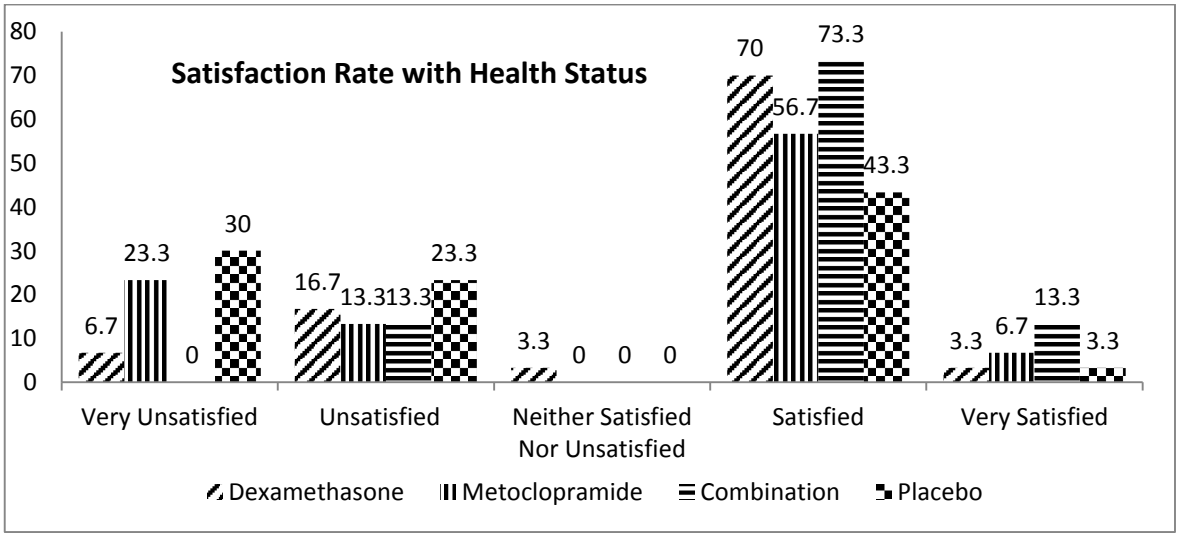


Figure 11: Self-Report Satisfaction rate of patients related to health status after receiving prophylactic antiemetics.

Chapter Five
Discussion

This study compared the antiemetic efficacy of prophylaxisDexamethasone and Metoclopramide either as alone or in combination,in female patients after laparoscopic surgery. Despite laparoscopic procedures being accepted and having reduced surgical morbidity, the elevated incidence of postoperative nausea and vomitingremains a main clinical concern (Koivuranta, Laara et al. 1997). The incidence of PONV may be related to the gas utilized to inflate the abdomen during the surgery, which puts pressure on the Vagus nerve, which in turn is connected to the vomiting center in the brain(Chatterjee, Rudra et al. 2011). Habib and Gan (2001) revealed that,the incidence of PONV ranges from (40%-77%) for patients undergoing laparoscopic surgery (Habib and Gan 2001). This is believed to be caused initially by the abdomen inflation, which is necessaryin this kind of procedure (Hambridge 2013).

Use of prophylactic anti-emetics should depend on a comprehensive assessment of an individual patient's risk for PONV (Apfel 2010). The simplified risk score of Apfel et al includes four independent predictors: female gender, non-smoking status, history of PONV or motion sickness, and planned usage of IV opioids. When 0, 1, 2, 3 or 4 of these predictors are present, the patient's risk is approximately 10%, 20%, 40%, 60% or 80%, respectively (Apfel, Laara et al. 1999).All patients in this study had a predicted risk score of more than 60%, wherethey were female, non-smoker patients, and opioids were applied intraoperative.

5.1 Risk Factors

The causes of nausea and vomiting after laparoscopic surgery are not clearlyexplained, but are possibly of multifactorial etiology (Watcha and White 1992). Several risk factors have been identified that may trigger PONV. However, in recent study, treatment groups identical with respect to age, BMI, LMP, span of anesthesia, span of surgery, and total dose of perioperative fentanyl and propofol are observed to clarify critical factors.

PONVconsidered asthe most widespread adverse-effects of perioperative opioids, irrespective of the route of administration (Toner, Broomhead et al. 1996). Premedication with opioids (Lerman 1992, Bryson, Frost et al. 2007) and intraoperative use raises the risk of PONV in a dose-dependent manner (Pierre and Whelan 2013). The Society for Ambulatory Anesthesia Consensus Guidelines recommend reducing the use of opioid intraoperative and postoperative in way to manage PONV (Gan, Diemunsch et al. 2014).

Opioids delaying gastric emptying by decreasing muscle tone and peristaltic movements, produce distension, and stimulate the vomiting reflex (Pierre and Whelan 2013). There is evidence that the emetic effects of opioids are mediated via opioids receptors in the postrema area, resulting in activation of the vomiting center (Toner, Broomhead et al. 1996). Paradoxically, Andersen and Krohg noted that opioids did not increase the frequency of nausea, but actually relieved it (Andersen and Krohg 1976).

In the present study, more patients in the placebo group requested rescue analgesic (Morphine) suggestive of higher incidence of PONV. Our results are congruent with the study conducted by Langevin and Lessard, which reported that the opioid's influence on PONV is likely to be regarding plasma concentrations at the time that emetic symptoms happenin place of intraoperative concentrations(Langevin, Lessard et al. 1999).

5.2 Postoperative Nausea and Vomiting

In the current study, the efficacy of Metoclopramide and Dexamethasone as mono therapies and their combination for prevention of PONV was compared. Risk factors were controlled by the study design. The span of surgery, anesthesia and anesthetics utilized were identicalbetween the groups. Therefore it's likely that, the pharmacological agents were responsible for variations in the occurrence of PONV between the groups instead of any confounding variables.

None of the available antiemetic agentsaretotally efficient for preventing PONV, particularly in patients with highriskPONV factor scores(Habib and Gan 2001). Because of the suspected multifactorial etiology of PONV, a superior prophylaxis effect perhapsobtained by giving a combination of antiemetic working at various receptor sites, given that at least four receptor systems are likely involved in in PONV (Chatterjee, Rudra et al. 2011). However, due to the elevated cost of the antiemetic agents, it was decided to use agents with minimalcosts agents in our study; Metoclopramide and Dexamethasone.

The study was performed on 120 female patients who underwent laparoscopic surgery under GA. They were assigned into four equal groups (30 of each) which differed by antiemetic agent used. It is necessary to observe that, in the 24 hour postoperative period 80% of patients had no nausea and vomiting in combination group compared to 76.7% in Dexamethasone group, 56.7% in Metoclopramide and 36.7% in placebo group.

Metoclopramide is a medication that has been utilized for 40 years in the prevention of postoperative vomiting(Manaa and Seif 2012). It's a pro-kinetic agent that decreases stomach emptying and bowel transit times by antagonizing the dopaminergic D2 receptor (Nesek-Adam, Grizelj-Stojcic et al. 2007).

The bestpractice recommended dosefor Metoclopramide is 10 mg IV for adults and 0.25mg/kg IV for children (Habib and Gan 2001).However, Metoclopramide is not effective in reducing PONV at a 10 mg dosage (Henzi, Walder et al. 1999, McCracken, Houston et al. 2008, Aziz, Naz et al. 2011). Metoclopramide has identical efficiency compared with another antiemetics at the 25– 50 mgdosage (Pierre and Whelan 2013).However, Gan et al. in their guidelines don't encourageusing Metoclopramide as a perioperative antiemetic(Gan, Diemunsch et al. 2014).

The efficacy of a 20 mg dose of Metoclopramide given at the end of LCis similar tothat of a 8 mg dose of Ondansetron in decreasing PONV(Quaynor and Ræder 2002).In addition, in a study includingover 3000 patients;the

effectiveness of Metoclopramide in doses over 20 mg, particularly in 25 and 50 mg doses, it performed similarly to Ondansetron 4 mg in early PONV but with a lesser effect for late PONV (Wallenborn, Rudolph et al. 2003). To the contrary, when compared with 12.5 mg Dolasetron, a 20 mg dose of Metoclopramide was found to be inefficient in the prevention of PONV(Piper, Suttner et al. 2002).

Because of its short duration of action, Metoclopramide must be given at the end of operation or after arrive to the PACU to produce aneffective antiemetic impact in the early time postoperatively(Watcha and White 1992). Henzi et al., demonstrate that, the antiemetic effect of metoclopramide seems to be exist only through the first six hours after administration(Henzi, Walder et al. 1999). In the present trial, when 20 mg metoclopramide was administered as single prophylactic antiemetic at the end of anesthesia reduced PONV the effects were comparative to a non-active placebo.

Dexamethasone is a steroid drug and is most commonly used for prevention of PONV, while its efficiency appears only when given as a prophylaxis (Doubravska, Dostalova et al. 2010). The mechanism of action of DexamethasoneIs not completely clear, but central suppression of prostaglandin synthesis and decreased 5-HT circulation in CNS or alterations in the permeability of the blood CSF barrier to serum proteins may be involved (Liu, Hsu et al. 1998). The low cost and excellent safety profile of Dexamethasone have lead to its being classified as a highly cost-

effective strategy in the prevention of PONV (Henzi, Walder et al. 2000, Apfel, Korttila et al. 2004).

Dexamethasone has been found effective in preventing PONV in various randomized, placebo controlled studies by different researchers in laparoscopic surgeries(Wang, Ho et al. 1999, Wang, Ho et al. 2000, Huang, Shieh et al. 2001, Bianchin, De Luca et al. 2007, Nesek-Adam, Grizelj-Stojcic et al. 2007, Ivanov, Ignatov et al. 2008, Karanicolas, Smith et al. 2008, Fukami, Terasaki et al. 2009, Aziz, Naz et al. 2011, Khalaj, Miri et al. 2013), orthognathic surgery (Gashi 2011), mastectomy(Gomez-Hernandez, Orozco-Alatorre et al. 2010), total abdominal hysterectomy(Wang, Ho et al. 2000), and thyroidectomy (Wang, Ho et al. 1999, Li and Wang 2014).

Henzi et al. analyzed 17 studies comparingthe efficacy of prophylactic Dexamethasone with a non-active placebo for PONV, andfound it more effective than placebo without any relevant clinical toxicity (Henzi, Walder et al. 2000). Conversely, Fujii et al. conducted a study in womenpatients subjected toGA for major gynecological operations, and they found that Dexamethasone at a8 mg dose alone did not reduce PONV (Fujii, Tanaka et al. 1995).

The minimalefficient dosage of Dexamethasone as prophylactic antiemeticas reported by Kang Liu et al. is 2.5 mg in patients undergoing gynecological surgeryunder GA(Liu, Hsu et al. 1999). However, the most frequently doseused for prevention of PONVis 8–10 mg (Bianchin, De

Luca et al. 2007, Ivanov, Ignatov et al. 2008, Fukami, Terasaki et al. 2009, Gomez-Hernandez, Orozco-Alatorre et al. 2010, Aziz, Naz et al. 2011, Gashi 2011, Khalaj, Miri et al. 2013).In addition, the most advised timing for administration is instantly before administration of anesthesia instead of at the end of operation(Wang, Ho et al. 2000). Therefore, for the present study, 8 mg dexamethasone was given one minute before induction.

The prophylaxis effect of single dosage of Dexamethasone was compared with a single dosage of Metoclopramidefor PONV in various trials afterLC and found that Dexamethasone demonstrates superior effects in the control of PONV(Nesek-Adam, Grizelj-Stojcic et al. 2007, Ivanov, Ignatov et al. 2008, Aziz, Naz et al. 2011, Khalaj, Miri et al. 2013).

In the last years, exploration has been concentrated on combination therapies as none of availableantiemetic agentsare completely effective for prevention of PONV in isolation. This fact may return tosuspected multifactorial etiology of PONV, where no single incentive factor for PONV has been identified(Kumar, Patodia et al. 2013).Use of prophylaxis combination therapy against PONV has shown to have superior efficiency than monotherapy and should be adopted in patients at high risk score for PONV (Jee, Yoon et al. 2010). The idea of prophylaxis using a Dexamethasone and Metoclopramide combination against PONV came from various studies; in addition to its availability and inexpensive cost.

Use of Metoclopramide in combination with other agents hasnot been found to decreasethe incidence of PONV more than monotherapy(Gan,

Meyer et al. 2007).In a study using a Metoclopramide plus Droperidol, the combinationdidn'tofferresultbetter than Droperidol alone (Michaloudis, O'Keeffe et al. 1993). Also, in children undergoing strabismus surgery, Metoclopramide pludOndansetroncombination was found to be noteffective to a greater extent thanOndansetron alone (Kathirvel, Shende et al. 1999). However, Jee et al. reported thata combination of 20 mg Metoclopramide with 5 mg dose of Dexamethasone had similar effect against PONV as a combination of 4 mg Ondansetron with 5 mg Dexamethasone in patients undergoing gynecological operation (Jee, Yoon et al. 2010).

Conversely, Dexamethasone was demonstrated to be an efficacious agent when used incombination with other agents in various studies (Gan, Diemunsch et al. 2014). McKenzie et al. reported that, a combination of 4 mg Ondansetronplus 8 mg Dexamethasone was as effective as Ondansetron alonein controlling delayed vomiting and significantly lowered nausea scores in females submitted to major gynecologic surge(McKenzie, Tantisira et al. 1994). Comparable outcomes were reported by Rajeeva and colleagues in female patients subjected to a diagnostic laparoscopy utilizing the same dosage (Rajeeva, Bhardwaj et al. 1999).

Furthermore, the addition of 20 mcg/kg Granisetronto 8 mg Dexamethasone was found to be more effective than either agent alone in obtaining a complete response during the study period in patients

undergoing GA for major gynaeeological surgery (Fujii, Tanaka et al. 1995).

Wallenborn et al. concluded that, an administration of 50 mg Metoclopramide with 8 mg Dexamethasone intra-operatively is an efficient, safe, and inexpensive way to reduce PONV. When a decreased dosage of Metoclopramide(to 25 mg) is used with a supplemental prophylaxis postoperativein patients with high risk score for PONVthe combination perhaps evenly efficient and produceless adverse effects(Wallenborn, Gelbrich et al. 2006).

However, a meta-analysis conducted by Henzi and colleaguesinformed that, 10 mg Metoclopramide has a poor antiemetic effect and its efficacy didn't improve when administered with 8 mg Dexamethasone (Henzi, Walder et al. 1999). In the recenttrial, a Dexamethasone plus Metoclopramide combination was found to be at least as effective as Dexamethasone used alone for the preventing of PONV in female patients after various laparoscopic surgeries under GA.

The current findings are identical to those reported byNesek-Adam and colleaguesin arandomized clinical study with 160 patients undergoingLC. They divided the patients into four groups of 40 each;placebogiven to first group; Metoclopramide 10 mg given at the end of operation for a second group; Dexamethasone 8 mg given subsequent to anesthesiaadministration for a third group; and Dexamethasone 8 mg givensubsequent toanesthesia administrationcombined with 10 mg Metoclopramidegiven at the end o

surgery for a fourth group. The results demonstratedno variance in the occurrence of PONV during the study period (24 hours) between the third group who received Dexamethasone aloneand fourth group who received the combination(Nesek-Adam, Grizelj-Stojcic et al. 2007).

The current results also are congruent to the of Ivanov et al; who studied 396 patients divided to four groups under the following conditions: 20 mg Metoclopramidegiven at the end of operation for a first group; 8 mg Dexamethasone given subsequent to anesthesia administration for a second group; Dexamethasone given subsequent to anesthesia administration combined withMetoclopramide given at the end of operation for a third group; and fourth group was without antiemetic. They found that, the administration of Dexamethasone alone or in combination with Metoclopramide was more efficient in reducing PONV compared with Metoclopramide alone or a lack of antiemetic (Ivanov, Ignatov et al. 2008).

However, Fujii et al. informed that, Granisetron and Dexamethasone combination was more efficient than Metoclopramide and Dexamethasone, in prevention PONV in female patients after major gynecological surgery under GA, where the incidence of a complete response(no PONV) was higher in Granisetron plus Dexamethasone group (96%) as compared witha Metoclopramide plus Dexamethasone group (51%) (Fujii, Tanaka et al. 1997).

5.3 Postoperative Symptoms

The most prevalent side effects reported in this trialwere tiredness, fatigue, and drowsiness which was relatively moderate with Dexamethasone alone or when combined with Metoclopramide and found with lower incidence than Metoclopramide and placebo. However, the difference was not statistically significant Therefore; it doesn't appear that, mental status is influenced by Metoclopramide plus Dexamethasone inducing either headache, tiredness, fatigue, or drowsiness.

The results of the current study are consistent with that of Ivanov et al. who reported that,in spite of the neuroleptic characteristics of Metoclopramide, its combination with Dexamethasone didn't increase incidence of headache

dizziness, sedation, or dry mouth (Ivanov, Ignatov et al. 2008).

Our results agree partially with the consensus guidelines for the management of PONV, which indicate the administrative of preoperative Dexamethasone at a dose of 8 mg to improve the quality of recovery post discharge andto minimize nausea, pain, and fatigue (Gan, Diemunsch et al. 2014).

Likewise, the current findings were similar to Huang et al. who used Dexamethasone and Metoclopramide as a prophylactic antiemetic for patients undergoing laparoscopic surgery and identified no side effects related to use it (Huang, Shieh et al. 2001). Fukami et al. and Karanicolas et al. reported that, Dexamethasone decreased postoperative fatigue,

headaches and dizziness after LC; ikewise Gashi after or thognathic surgery (Gashi 2011), and moreover, supported by meta-analyses which demonstrated that, adverse effects have not been shown follow a single dosage of Dexamethasone (Henzi, Walder et al. 2000).

Coloma et al., reported that, a single dosage of Dexamethasone decreased recovery time after surgical procedures and minimized postoperative pain scores (Coloma, Duffy et al. 2001). Due to its anti-inflammatory characteristic, Dexamethasone should be useful for both acute pain after surgery, as well as for moderate pain, like after tooth extraction, to a range that most patients can sense a noticeable alteration in pain severity (Liu, Hsu et al. 1999).Moreover, when using asingledose of Dexamethasone to manage postoperative pain and PONV, the sideeffectsare benignant, as reported in various studies and meta-analysis (Liu, Hsu et al. 1999, Holte and Kehlet 2002, De Oliveira, Almeida et al. 2011).This result is consistent with the findings of the current study.

In the present study, postoperative pain was reduced significantly by the use of Dexamethasone when compared with Metoclopramide and placebo. Identical findingshave been noted after LC(Karanicolas, Smith et al. 2008, Fukami, Terasaki et al. 2009), and after mastectomy (Gomez-Hernandez, Orozco-Alatorre et al. 2010), however others using IVD examethasone have failed to display any analgesic effect after LC(Wang, Ho et al. 1999, Elhakim, Nafie et al. 2002, Bianchin, De Luca et al. 2007), and thyroidectomy (Li and Wang 2014).

The current findings related to reducing pain using Dexamethasone and combination groups are consistent with the study of Holte and Kehletincluding use of perioperative single dose glucocorticoid in procedures extending from minor to major surgery. They summarize that a single dose of glucocorticoid decreased painafter minor laparoscopic procedures and orofacial surgery (Holte and Kehlet 2002). Moreover, our results are congruent regarding reducing postoperative pain and opioid consumption with Dexamethasone and combination therapies as well as witha well conducted meta-analysis examining the analgesic effects of perioperative Dexamethasone in a dose-dependent manner which found that, Dexamethasone dosages higher than 0.1 mg/kg are an efficient agent in multimodal the rapiesto decrease pain and opioid usepostoperatively (De Oliveira, Almeida et al. 2011).

5.4 Rescue antiemetic

Rescue antiemetic in 24 hour postoperative period was required in 6(20%), 7(23.3%) of the patients in the combination and Dexamethasone groups respectively, which was significantly lower compared to 13(43.3%) those receiving Metoclopramide or placebo19 (63.3%). On the contrary, Ivanov et al. found that, rescue anti-emetic was not required in patients receiving Dexamethasone plus Metoclopramide or those receiving only Dexamethasone, as compared with 4 patients in the Metoclopramide group and 6 patients in the control group in patients after laparoscopic surgeries (Ivanov, Ignatov et al. 2008).Nevertheless,similar results were found by

Wang et al. in female patients undergoing abdominal total hysterectomy. They found that, patients who received Dexamethasone prior the anesthesia administration or at the termination of anesthesia requiredlower rescue antiemetics (13% and 15% respectively) compared witha non-active placebo group (38%) (Wang, Ho et al. 2000).Moreover, in a meta-analysis conducted by Karanicolas et al. , it was found that, patients inDexamethasone group requested fewer rescue antiemeticscompared withthose in control group (Karanicolas, Smith et al. 2008).

5.5 Rescue analgesic

Dexamethasone reduced postoperative pain and analgesic requirements in comparison with the administration of Metoclopramide or a placebo. During hospitalization, 17(56.7%), 18(60%) patients in the Dexamethasone and combination groups respectively required a rescue analgesic, compared with 22(73.3%) in the Metoclopramide group and 26(86.7%) in the placebo group.

Similar results were obtained by Fukami et al. where they found that Dexamethasone significantly reduced postoperative pain and analgesic requirements after LC compared with the placebo group (Fukami, Terasaki et al. 2009). Additionally, in a well-conducted meta-analysis published about LC, there was a lowerrequirement for rescue analgesics in the Dexamethasone group compared with placebo (Karanicolas, Smith et al. 2008).Moreover, Gómez-Hernández et al. demonstrated that analgesics were required more in patients of the control group than in the

Dexamethasone group following breast surgery (Gomez-Hernandez, Orozco-Alatorre et al. 2010). However, in females undergoing thyroidectomy, there were no significant variations among dexamethasone and placebo groups related to the percentage of patients requiring rescue analgesic (Wang, Ho et al. 1999).

Conclusion

Dexamethasone and Metoclopramide combination was found to be not more effective than administration of Dexamethasone alone in the prevention of nausea and vomiting after laparoscopic surgery, without increase in adverse effects after use it.

Intensity of nausea was reduced only with the combination of dexamethasone and metoclopramide. Number of patients with complete response (no nausea, no vomiting, no retching and no rescue medication medication) increased using the combination of metoclopramide and dexamethasone.

Administration of a combination of 8 mg Dexamethasone and 20 mg Metoclopramide is an efficient, safe, and cheap way to prevent PONV after laparoscopic surgery compared withmetoclopramide or placebo.

Recommendation

A pre-anesthetic interview should be conducted with patients to help healthcare providers to identify patients who may experience PONV and to detect who is most likely to benefit from prophylactic anti-emetic therapy.

In patients with high risk of developing PONV, combination antiemetic therapy should be considered. We recommend a combination of 8 mg Dexamethasone before the induction of anesthesia and 20 mg Metoclopramide given before the end anesthesia to decrease the overall incidence of PONV and intensity of nausea. Supplemental drugs may be administered after surgery, but should be considered dependent on the patient's risk profile. Rescue antiemetic should be provided after postoperative nausea and vomiting to prevent further episodes. Although adverse reactions such as extrapyramidal symptoms are rare, healthcare providers should be aware of them and should be informed about appropriate treatment options.

Anesthesia nurse implications

A group of patients at high risk for PONV were examined and demonstrated improved recovery after PONV prophylaxis. PONV is a major concern for patientsundergoing surgery. By identifying patients at risk, a systematic evidence-based approach canbe added into the anesthetic plan to prevent PONV. If the patient does not respondtoprophylactic therapy, an antiemetic agent from a different class (i.e. Different

mechanism ofaction) should be given. Pain control, adequate hydration, slow deep breathing,avoiding sudden movement, not forcing fluid intake, and maintaining blood pressure areimportant in the care of the patient.

Further Research

- Further studies should be performed on patients who are at high risk for PONV by using prophylaxis with combination of three drugs from different classes.
- Further studies should be carried out on high-risk patients for PONV by using a multimodal approach that includes 2 or more pharmacological and non-pharmacological interventions.
- Further studies are required to examine the effect of combination of Dexamethasone with different antiemetic class as 5-HT3 receptor antagonists (ex. Ondansetron) in patients with high risk for PONV.

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Annexes

Appendix 1

Consent Form

جامعة النجاح الوطنية

كلية الدراسات العليا

موافقة للإشتراك في البحث العلمي

الباحث: محمد حسن دويكات. رقم الهاتف: 0569654148 0599654148

أنتي مدعوة للمشاركة ببحث علمي سريري سيجرى في مستشفى رفيديا الجراحي في نابلس. الرجاء أن تأخذي الوقت الكافي لقراءة المعلومات التالية بتأن قبل أن تقرري إذا كنت تريدين المشاركة أم لا. بإمكانك طلب إيضاحات أو معلومات إضافية عن أي شيء مذكور في هذه الإستمارة أو عن هذه الدراسة ككل من الباحث.

- **عنوان الدراسة**

فعالية ال (ديكساميثازون والميتوكلوبرمايد) الوقائية المضادة للقيء والغثيان بعد عملية المنظار عند النساء المعرضات لخطر عالي للتقيء والغثيان بعد العملية.

- **الهدف من الدراسة**

دراسة مدى فعالية ادوية ال (ديكساميثازون والميتوكلوبرمايد) كل على حدا و في حالة اعطاءها معا على تخفيف الغثيان والتقيؤ بعد عملية المنظار عند النساء المعرضات لخطر عالي للغثيان والتقيؤ بعد العملية.

- **فترة المشاركة في الدراسة**

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

- **اجراء الدراسة**

سيتم توزيع المشاركين في الدراسة الى اربع مجموعات عشوائيا، حيث ستتلقى المجموعة الاولى علاج ال "ديكساميثازون" قبل بدء التخدير، والمجموعة الثانية سوف تتلقى علاج "ميتوكلوبرمايد"

قبل انتهاء العملية، والمجموعة الثالثة سوف تتلقى العلاجين معا، بينما المجموعة الرابعة لن تتلقى اي نوع من العلاج.

- **الفوائد المتوقعة للمشاركة في الدراسة**

تخفيف المضاعفات المحتمل حدوثها بعد العملية (الغثيان والتقيؤ)، والتخفيف من حدة الالم بعد العملية.

- **التأثيرات السلبية للمشاركة في الدراسة**

التأثيرات المتوقعة هي من الاعراض الجانبية للادوية المستعملة في هذه الدراسة مثل الدوار والنعاس والتأثير على المزاج.

الادوية سوف تعطى في جرعات خفيفة مما يقلل من الاعراض الجانبية لها، وفي حال حدوث هذه الاعراض سيتم تقديم العلاج المناسب لها.

- **سرية المعلومات**

لحماية خصوصيتك، سوف يتم تسجيل النتائج مع رمز سري. سوف يتم تسجيل فقط اسمك في نموذج الموافقة. وسيتم الإبقاء على الرمز السري المعين في ملف مغلق ومحمي بعناية.

الوصول لهذه المعلومات يتم فقط من قبل الباحث الرئيسي للدراسة والأفراد المرخص لهم. مع ذلك، قد تتم مراجعة سجلات الدراسة من قبل اللجنة الأخلاقية التي تجري على البشر في جامعة النجاح الوطنية. ستتم مراقبة السجلات الخاصة بك ويمكن مراجعتها دون انتهاك السرية وأية بيانات يمكن ان تنتج عن هذه الدراسة لن تذكر أسماء المشاركين في الدراسة.

- **المشاركة الطوعية / الانسحاب**

ان المشاركة في هذه الدراسة طوعية تماما، يمكنك سحب موافقتك في أي وقت. وإذا اخترتي عدم مشاركتك في الدراسة أو انسحابك في وقت لاحق من هذه الدراسة لن تتأثر الرعاية الطبية المقدمة لك او تتغير بأي شكل من الأشكال. إذا كنتي ترغبي في الانسحاب من الدراسة، يمكنك الاتصال بالباحث.

- **الاتصال للحصول على أجوبة على أسئلتك ومخاوفك وشكواك**

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

- **الموافقة على المشاركة في الدراسة**

لقد قرأت الوصف أعلاه من هذه الدراسة. وقد تمت الاجابة على جميع أسئلتي. وأنا أعلم أنه يمكنني ان ارفض المشاركة في أو الانسحاب من الدراسة في أي وقت. وعلى ذلك أعطي موافقتي بحرية على المشاركة في هذه الدراسة.

اسم المريضة:

التوقيع:

التاريخ:

Appendix 2

Questionnaire

Post-operative symptom questionnaire
PONV/Discomfort
This questionnaire will be filled by CRNA in PACU (0-2 h) postoperatively and by RN in ward (2-24 h) postoperatively.
To describe who much patient experience PONV and other discomfort symptoms such as pain, headache, drowsy, etc.

- Patient number: File number:
- Type of surgery:
- Age:
- Weight (kg): Height (cm):

  BMI:
- Last menstrual period (days): 0-8 ( ) 9-16 ( )

  16-28 ( ) >28 ( )
- Duration of anesthesia (min):
- Time end of anesthesia:
- Duration of surgery (min):
- Total doses of perioperative fentanyl (µg):

In PACU (0–2 h postoperatively**)**

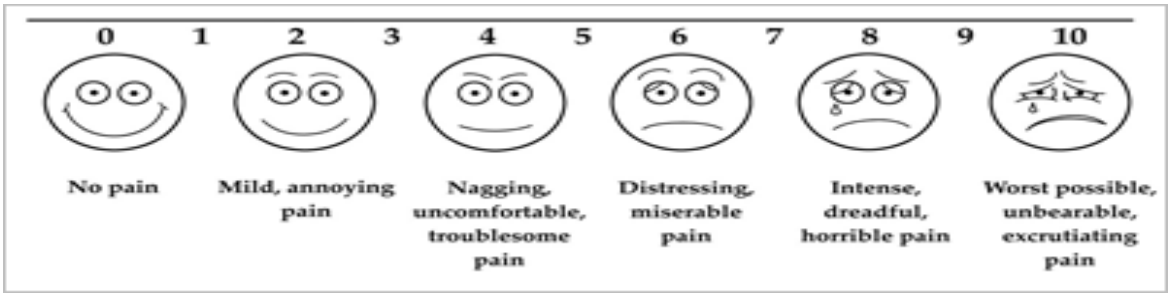
- Incidence vomiting: ( ) Yes ( ) No
- How often with time:

- Intensity of nausea (0-6): ( )

"0 for no nausea; 1 for very mild nausea, 2; mild, 3; moderate, 4; severe, 5: very severe, 6: intolerable"

- Are you retching? ( ) Yes ( ) No
- Do you have pain in the area of surgery? ( ) Yes ( ) No
- Do you have headache? ( ) Yes ( ) No
- Are you tired? ( ) Yes ( ) No
- Are you drowsy? ( ) Yes ( ) No
- Are you fatigued? ( ) Yes ( ) No
- Do you have any other discomfort? ( ) Yes ( ) No

- VAS for pain (0-10): ( )



- Rescue antiemetic (Ondansetron): ( ) Yes ( ) No
- Rescue analgesic (Morphine): ( ) Yes ( ) No

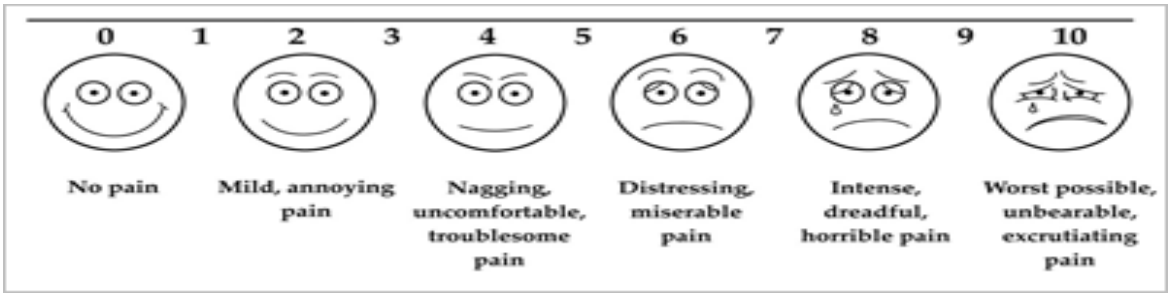
In Ward (2-24 h postoperatively)

- Incidence vomiting: ( ) Yes ( ) No

- How often with time:
- Intensity of nausea (0-6): ( )

"0 for no nausea; 1 for very mild nausea, 2; mild, 3; moderate, 4; severe, 5: very severe, 6: intolerable"

- Are you retching? ( ) Yes ( ) No
- Do you have pain in the area of surgery? ( ) Yes ( ) No
- Do you have headache? ( ) Yes ( ) No
- Are you tired? ( ) Yes ( ) No
- Are you drowsy? ( ) Yes ( ) No
- Are you fatigued? ( ) Yes ( ) No
- Do you have any other discomfort? ( ) Yes ( ) No
- VAS for pain (0-10): ( )



- Rescue antiemetic (Ondansetron): ( ) Yes ( ) No
- Rescue analgesic (Morphine): ( ) Yes ( ) No
- Satisfaction rate with your health status?

( ) Very unsatisfied ( ) Unsatisfied ( ) Neither Satisfied nor unsatisfied

( ) Satisfied ( ) Very satisfied

- Do you think we know how you feel after we have read your answers?

( ) Yes ( ) No

Appendix 3

IRB Approval

بسم الله الرحمن الرحيم

An - Najah National University
Faculty of Medicine & Health Sciences
Department of Graduate Studies

جامعة النجاح الوطنية
كليـة الطب وعلـوم الصـحة
دائرة الدراسات العليا

IRB Approval letter

Study title:
Anti-Emetic Efficacy of Prophylactic Dexamethasone and Metoclopramide, and their combination in the prevention of postoperative nausea and vomiting after Laparoscopic Surgery in patients at high risk of post-operative nausea and vomiting: A Randomized, Double Blind, and Placebo-Controlled Trial.

Submitted by:
Mohammed H.Dwaikat.

Date Reviewed:
April 5,2015

Date approved:
April 27, 2015

Your study titled: "Anti-Emetic Efficacy of Prophylactic Dexamethasone and Metoclopramide, and their combination in the prevention of postoperative nausea and vomiting after Laparoscopic Surgery in patients at high risk of post-operative nausea and vomiting: A Randomized, Double Blind, and Placebo-Controlled Trial." with archived number 31/April/2015 , Was reviewed by An-Najah National University IRB committee & approved on April 27, 2015 .

Hasan Fitian , MD

IRB Committee Chairman,
An-Najah National University

نابلس – ص.ب 7 او 707 هاتف 14/8/7/4/2342902(09)(970) ، فاكسميل 2342910 (09) (970)
Nablus – P.O.Box: 7 or 707 – Tel (970) (09) 2342902/4/7/8/14 – Faximile (970)(09)2342910
Email: hgs@najah.edu Web Site: www.najah.edu

Appendix 4

MOH Correspondence

An- Najah
National University
Faculty of Medicine & Health Sciences
Department of Nursing

بسم الله الرحمن الرحيم

جامعة النجاح الوطنية
كلية الطب وعلوم الصحة
دائرة التمريض

التاريخ: 2015/04/28

حضرة الدكتورة أمل أبو عوض المحترمة / مدير عام التعليم الصحي في وزارة الصحه الفلسطينية .

الموضوع: تسهيل مهمة الطالب محمد دويكات

تحية طيبة وبعد،

تهديكم دائرة التمريض والقبالة في كلية الطب وعلوم الصحه/ جامعة النجاح الوطنية أجمل التحيات ونشكر لكم حسن تعاونكم المستمر معنا، أرجو من حضرتكم التكرم بالموافقه للطالب محمد دويكات باجراء الدراسة البحثيه حيث أنه يدرس ماجستير تمريض التخدير وكمتطلب للتخرج يجب أن ينهي رسالة الماجستير تحت عنوان:

Anti-Emetic Efficacy of Prophylactic Dexamethasone and Metoclopramide, and their combination in the prevention of postoperative nausea and vomiting after Laparoscopic Surgery in patients at high risk of post-operative nausea and vomiting: A Randomized, Double Blind, and Placebo-Controlled Trial.

لذا أرجو التكرم بالموافقه للطالب بالسماح له باجراء دراسته في مستشفى رفيديا الحكومي في قسم العمليات والجراحه والايعاز لمدير المستشفى ورئيس قسم التخدير بذلك.

- مرفق IRB، Proposal

وتفضلو بقبول وافر الاحترام والتقدير ، ،

مديرة دائرة التمريض والقبالة

منسقة برنامج ماجستير تمريض التخدير

د. عائدة القيسي

نابلس - ص.ب 7 أو 707 هاتف 2342902;4;7;8;14 (09) (970) فاكسميل 2342910 (09) (970)
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Appendix 5

Alenjeli Hospital Correspondence

An- Najah
National University
Faculty of Medicine & Health Sciences
Department of Nursing

بسم الله الرحمن الرحيم

جامعة النجاح
الوطنية
كلية الطب وعلوم الصحة
دائرة التمريض

التاريخ: 29-09-2015

حضرة د.وليد القرة المحترم/ مدير عام المستشفى الانجيلي العربي،،

الموضوع: تسهيل مهمة الطالب محمد دويكات

تحية طيبة وبعد،

تهديكم دائرة التمريض والقبالة في كلية الطب وعلوم الصحه/ جامعة النجاح الوطنية أجمل التحيات ونشكر لكم حسن تعاونكم المستمر معنا، أرجو من حضرتكم التكرم بالموافقه للطالب محمد دويكات باجراء الدراسة البحثيه حيث أنه يدرس ماجستير تمريض التخدير وكمتطلب للتخرج يجب أن ينهي رسالة الماجستير تحت عنوان:

Anti-Emetic Efficacy of Prophylactic Dexamethasone and Metoclopramide, and their combination in the prevention of postoperative nausea and vomiting after Laparoscopic Surgery in patients at high risk of post-operative nausea and vomiting: A Randomized, Double Blind, and Placebo-Controlled Trial.

لذا أرجو التكرم بالموافقه للطالب بالسماح له باجراء دراسته في مستشفاكم الموقر في قسم العمليات والجراحه والايعاز لرئيس قسم التخدير بذلك.

- مرفق IRB، Proposal

وتفضلو بقبول وافر الاحترام والتقدير ، ،

مديرة دائرة التمريض والقبالة

منسقة برنامج ماجستير تمريض التخدير

د. عائدة القيسي

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Appendix 6

ASA physical status classification system for assessing a patient before surgery

I. Normal healthy patient

II. Patient with mild systemic disease

III. Patient with severe systemic disease

IV. Patient with severe systemic that is a constant threat to life

V. Moribund patient who is not expected to survive without the operation

VI. Patient declared brain dead whose organs are to be harvested for donor purposes

جامعة النجاح الوطنية

كلية الدراسات العليا

ديكساميثازون وميتوكلوبراميد، ومزيجهم للوقاية من القيء والغثيان بعد العملية في المرضى الإناث بعد الخضوع لجراحة المنظار.

اعداد

محمد دويكات

اشراف

د.عايدة القيسي

د. نور الدين مصري

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

2017

ديكساميثازون وميتوكلوبراميد، ومزيجهم للوقاية من القيء والغثيان بعد العملية في المرضى الإناث بعد الخضوع لجراحة المنظار.

اعداد

محمد دويكات

اشراف

د.عايدة القيسي

د. نور الدين مصري

الملخص

المقدمة: ذكرت الدراسات السابقة ان نسبة حدوث الغثيان والقيء بعد العملية في المرضى الذين يخضعون لعملية المنظار تكون بنسبة (40–77 %). ولم يثبت اي دواء مضاد للقيء ان يكون حل احادي عالمي لعلاج الغثيان والقيء بعد العملية. وجدت ادلة على ضرورة الاخذ بعين الاعتبار استعمال مزيج من الادوية المضادة للقيء عند المرضى الذين يملكون خطر كبير لحدوث القيء والغثيان بعد العملية.

الهدف من هذه الدراسة هو تقييم تأثير الديكساميثازون والميتوكلوبرمايد كعلاج احادي او في حالة دمجهما كعلاج وقائي في المرضى الاناث الاتي يملكن خطر عالي لحدوث القيء والغثيان بعد العملية بعد الخضوع لعملية المنظار تحت التخدير العام.

تصميم الدراسة وطريقتها: دراسة متعددة المراكز، مستقبلية، عشوائية، مزودجة التعمية، وخاضعة للعلاج الوهمي.

شملت الدراسة مائة وعشرون مريضة تم توزيعهم عشوائيا على واحدة من المجموعات الاربعة للدراسة ثلاثين مريضة في كل منها. مجموعة الديكساميثازون تلقت (8) ملغم ديكساميثازون قبل دقيقة واحدة من بدء التخدير و(10) مليميتر محلول وهمي (نورمال سلاين) قبل نهاية التخدير. مجموعة الميتوكلوبرمايد تلقت(10) مليميتر محلول وهمي (نورمال سلاين) قبل دقيقة واحدة من بدء التخدير و(20) ملغم ميتوكلوبرمايد قبل نهاية التخدير.مجموعة الدمج تلقت (8) ملغم

ديكساميثازون قبل دقيقة واحدة من بدء التخدير و (20) ملغم ميتوكلوبرمايد قبل نهاية التخدير. ومجموعة العلاج الوهمي تلقت (10) مليميتر محلول وهمي (نورمال سلاين) قبل دقيقة واحدة من بدء التخدير و (10) مليميتر محلول وهمي (نورمال سلاين) قبل نهاية التخدير.

النتائج: هناك فروق ذات دلالة احصائية في حدوث القيء خلال (24) ساعة بعد العملية بين مجموعة العلاج الوهمي 17(56,7%) ومجموعة الدمج 6(20%) ومجموعة الديكساميثازون 6(20%)، P = 0.0037. واظهرت النتائج ان حدوث القيء انخفض بشكل كبير عند استخدام الديكساميثازون كعلاج احادي او عند دمجه مع الميتوكلوبرمايد.

هناك فروق ذات دلالة احصائية في حدوث الغثيان خلال (24) ساعة بعد العملية بين مجموعات العلاج (ديكساميثازون، ميتوكلوبرمايد، والدمج) عند مقارنتها مع مجموعة العلاج الوهمي 0.05 > P. ولم تكن هناك فروق ذات دلالة احصائية بين مجموعات العلاج الثلاث 0.05 < P. تلخص النتائج بان استعمال الديكساميثازون والميتوكلوبرمايد كعلاج احادي او عند دمجهما يخفض نسبة حدوث الغثيان خلال (24) ساعة بعد العملية مقارنة بالعلاج الوهمي.

هناك فروق ذات دلالة احصائية في حدة الغثيان خلال (24) ساعة بعد العملية بين مجموعة الدمج 1.05 (±0.90) مقارنة مع مجموعة الديكساميثازون 1.78 (±1.14) P = 0.008، ومجموعة الميتوكلوبرمايد 2.43 (±1.03) P = 0.000، ومجموعة العلاج الوهمي 3.07 (±1.34) P = 0.000. وتظهر النتائج انه عند استخدام الدمج بين الديكساميثازون والميتوكلوبرمايد يقلل بشكل ملحوظ من حدة الغثيان خلال (24) ساعة بعد العملية.

هناك فروق ذات دلالة احصائية في استعمال علاج للقيء خلال (24) ساعة بعد العملية، حيث كان العدد الاجمالي للمرضى الذين احتاجوا علاج للقيء في مجموعة الدمج 6(20%) ومجموعة الديكساميثازون 7(23,3%) اقل من اولئك في مجموعة العلاج الوهمي 19(63,3%) P 0.05 >، ولا يوجد فرق بين مجموعة العلاج الوهمي ومجموعة الميتوكلوبرمايد 13(43,3%) 0.1237

P =، وتظهر النتائج انه عند استخدام الديكساميثازون كعلاج احادي او دمجه مع الميتوكلوبرمايد خفض بشكل كبير حاجة المرضى الى علاج للقيء خلال (24) ساعة بعد العملية.

هناك فروق ذات دلالة احصائية في حدوث الألم خلال (24) ساعة بعد العملية بين مجموعة الدمج 22(77,3%) ومجموعة الديكساميثازون21(70%) مقارنة مع مجموعة العلاج الوهمي 29(96,7%) P < 0.05، وبالمقارنة مع مجموعة الميتوكلوبرمايد 28(93,3%) P < 0.05، واظهرت النتائج ان حدوث الألم انخفض بشكل ملحوظ في مجموعات الديكساميثازون والدمج.

الخلاصة: ان دمج الديكساميثازون مع الميتوكلوبرمايد كعلاج وقائي هو أكثر فعالية في تخفيض حدة الغثيان مقارنة بالديكساميثازون والميتوكلوبرمايد كعلاجات احادية او العلاج الوهمي. وكان الديكساميثازون والدمج بين الديكساميثازون والميتوكلوبرمايد أكثر فعالية كعلاج وقائي في منع القيء والغثيان وتخفيض حدة الألم بعد العملية مقارنة بالميتوكلوبرمايد كعلاج احادي والعلاج الوهمي.

يجب استعمال دمج من الادوية المضادة للقيء عند المرضى الذين لديهم احتمالية عالية لحدوث القيء والغثيان بعد العملية وتبين عدم وجود اي اعراض جانبية لاستعمال ذلك.

الكلمات المفتاحية: القيء والغثيان بعد العملية، ديكساميثازون، ميتوكلوبرمايد، اعراض ما بعد العملية الجراحة.