An-Najah National University

Faculty of Graduate Studies

THE EFFECT OF INTRAOPERATIVE CONTINUOUS INFUSION OF ESMOLOL ON PAIN REDUCTION, VOMITING AND HEMODYNAMICS STABILITY POSTOPERATIVE ON LAPAROSCOPIC CHOLECYSTECTOMY PATIENTS

By

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Dedication

I thank God Almighty and i dedicate this research to the owner of a fragrant biography and enlightened thought, for he had the first credit in attaining higher education (my beloved father), may God prolong his life.

To those who set me on the path of life, made me calm, and took care of me until I become old (my great mother).

I dedicate this achievement to my lovely and kind wife who has always been beside me and supported me in my period of study.

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It would not be possible to achieve this without the support of my family, especially my parents, my wonderful wife. This accomplishment would have been impossible without them.

Thanks To everyone who gave me moral support for the completion of this task.

Author

Ahmad Bast

Declaration

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

THE EFFECT OF INTRAOPERATIVE CONTINUOUS INFUSION OF ESMOLOL ON PAIN REDUCTION, VOMITING AND HEMODYNAMICS STABILITY POSTOPERATIVE ON LAPAROSCOPIC CHOLECYSTECTOMY PATIENTS

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

Student's Name: Ahmad Mohmmad Ahmad Basi

Signature: Basi

Date: 19/1/2022

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THE EFFECT OF INTRAOPERATIVE CONTINUOUS INFUSION OF ESMOLOL ON PAIN REDUCTION, VOMITING AND HEMODYNAMICS STABILITY POSTOPERATIVE ON LAPAROSCOPIC CHOLECYSTECTOMY PATIENTS

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ABSTRACT

Background: Alleviation of postoperative pain often requires administration of potent analgesics like opioids. Reduction of opioid analgesic doses, incidence, frequency, and intensity of postoperative pain can improve patient outcomes.

Objective: This study was conducted to assess the effects of continuous intraoperative infusion of esmolol on reducing postoperative pain among patients who underwent laparoscopic cholecystectomy under general anesthesia. The study also assessed the effects of continuous intraoperative infusion of esmolol on reducing nausea and vomiting among the included patients. also the associations between demographic characteristics of the patients and the effects of continuous intraoperative infusion of esmolol on reducing postoperative pain, duration of the laparoscopic cholecystectomy operation, and degree of postoperative pain were also investigated.

Methods: This study was conducted using a double-blind randomized controlled clinical trial design. Patients in both control and intervention groups were adults (>18 years old) who were recruited from Rafedia hospital. Patients in the intervention group started on continuous intraoperative infusion of 5-10mcg/kg/min esmolol until the completion of surgery. In the control group, patients received n/s0.9% at same rate. Postoperative pain was measured by visual analogue scale (VAS). Demographic and hemodynamic variables of the patients were collected on an assessment sheet that was developed for this study.

Results: A total of 65 patients were randomly allocated into control (n = 36) and intervention (n = 29) groups. There were no statistical differences in the demographic data and preoperative hemodynamic variables of the patients in both groups before the

intervention was administered. In this study, esmolol continuous intraoperative infusion was shown to maintain PACU hemodynamic parameters and significantly reduced postoperative pain (up to 1 hour postoperatively) among patients who underwent laparoscopic cholecystectomy. The average time to require the first dose of rescue analgesia was longer in the esmolol group compared to the control group. However, this difference was not statistically significant.

Conclusion: Postoperative pain continues to present a heavy burden on patients who undergo surgical interventions, notably, laparoscopic cholecystectomy. In conclusion, continuous intraoperative infusion of esmolol during maintenance anesthesia of patients undergoing laparoscopic cholecystectomy was shown to significantly reduce postoperative pain without destabilizing the hemodynamic parameters. Furthermore, rescue analgesia was less frequently needed in the esmolol group, nausea and vomiting were not reduced by esmolol and are still a major concern. Results of this study might be used to improve future perioperative care of patients scheduled for laparoscopic cholecystectomies.

Keywords: Analgesia, esmolol, laparoscopic cholecystectomy, opioid sparing, postoperative pain, recovery.

Chapter One

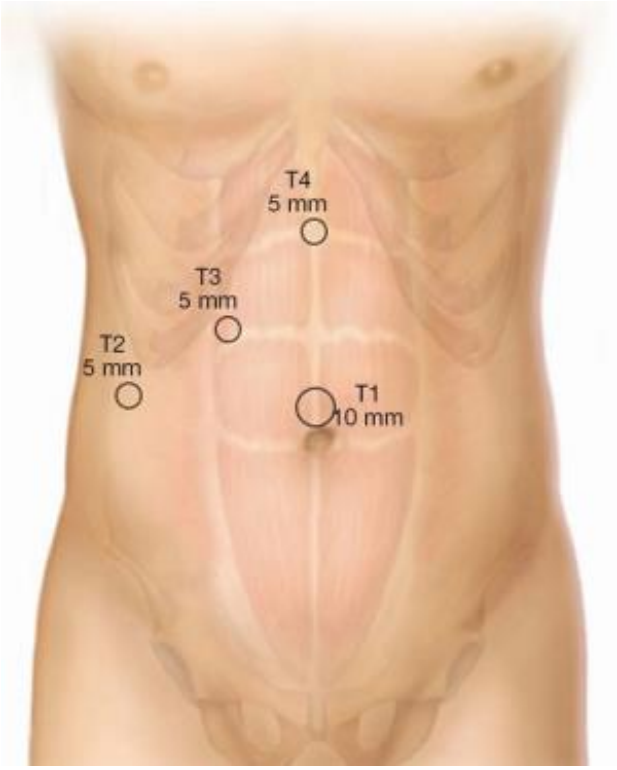
Introduction

Laparoscopic cholecystectomy developed for the first time in Germany in 1986 than in France in 1987, after that United States start to use this procedure in 1988.' permission of this new procedure was rapid. By 1992, more than 80% of the general surgeons and physicians in the United States had permitted and adopted the procedure. Laparoscopic cholecystectomy these days is the management of choice for symptomatic gallbladder diseases and complications. The German general surgeon Mühe for the first time introduced his practice in April of 1986 at the Congress of the German Surgical Society (GSS). Mühe's procedure was called “Mickey Mouse surgery” At the same time and continent, in Lyon city in France a French plastic surgeon called, Philippe Mouret, likewise became attracted in conducting the endoscopic procedure to general surgery (Blum & Adams, 2011).

The procedure technique started by using carbon dioxide, the abdomen is insufflated to 15 mmHg, and then trocars are gently inserted within four small incisions (one in subxiphoid, one in supraumbilical, and two in right subcostal) see the following figure1.1 , gallbladders are retracted over the liver using a laparoscope and long instruments, Cautious dissection is accomplished to achieve the critical safety sight, after the operating surgeon has successfully isolated the cystic major artery and cystic duct, the surgeon now can continue confidently, by carefully cutting and transecting both structures, by using electro cautery or harmonic scalpel the gallbladder is detached from the liver tissue , after that permitting the abdomen to deflate to eight mmHg for two minutes, hemostasis have to be attained, the gallbladder is removed from the abdomen and put in a special specimen pocket, as a final point all trocars should be removed under direct visualization and the small wounds will be closed(Hassler et al., 2021).

Figure 1.1

the insertion site of the trocars.



Regarding that all of us seeking for the safety, many studies confirmed that laparoscopic cholecystectomy is a harmless and safe procedure farther than patients recover more quickly afterward laparoscopic than after open cholecystectomy (Nijssen et al., 2015).

Any procedure is not without risk, Complications for this operation such as perforations of the intestines (bowels) and injuries of the bile duct (Majumder, Altieri, & Brunt, 2020).

The most common complications were wound infections and non-specific abdominal pain, in some cases, laparoscopic cholecystectomy was changed to an open procedure. Generally, this was done because of the huge infiltration and layers adhesions (90%) nearby the gallbladder, all of these increase the risks of morbidity and mortality of the procedure (Nijssen et al., 2015), furthermore increase the interval of hospital stay, Conversion is related to many complications such as bleeding leads to redo the operation or transfusion of blood components, bile duct injury or leakage and finally death(Hu, Menon, Gunnarsson, & De Costa, 2017).

The major indications for laparoscopic cholecystectomy are acalculous cholecystitis, symptomatic cholelithiasis, biliary dyskinesia, acute or chronic cholecystitis, gallstone pancreatitis, and gallbladder lesions or masses like polyps, in the United States, there are approximately 20 million people with gallstones, of whom approximately 300,000 require cholecystectomies annually, there are about 10% to 15% of the populace who have gallstones but without any symptoms, while 20% of these people experience symptomatic gallstone formation (biliary colic), gallstones formation more often in females as they get older; males are less likely to develop gallstones(Hassler, Collins, Philip, & Jones, 2021).

Most surgical operations followed by Pain, pain is well-defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage ", or termed as such damage, and are often influenced by several factors. Mostly it is common to be a subjective condition that leads people to seek for a health care specialties and services. (Correia & Duran, 2017).

Regarding the known and most common side effects of any operation are nausea and vomiting this study agrees that esmolol reduction the occurrence of postoperative nausea and vomiting leads to an earlier discharge, and increases patient satisfaction. A sympathetic nerve blocking effect is one of the characteristics of this beta-adrenergic receptor antagonist has on pain and (post-operative nausea and vomiting [PONV]) (S.-J. Lee & Lee, 2010).

Surgical patients have been anesthetized in large numbers since anesthesia was discovered in 1840, but until a century later, doctors had no idea nausea and vomiting following surgery were operative complications rather than accidents, PONV is primarily affected by female gender, non-smoking, postoperative treatment of opioid and motion sickness, in high-risk patients the percentage can increase to about eighty percent, where 30% of surgical patients have this unpleasant experience, if you are suffering from PONV, you won't die, but if you experience electrolyte imbalance, dehydration, rupturing or tearing in the esophagus , the condition will worsen and can actually leads to decease, antiemetic drugs, such as histamine type 1 receptor antagonists, and neurokinin-1 receptor antagonists, 5-hydroxytryptamine receptor antagonists, dopamine receptor antagonists, corticosteroids, have been developed to reduce PONV, there is evidence that every drug can reduce PONV risk between 20 and

25 percent and that combining antiemetics can reduce PONV risk by up to 60 percent, unfortunately histamine receptor antagonists commonly cause drowsiness and headaches, long-QT interval and malignant ventricular arrhythmias, which is lethal , all of these findings lead that still we need to improve another way to decrease the PONV and its effects(Fu, Wu, Shu, Song, & Jiao, 2020).

Esmolol is an ultrashort-acting β-1 receptor blocker. It is currently approved to control the tachyarrhythmia, and reduction of heart rate (HR) in non-compensatory sinus tachycardia, current studies propose that esmolol may affect the perioperative pain response and reduce anesthetic requirements like opioids. However, opioids have a great number of side effects, and the decrease of their use pre-operative improves the patient outcome and enable the early discharge (Gelineau et al., 2018).

Esmolol intraoperatively has consistently proved beneficial as an analgesic postoperatively in a variety of studies, an increase in nociception may result from hippocampal activation during stressful situations by stimulating n-methyl-d-aspartate receptors,(hippocampus is located in the temporal lobe of the brain contains complex brain structures), therefore, we hypothesize that esmolol attenuates perceived pain intensity by blocking beta-adrenergic receptors in the hippocampus(De Oliveira Jr, Kendall, & McCarthy, 2018).

Form other side opioids do not give the expected quality of postoperative pain relief, knowing that serious pain after laparoscopic cholecystectomy has some features not common in other laparoscopic procedures. these 3 components are specific to laparoscopic cholecystectomy pain: first major and central one is incisional pain, second one is visceral deep pain and finally shoulder radiated or referred pain (Vincent Collard et al., 2007).

Hagelüken et al. (1994) discussed the mechanism of action that showed an antagonist to beta-adrenergic receptors triggers and motivates G proteins in insulated cell membranes and this property could explain the mechanism by which clonidine induces analgesia in the central nervous system.

1.1 Problem statement

Pain is the most bad expected post- operative complication that all over the world medical experts try to overcome this problem or this side effect, in order to provide comfort for all patients, Unfortunately their trend is to use opioids due to its strong effect on pain control, but as we know, Despite the widely use of opioids for pain control ,there is big miss use and bad outcomes also they have many related side effects and delayed patients discharge, farther more this will increase the costs of treatment that was covered by the government, from other side the length of stay in hospital need more and more medical team and farther costs, as we know in Palestine there is a shortage in the medical human resources, therefore treatment requires not to be restricted to one intervention, so a multimodal therapy would offer better quality of pain relief, spare opioids, and thus facilitate the recovery process, so This study attempted to see the effects of use continuous infusion of esmolol during operation on pain reduction post operation in laparoscopic cholecystectomy with the patient under general anesthesia.

During the period of searching in the permitted database, there are no studies done in Palestine related to my study.

1.2 Aims and objectives of the study

- To assess the effect of intraoperative use of a continuous infusion of esmolol on decreasing post-operative pain in laparoscopic cholecystectomy patients.
- To evaluate the effect of the use of continuous esmolol infusion on reducing vomiting post-operative on laparoscopic cholecystectomy patients.
- To assess that if demographic characteristics of laparoscopic cholecystectomy patients affect the relation between continuous infusion of esmolol intraoperative and postoperative pain.
- To assess if the duration of the laparoscopic cholecystectomy operation affects the degree of post-operative pain.
- To assess the stability of hemodynamics pre-post operation.
- To evaluate the need for rescue analgesia.

1.3 Significance of the study

Although Opioid has a perfect analgesic effect and it is widely used, it is actually impossible to get rid of them , but it is great if we can reduce its consumption which can help us avoid the bad outcome that may occur after using it, therefore using other modes of pain reduction like esmolol can help in two pathways the first one is the potent effect of this Beta 1 blocker on controlling BP in hypertensive patient and from other side utilize its effect on pain reduction upon laparoscopic cholecystectomy patient.

From other side early discharge of these patients will save the costs and the humane medial recourse that are needed to follow up such of these cases, also this can save the beds leading to more and more patients can utilize the medical service, so this study could be adopted by the ministry of health and being a policy to be used in the management of pain post operations.

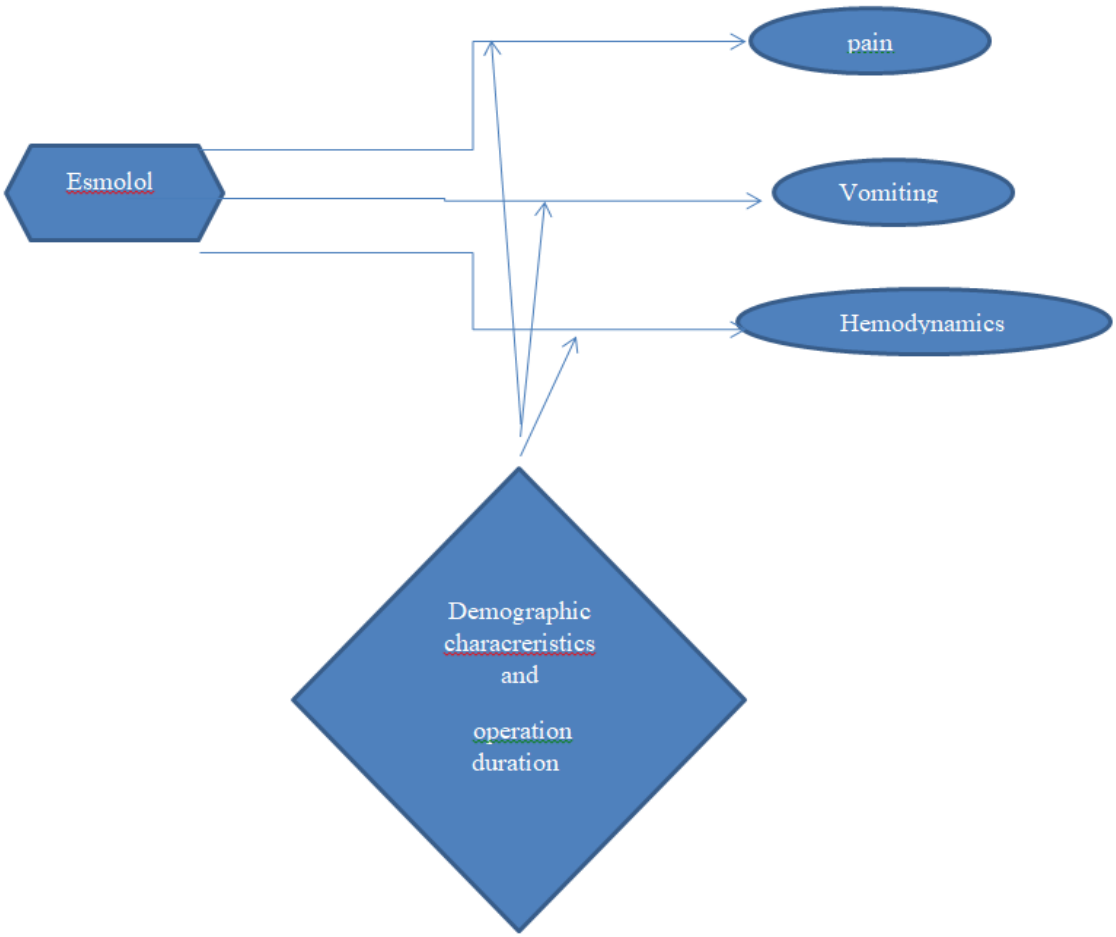
1.4 Study variables

Dependent variable: pain, vomiting, hemodynamics (BP, HR, SPO2)

- Note: temperature was excluded because of the cold environment of the operation room can make difference

Independent variables: esmolol, demographic characteristics. operation duration

1.5 conceptual framework



1.6 Definitions of terms

- **Conceptual definition of pain**: "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage, and it can be influenced by multiple factors. " (Correia & Duran, 2017).

- **Operational definition of pain**: pain measured by using visual analogue scale that gives a pain rate from 0-10. Zero means that no pain, ten is the most horrible pain that felt according to the patient.

- **Conceptual definition of nausea**: It is a Greek term which designated the signs and symptoms of seasickness (Balaban & Yates, 2017).

- **Operational definition of nausea**: It is usually determined through self-reporting from patients.

- **Conceptual definition of vomiting**: oral expulsion of stomach substances, due to contractions of the gastrointestinal smooth muscles and the wall of thoraco-abdominal muscles (Morra et al., 2017).

- **Operational definition of vomiting:** Both the occurrence and the frequency of vomiting may be objectively measured.

- **Conceptual definition of hemodynamics**: a branch of physiology deals with the circulation of the blood, the association between pressures and flows in a system of blood vessels (Secomb, 2011).

- **Operational definition of hemodynamics:** measured by taking vital signs (BP, HR , O2 saturation) by connecting the patient to monitor.

- **Conceptual definition of esmolol:** Ultrashort-acting β-1 receptor blocker, used to treat tachyarrhythmia (Gelineau et al., 2018) **.**

- **Operational definition of esmolol:** the drug effect can be assessed by connecting the patient on a cardiac monitor for continuous vital signs monitoring.

- **Conceptual definition of demographic characteristics**: defined as Information about the characteristics of a population, including the age of the people, their sex, and the income they earn. (Demographics. (n.d.). In *YourDictionary*. Retrieved from https://www.yourdictionary.com/DEMOGRAPHICS**)**

- **Operational definition of demographic characteristics:** this appears to be taken by asking patients and seeking from patient files.

- **Definition of operation duration**: the length of stay in the operation room post induction of anesthesia until emergence.

1.7 Research questions

Is there a relationship between demographic data of patients undergone laparoscopic cholecystectomy and continuous infusion of esmolol regarding intra and post-operative pain?

Does the use of continuous esmolol infusion during operation on laparoscopic cholecystectomy patients reduce nausea and vomiting?

Does the duration of the operation affect the pain post-operation?

1.8 Research hypothesis

Null hypothesis: There are no statistically significant correlation at (α=0.05) between intraoperative continuous infusion of esmolol on pain reduction post-operative on laparoscopic cholecystectomy patients.

Alternative hypothesis: There are statistically significant correlation at (α=0.05) between intraoperative continuous infusion of esmolol on pain reduction post-operative on laparoscopic cholecystectomy patients.

1.9 Literature review

M. H. Lee et al. (2014) a study took Sixty patients planned to do lap. cholecystectomy technique were distributed haphazardly into 3 groups. All patients had sevoflurane anesthesia and 4 ng/ml remifentanil throughout the procedure. The first group is esmolol, the second one is ketamine and normal saline for the third group as a control group. For the first six hours after surgery, we compared postoperative pain (on a visual analog scale [VAS]) and analgesic supplies. Compared with the control group, esmolol and ketamine groups reported lower pain scores (VAS) and lower fentanyl needs for 15 min after surgery ($P < 0.05$).esmolol and ketamine groups display no differences.

In this study that was conducted in Iran in 2018, a double blinded-randomized clinical trial aimed to use esmolol perioperatively to assess its effect on pain and hemodynamic postoperative in patients undergoing rhino-plastic surgery, fifty-six patients went through rhinoplasty operation were randomly scattered into 2 groups. Patients in Group number one (E) were given intravenous 5–10 mcg/kg/min of esmolol combined with

remi-fentanil and propofol adjusted to the responsiveness and stability of the hemodynamics. Patients in Group number two (C) were managed with normal saline 0.9%, also given the same volume as the previous group (E), mean BP , opioid amounts and requests , the degree of pain, and HR were assessed respectively at 30 min, 60min and 3 h, after the operation. They found that in the first three hours after surgery, postoperative pain was significantly reduced, a decrease in morphine consumption was observed in the group that treated with esmolol. The BP and HR of the postoperative Group (E) patients had fewer variations than those of the other group (Vahabi, Rafieian, & Abbas Zadeh, 2018).

As noted the approximately the sample size of these studies are the same around 60 participants, another study supported the result, López-Álvarez, Mayo-Moldes, Zaballos, Iglesias, and Blanco-Dávila (2012). Sixty patients from ASA I-II undergoing laparoscopic cholecystectomy, sevoflurane as gas anesthesia was maintained for both groups. (E) patients given a stat dose of esmolol 0.5 mg/kg intravenously at induction followed by esmolol pump of 5-15 mcg/kg/min, remifentanil and ketamine patients received a stat dose of 0.5 mg/kg intravenously and 0.5 mcg/kg iv at start of the operation then append by a remifentanil pump changed accordingly over a range of 0.1-0.5 mcg/kg/min. After the procedure (LC) fixed bolus dose of morphine was given according to a verbal numerical evaluation scale for pain potency. they found that the requirements of morphine were reduced in the esmolol group and offers more effective analgesia when compared with the remifentanil-ketamine combination.

Sixty adult patients from both gender as the same size sample of other studies , from (ASA) stage one and two, arranged for laparoscopic cholecystectomy underneath general anesthesia. separated into two Groups E or C, Group E Patients was given a loading dose of esmolol 0.5 mg/kg in normal saline before induction of anesthesia, then followed by an intravenous infusion pump of esmolol 0.05mg/kg/min till the termination of the surgery, while in Group C, patients received the same volume of saline0.9% as loading dose and then continuous infusion of normal saline at the same rate until the surgery finished. Any episode of bradycardia managed with atropine 0.01 mg/kg and any event of hypotension was treated with ephedrine 0.05 mg/kg . Vital signs Were monitored each 5 min for the first 1/2h , and then every 30min till 4th hour and then every 4 hours till end of 24 hrs. supplementary dose of tramadol was given to

patients for pain controlling according to VAS score. The total amount of required rescue analgesics was documented .regarding the result was in Group C, four patients given first rescue analgesic after two hours of the operation, twenty one patients need pain killers at the third post operation hour, and five patients wanted analgesics in the fourth postoperative hour .from another side of the study none of the patients in Group E, required first rescue analgesic until the 4th hour post-operation. Only one patient was given the first pain killer at the 4th hour, nine patients given bolus dose of analgesia at 8th hour, 17 of patients were requested and given first rescue analgesic at the 12th postoperative hour. the conclusion was the intraoperative use of esmolol reduced intraoperative and postoperative anesthetic and analgesic requirements(Dhir, Singh, Kaul, Tewari, & Oberoi, 2015).

A literature systematic review and a meta-analysis study from many databases exploring the beta-blockers outcome on perioperative pain RCT, 11 randomized control trials have the records of 701 adult participants were fit for this method of study. propranolol assessed in 1 trial and Esmolol was monitored in 10 trials. Esmolol decreased the necessity and needs for rescue painkillers by approx. 32–50 % and 100 to 65 % for the percentage of patients those needing rescue analgesia, however propranolol lowers the need for rescue analgesics by 72 %; the study noticed that patients who were given beta-adrenergic antagonists asked for the first rescue analgesia take a long time In contrast 2 opioid-controlled studies showed that esmolol-treated patients were twice as likely to require rescue analgesia during tubal ligation and knee arthroscopy than opioid-treated patients:52–57% versus 23–34% Adversative side effects stayed rare, and as described were mostly circulatory cardiac variations (Härkänen, Halonen, Selander, & Kokki, 2015).

Postoperative nausea vomiting has been the most known postoperative worse side effect from opioid and anesthesia that make the medical team concerned about trying to avoid or at least decrease the incidence of it, meta-analysis study reviews compared esmolol to opioids effects on postoperative nausea and vomiting on non-cardiac surgery, 8 clical trials were recognized including 439 participants, 228 of whom administered esmolol while 211 received opioids, A meta-analysis random-effects presented that in comparison with opioids, esmolol run to a sixty nine percent decrease in the occurrence

of postoperative nausea and vomiting(Thiruvenkatarajan, Watts, Calvert, Newcombe, & Van Wijk, 2017).

A study was performed to assess the effect of esmolol on the amount of an inhalational agent requirements and also its effect on pain score immediately after operation, 50 patients as a representative sample from ASA 1 and 2, their age are between 25-65years of age and body mass index <25 who go through surgeries of the lower abdomen were randomly assigned to 2 groups: Group S and Group E they assign 25 participants in each Group . E patients started on infusion pump of esmolol, while Group S given the same amount of saline infusion, ordinary monitoring which involved (ECG), (HR), (MAP), (SpO2), (FiO2) and M Entropy. Induction was started by using propofol 1.25-2.0 mg/kg , fentanyl 3.0 mcg/kg and muscle relaxation was attained with Atracurium 0.5 mg/kg as induction dose then keept on by a bolus dose of Atracurium 0.15 mg/kg as and when needed. During the course of the operation, fentanyl bolus doses of 1.0 mcg/kg were given every 60 minutes to maintain intraoperative analgesia. Form the sides of following up patients were observed for 30 minutes in the postoperative room to assess pain and administered morphine boluses during this time. The patients were examined after 24 h. using morphine as the pain relief agent, the doses for both groups were calculated and compared. Five, ten, twenty-five and thirty minute intervals were statistically significant differences in morphine consumption, There was also a significant difference in the entire amount of the used morphine in Group E compared to Group S in 30 minutes (Bhawna, Lalitha, Dhar, & Kumar, 2012)**.**

On the other side of comparison drug vs. drug , a double-blind study compared esmolol versus lidocaine infusions rather than placebo on analgesic requirement, hemodynamic changes and recovery. sixty patients from ASA I and II planned for laparoscopic cholecystectomy The medication was given 3 min before induction of anesthesia and was immediately stopped after extubation . group (L) started om intravenous lidocaine pump infusion slowly at a rate of 1.5 mg/kg/min. The 2nd group (E) was given infusions of esmolol infused slowly at the rate of 1 mg/kg/min for a full dose of 15 mg/kg/h, results showed that the systolic BP was significantly lower in the esmolol group but diastolic were not changed, regarding pain according to VAS were significantly higher in the lidocaine group in the postoperative period (10min and 20 min after extubation). Neither group showed statistically significant differences in the demand for and amount

of analgesics administered, nor in the time before the first requirement for analgesia. (Dogan et al., 2016b).

As we know any operation may have side effects, a retrospective study takes 1116 patients with symptoms of gallstone disorders who underwent a laparoscopic cholecystectomy surgery, the process by reviewing retrospectively videos if available, Medical records, and the operative notes. Complications were defined approximately within 30 days post-surgery. Among the patients who did not have complications in the control group, a total of ninety eight patients developed complications, the most common is not specific abdominal pain (3.06) and wound infections form contamination (1.96) other complication are listed as the following. hernia from the site Trocar (0.09), Biliary damage about (1.71), surgical wound bleeding (0.90) intestine harm or damage (0.27) ,Frequent cholithiasis (0.81) , bleeding in the abdomen (0.36), Septic shock causing death (0.09). (Nijssen et al., 2015).

Finally, all medical concerns are the safety and the stability of hemodynamics of the patients, this study supported that esmolol can maintain the hemodynamic stability of the patients so it compares the effect on extubation quality, hemodynamic reaction to extubation, and postoperative pain were assessed when esmolol, nitroglycerin, lidocaine, and placebo were used separately, 120 patients form ASA 1 and 2 were divided into 4 groups, and were given the same anesthesia and same protocol, they found that when compared to the Placebo group based on post-extubation measurements esmolol group had no significant difference for MBP at any time but lower HR was documented at the 5^{th} minute (Kucukosman & Aydin, 2020).

Chapter Two

Methodology

2.1 Study design

True experimental double blinded- randomized clinical trial study

2.2 Site and setting

The study was conducted in Nablus city – Rafedia hospital, in operation room, and followed up in the open wards.

2.3 Population

Physical status I or II categories for adults who are ASA members over 18 y, undergoing laparoscopic cholecystectomy.

2.4 Sample and sampling

A random allocation process was used to assign patients to either Group C or E according to coin randomization as random assignment.

The estimated Sample size using sample size is 60 patients in both groups , based on effect size 0.76 (Dhir et al., 2015) power of 0.80 and alpha level of 0.05 that calculated by G power . the researcher added another 5 participants to overcome the possibility of withdrawal.

2.5 Inclusion criteria

Physical status I or II categories for adults who are ASA members over 18 y, undergoing laparoscopic cholecystectomy, and a body mass index between 18-35 kg/m**2**

2.6 Exclusion criteria

- Diseased liver patients.
- heart disease ,renal failure.

- Chronic opioid or beta-blocker use.
- The presence of asthma history or bronchial hyperactivity.
- Allergy to any medication in the study.
- Having an airway disease.
- Pain killer use in the previous 12 h.

2.7 Validity and reliability: the researcher consulted three faculty members of An-Najah National University who are experts in different medical departments, and they agreed to review my assessment tool with little editing.

VAS scale was appeared to be valid and reliable for acute pain. Reliability was evaluated using the correlation coefficient between VAS scores, supplemented by Bland-Altman analysis. Differences in VAS scores linearly increased as pain descriptors escalated from "much less" to "much more" pain (P <.001). Reliability was high, CC = 0.99 (Gallagher, Bijur, Latimer, & Silver, 2002).

2.8 Study protocol

- Patients were randomly selected by the anesthesiologist (esmolol group or placebo group) and signed the consent of the study
- Demographic data and patient weight taken in the recovery room.
- Patients then go to operation room attached to standard monitoring (EKG, spo2,BP, etco2), A patent IV access achieved,pre-oxygenated 2-3 min with mask, FiO_2 100 %.
- The anesthesiologist will give fentanyl 1.5mcg/kg before incision and fentanyl 1mcg/kg will be given after incision, propofol 2mg/kg, atracurium 0.5 mg/kg repeated with a dose of 0.1 mg/kg as a muscle relaxant if necessary.
- Cuffed tube inappropriate size will be used, attached to a ventilator with isoflurane anesthesia gas 1-1.2 %, o2:air 50:50.

- Esmolol given by the anesthesiologist according to the developed protocol that structured in cooperation with the anesthesiologist, the researcher, and from previous studies, at induction the patient given (0.5mg/kg) iv esmolol bolus (S. C. Lee, Kim, & Ham, 1993).

- Esmolol pump started just after intubation at a rate 5-10mcg/kg/min till the end of the surgery.

- Control group received n/s0.9% at the same rate.

- Any incidence of bradycardia <50beats/min managed with atropine 0.01 mg/kg and any event of hypotension bp <90mmhg was treated with ephedrine 0.05 mg/kg (Dhir et al., 2015).

- In all cases the duration of surgery was recorded.

- At the end of the surgery, infusion stopped for the patients. The remaining muscle relaxants was antagonized with intravenous neostigmine 2.5 mg and atropine 1 mg.

- After extubation, patients were shifted to post-anesthesia recovery care unit where HR, NIBP, RR, and SpO2 were recorded,Visual analogue scale was assessed by the researcher at 0 min, 5 min, 15 min, 30 min, 1 h, 4 h, 24h. Episodes of vomiting recorded by asking the patient after 24hr of operation.

2.9 Study instrument

Self-developed well-structured assessment sheet, using VAS as the main tool.

2.10 Data analysis plan

Data were analyzed with SPSS (24) program, descriptive data such as demographic presented by mean, SD, percentage, min and max.

parametric data then tailed t-test used to assess the relationship, p-value <0.05.

2.11 Ethical consideration

IRB was obtained from the university research committee(check appendix) , consent form taken from all participants, privacy of the data from the patient is on the top of consideration , the participants informed clearly about the study benefits and hams , and they informed that they can withdraw form my study at any time they want.

Chapter Three

Results

Introduction:

This study attempted to evaluate the effects of the using continuous infusion of esmolol during operation on pain reduction post-operatively in patients who underwent laparoscopic cholecystectomy under general anesthesia.

In addition, to assess if using continuous infusion of esmolol during operation in patients underwent laparoscopic cholecystectomy under general anesthesia can reduce the frequency of nausea and vomiting and if can maintain and stabilize patients' hemodynamics parameters post-operatively.

Lastly, to evaluate if the above mentioned effects (esmolol on reduction of pain and occurrence of nausea and vomiting) can be affected by characteristics of patients underwent laparoscopic cholecystectomy under general anesthesia.

Demographic and characteristics of laparoscopic cholecystectomy participants:

Although the personal and demographic characteristics between the patients in the two groups did not have any statistically significant difference (p values > 0.05), the proportion of females (55.6%) was slightly higher in the control group, while the ages of the interventional group patients were slightly older (85% vs. 82% above 35 years).

The proportion of patients in the interventional group who were uneducated or had a basic level of education was slightly higher in the interventional group (48.2% vs. 30.5% respectively). The control group contained a slightly higher percentage than the interventional group of patients working in the private sector (26.5% vs. 20.7% respectively) and the income (above 3500 NIS 22.2% vs. 13.8% respectively), while the percentage of married people was slightly higher among the participants in the control group compared with patients in the interventional group (75.8% vs.63% respectively).

The two groups are comparable regarding the personal and demographic characteristics between the patients, the differences between them were few and did not produce any statistical significance, See table 3.1.

Table 3.1

the demographic and characteristics of laparoscopic cholecystectomy participants

		Group					
		Total	Control	Intervention	X^2	DF	*P* Value
Gender	Male	32(49.2%)	16(44.4%)	16(55.2%)	.740	1	.390
	Female	33(50.8%)	20(55.6%)	13(44.8%)			
Age	<20years	2(3.2%)	1(2.9%)	1(3.4%)	1.280	3	.734
	20-34 years	8(12.7%)	4(11.8%)	4(13.8%)			
	35-49years	22(34.9%)	14(41.2%)	8(27.6%)			
	>50years	31(49.2%)	15(44.1%)	16(55.2%)			
Occupation	Governmental	12(19.0%)	6(17.6%)	6(20.7%)	.316	2	.854
	Private	15(23.8%)	9(26.5%)	6(20.7%)			
	Other	36(57.1%)	19(55.9%)	17(58.6%)			
Educational level	Not educated	11(16.9%)	4(11.1%)	7(24.1%)	4.836	5	.436
	Basic level	14(21.5%)	7(19.4%)	7(24.1%)			
	High level	19(29.2%)	12(33.3%)	7(24.1%)			
	Diploma	3(4.6%)	3(8.3%)	0(0.0%)			
	Bachelor	15(23.1%)	8(22.2%)	7(24.1%)			
	Postgraduate	3(4.6%)	2(5.6%)	1(3.4%)			
Social status	Single	11(18.3%)	5(15.2%)	6(22.2%)	1.227	3	.747
	Married	42(70.0%)	25(75.8%)	17(63.0%)			
	Widow	5(8.3%)	2(6.1%)	3(11.1%)			
	Divorced	2(3.3%)	1(3.0%)	1(3.7%)			
Economic status	< 1500	6(9.2%)	2(5.6%)	4(13.8%)	1.979	3	.577
	1500 – 2499	23(35.4%)	12(33.3%)	11(37.9%)			
	2500 – 3499	24(36.9%)	14(38.9%)	10(34.5%)			
	> 3500	12(18.5%)	8(22.2%)	4(13.8%)			

The second table enhances the possibility of comparison between the two groups (interventional and control), as the average duration of the operation time was close between the two groups (48.9 ± 8 min vs. 46.1±6.7 min) and had no statistical significance (p=0.14). this can be attributed to that the procedure and the way of surgical intervention (steps) for removing the gallbladder by laparoscope is the same for both groups and giving of esmolol has no consideration for the surgeon to do special things in the op that may take more or less time so it is not significant.

Table 3.2

average duration of the operation time comparison between the two groups (interventional and control)

	Group	N	Mean	Std. D	T	df	Sig. (2-tailed)
Operation Time	Control	36	48.9	8.05673	1.48	61	.143
	Intervention	29	46.1	6.78077			

As for the pre-operative hemodynamic parameters (SBP, DBP, HR, SPO2) for patients who underwent laparoscopic cholecystectomy, the third table and the first figure, using the t test, confirm that the differences were few and were not statistically significant (p values 0.74 to 0.93). All hemodynamic parameters were within normal range with slight elevation in systolic blood pressure among the two groups (139.2 mmHg vs. 137.8 mmHg).

Table 3.3

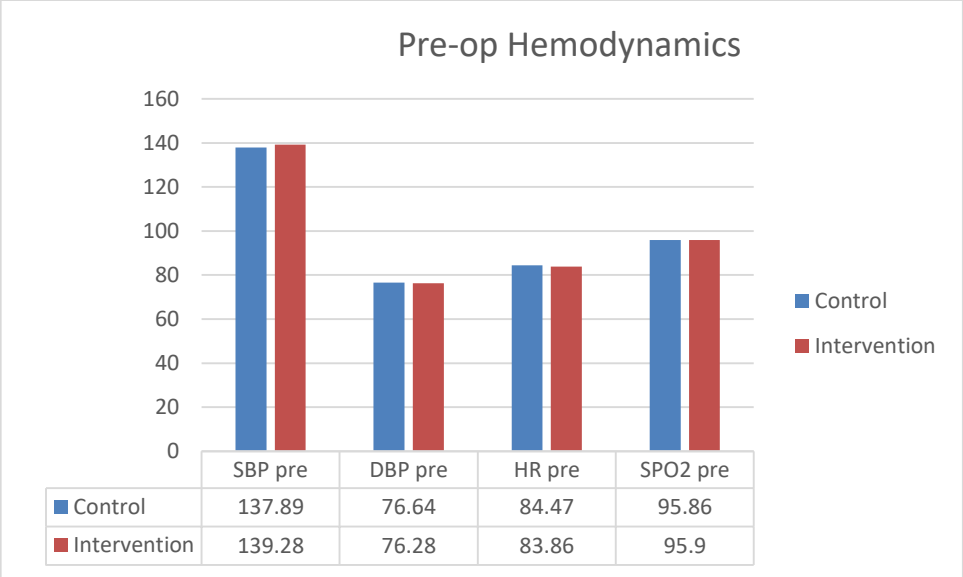
pre-operative hemodynamic parameters (SBP, DBP, HR, and SPO_2) for patients who underwent laparoscopic cholecystectomy

Preoperative:	Group	N	Mean	Std. D	t	df	Sig. (2-tailed)
SBP	Control	36	137.89	15.61	-.333	63	.741
	Intervention	29	139.28	17.99			
DBP	Control	36	76.64	9.63	.140	63	.889
	Intervention	29	76.28	11.24			
HR	Control	36	84.47	8.44	.242	63	.809
	Intervention	29	83.86	11.84			
SPO2	Control	36	95.86	1.84	-.087	63	.931
	Intervention	29	95.90	1.35			

p values < 0.05

Figure 3.1

pre-operative hemodynamic parameters (SBP, DBP, HR, and SPO2) for patients who underwent laparoscopic cholecystectomy



It is clear by looking at the results listed in Table 3.4 and Figure 3.2, that the post-operative hemodynamic parameters (SBP, DBP, HR, SPO2) at PACU of the two groups patients who underwent laparoscopic cholecystectomy were close and within the normal range, and there were no statistically significant differences between the values of the two groups (p values 0.10 to 0.91).

Table 3.4

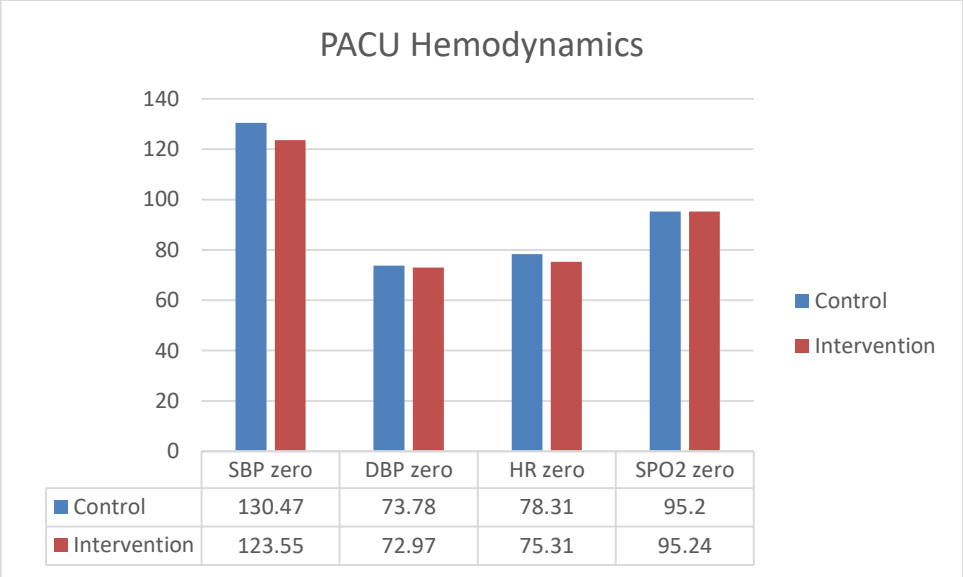
PACU hemodynamic parameters (SBP, DBP, HR, and SPO2) for patients who underwent laparoscopic cholecystectomy

PACU:	Group	N	Mean	Std. D	t	df	Sig. (2-tailed)
SBP	Control	36	130.47	17.14	1.654	63	.103
	Intervention	29	123.55	16.30			
DBP	Control	36	73.78	10.32	.316	63	.753
	Intervention	29	72.97	10.30			
HR	Control	36	78.31	11.03	1.193	63	.237
	Intervention	29	75.31	8.69			
SPO2	Control	35	95.20	1.59	-.110	62	.913
	Intervention	29	95.24	1.38			

p values < 0.05

Figure 3.2

PACU hemodynamic parameters (SBP, DBP, HR, and SPO2) for patients who underwent laparoscopic cholecystectomy



	SBP zero	DBP zero	HR zero	SPO2 zero
Control	130.47	73.78	78.31	95.2
Intervention	123.55	72.97	75.31	95.24

It seems that the esmolol administration during operation had a clear effect on the level of post-operative pain level after laparoscopic cholecystectomy.

As the post-operative average pain level among the experimental group patients was less than the post-operative average pain level among the patients in the control group during the whole period of the study; at PACU (5.8 vs. 7.2 out of 10), 5 min (5.9 vs. 7.1 out of 10), 15min (5.7vs. 7.1 out of 10), 30 min (5.5 vs. 6.5 out of 10), 1 h (4.6 vs. 5.9 out of 10), 4 h(3.4 vs. 3.9 out of 10), and 24 h (1.8 vs. 2.2 out of 10).

In addition, these differences in the average level of post-operative pain had a statistical significance differences (p values < 0.05), especially during the readings for the first hour after the operation.

Moreover, the average level of post-operative pain was still lower among patients in the intervention group compared with the patients in the control group after the first hour postoperatively, but it had no statistical significance differences (3.4 &1.8 vs. 3.9 & 2.2 out of 10). See table 3.5 and figure 3.3.

Table 3.5

the level of post-operative pain level after laparoscopic cholecystectomy.

Post-Operative Pain at:	Group	N	Mean	Std. D	T	Df	Sig. (2-tailed)
PACU	Control	36	7.22	1.27	4.62	63	<.001
	Intervention	29	5.86	1.06			
5 min	Control	36	7.14	1.27	4.00	63	<.001
	Intervention	29	5.93	1.13			
15 min	Control	35	7.11	1.35	4.56	62	<.001
	Intervention	29	5.72	1.03			
30 min	Control	35	6.51	1.44	2.99	62	.004
	Intervention	29	5.55	1.06			
1 h	Control	36	5.97	1.89	2.74	63	.008
	Intervention	29	4.69	1.85			
4 h	Control	36	3.94	1.55	1.05	63	.295
	Intervention	29	3.48	1.98			
1 day	Control	36	2.28	1.49	1.26	63	.209
	Intervention	29	1.86	1.06			

p values < 0.05

Figure 3.3

the level of post-operative pain level after laparoscopic cholecystectomy

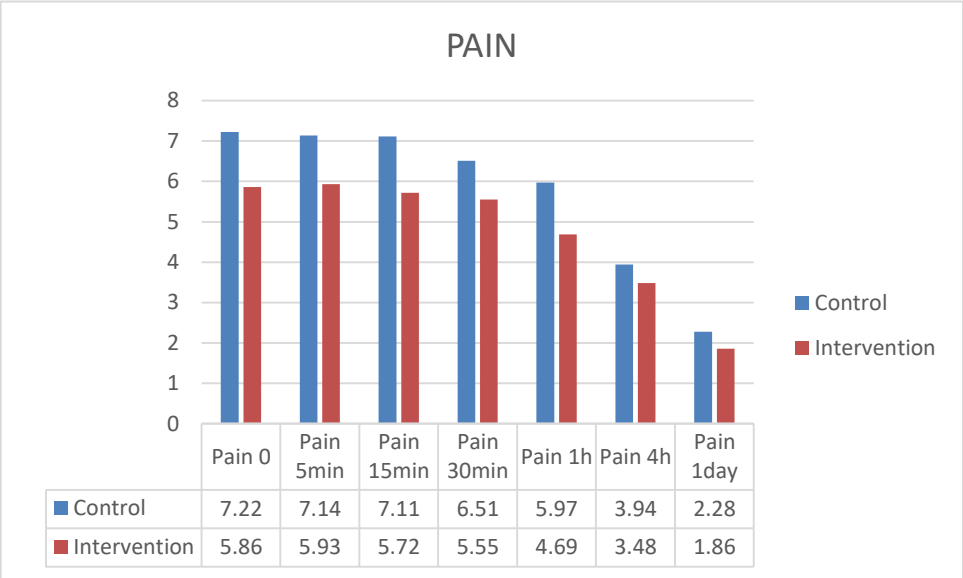
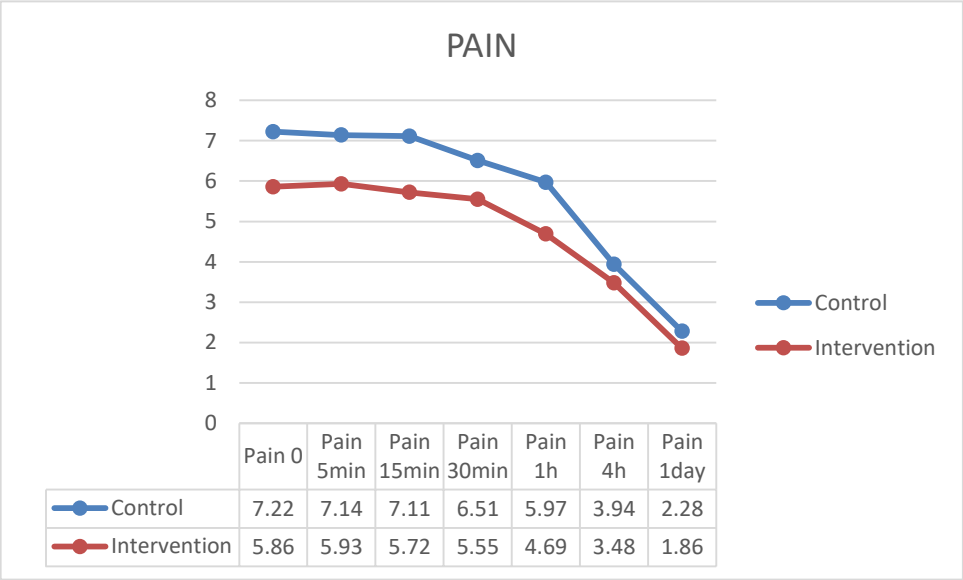


Figure 3.4

the level of post-operative pain level after laparoscopic cholecystectomy



Although the post-operative cholecystectomy average time to request the first dose of rescue analgesia was longer in the experimental group patients whom received esmolol during operation compared to the patients in control group whom did not received esmolol, but this difference between the two groups for the time of request for rescue analgesia was not statistically significant (p =0.33). See table 3.6 and figure 3.4.

Table 3.6

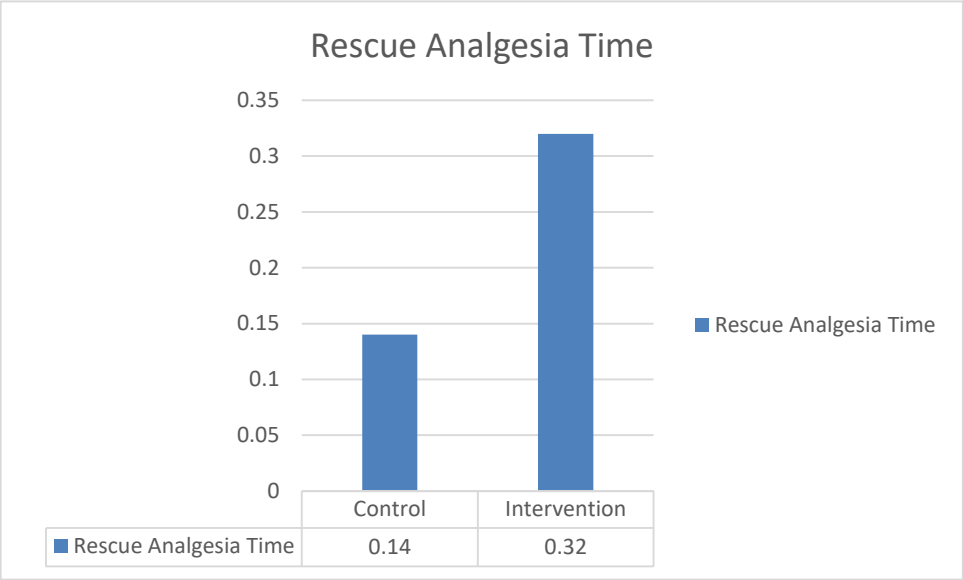
Post-operative cholecystectomy average time to request the first dose of rescue analgesia

	Group	N	Mean	Std. D	t	df	Sig. (2-tailed)
Rescue Analgesia Time	Control	36	0.14	0.33	-.98	62	.331
	Intervention	29	0.32	1.06			

p values < 0.05

Figure 3.5

Post-operative cholecystectomy average time to request the first dose of rescue analgesia



Although the occurrence of nausea and vomiting among patients in the experimental group was slightly higher compared to the occurrence of nausea and vomiting in patients in the group control (0.58 vs. 0.69), thus it seems that the administration of esmolol during the operation had no clear effect on the occurrence of post-operative vomiting after laparoscopic cholecystectomy, as the statistical results did not show any statistical significance difference (p=0.33) between the two groups in terms of the occurrence of nausea and vomiting.

In addition, there were no statistically significant differences in of occurrence of post-operative vomiting related to gender (p=0.95), age (p=0.86), occupation (p=0.08), education (p=0.39), social (p=0.15), and economic (p=0.99). See table 3.7.

Table 3.7

post-operative nausea and vomiting after laparoscopic cholecystectomy.

Source	Type III Sum of Squares	Df	MS	F	Sig.	ηp2
Intercept	.961	1	.961	2.08	.155	.041
	22.588	48.991	.461			
Gender	.002	1	.002	.004	.953	.000
	22.149	48	.461			
Age	.014	1	.014	.030	.864	.001
	22.149	48	.461			
Occupation	1.455	1	1.455	3.15	.082	.062
	22.149	48	.461			
Educational	.341	1	.341	.739	.394	.015
	22.149	48	.461			
Social	.960	1	.960	2.08	.156	.042
	22.149	48	.461			
Economic	2.349	1	2.349	.000	.994	.000
	22.149	48	.461			
Group	.442	1	.442	.958	.333	.020
	22.149	48	.461			

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

The intraoperative administration of esmolol had a clear effect on the average level of postoperative pain after laparoscopic cholecystectomy, as the statistical results showed that there was a statistically significant difference ($p < 0.001$) between the two groups in terms of the average level of postoperative pain.

In addition, the average level of pain after laparoscopic cholecystectomy was lower among patients in the experimental group whom received esmolol during operation compared with the average level of pain after laparoscopic cholecystectomy in patients in the control group. See table 8 and figure 3.5.

Table 3.8

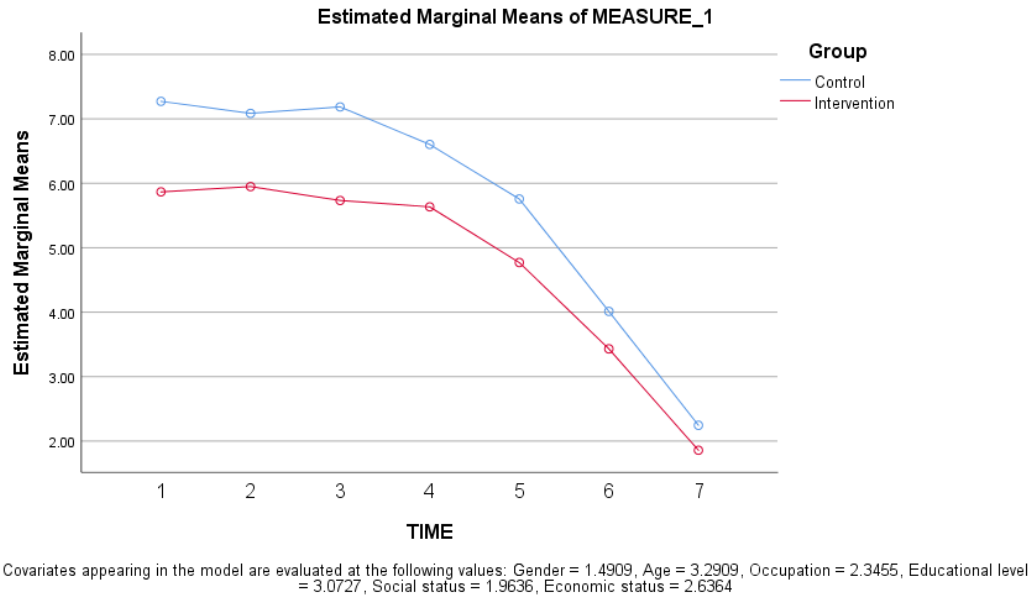
*post-operative pain level after laparoscopic cholecystectomy***.**

Source	Type III Sum of Squares	Df	MS	F	Sig.	ηp2
Intercept	127.862	1	127.862	20.472	.000	.303
Gender	3.528	1	3.528	.565	.456	.012
Age	.742	1	.742	.119	.732	.003
Occupation	1.768	1	1.768	.283	.597	.006
Educational	12.764	1	12.764	2.044	.159	.042
Social	.088	1	.088	.014	.906	.000
Economic	1.148	1	1.148	.184	.670	.004
Group	88.006	1	88.006	14.091	**<.001**	.231
Error	293.543	47	6.246			

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

Figure 3.6

post-operative pain after laparoscopic cholecystectomy



Chapter Four

Discussion and Conclusion

Summary of the key findings

Reduction of postoperative pain and reduction of opioid analgesics required postoperatively have been a subject for many research studies over the last few decades. Administration of esmolol was shown to reduce postoperative pain and analgesics required postoperatively (Bajracharya, Subedi, Pokharel, & Bhattarai, 2019; Haghighi et al., 2015; Watts, Thiruvenkatarajan, Calvert, Newcombe, & van Wijk, 2017).

This study assessed for the first time the effects of continuous intraoperative infusion of esmolol on reducing postoperative pain among patients who underwent laparoscopic cholecystectomy under general anesthesia. The study also assessed the effects of continuous intraoperative infusion of esmolol on reducing vomiting among patients who underwent laparoscopic cholecystectomy.

Associations between demographic characteristics of the patients and the effects of continuous intraoperative infusion of esmolol on reducing postoperative pain were also investigated. Additionally, associations between the duration of the laparoscopic cholecystectomy operation and the degree of postoperative pain were also investigated.

In this study, continuous intraoperative infusion of esmolol was shown to maintain PACU hemodynamic parameters and significantly reduced postoperative pain (up to 1 hour postoperatively) among patients who underwent laparoscopic cholecystectomy. The average time to require the first dose of rescue analgesia was longer in the esmolol group compared to the control group. However, this difference was not statistically significant.

Findings of this study could be informative to anesthesiologists, surgeons, nurses, and other healthcare providers in the perioperative care team who could be interested in reducing postoperative pain among patients who were planned to undergo laparoscopic cholecystectomy. Findings of this study also could enrich the accumulating literature on the effects of esmolol on reducing postoperative pain.

Appraisal of the methods used in this study

This study was conducted using a double-blind randomized controlled clinical trial design. Double-blind randomized controlled clinical trial designs occupy a high place at the top of the evidence hierarchy pyramid (George, Kleinlugtenbelt, & Madden, 2021; Glasofer & Townsend, 2019; Mulimani, 2017).

Findings obtained from double-blind randomized controlled clinical trials are superior to those obtained from ideas/expert opinions/editorials, in vitro investigations, animal investigations, case reports, case report series, case-control studies, cohort studies, non-randomized trials, quasi-randomized studies, open-label randomized trials, and single-blind randomized trials, respectively (Voudouris, 2014). Additionally, findings obtained from double-blind randomized controlled clinical trials might influence evidence-based clinical practice and are more likely to be adopted in clinical guidelines.

The size used in this study was calculated using a robust methodology to produce acceptable power and effect size. This should have added strength to the findings of this study (Hickey, Grant, Dunning, & Siepe, 2018; Jones, Carley, & Harrison, 2003).

This study was conducted in Rafidia Surgical Hospital which is one of the main governmental referral hospitals in the north of the West Bank. At this hospital, a considerable number of patients receive surgical services including laparoscopic cholecystectomy. Because this hospital is one of the main governmental referral surgical hospitals, many patients from all over the West Bank are operated on daily basis. Conducting this study at this main hospital should have allowed recruitment of a representative sample of patients admitted to Palestinian governmental hospitals for laparoscopic cholecystectomy. Many stakeholders have called for improving representativeness and inclusions of different segments of the population in clinical trials (Chari et al., 2020; Susukida, Crum, Stuart, Ebnesajjad, & Mojtabai, 2016).

The assessment tools used in this study were assessed for face validity and suitability of use by three experts who were academicians, researchers, and healthcare practitioners. Conducting this face validity before the tools were used should have ensured the suitability of the tools used in this study (Umanath & Coane, 2020). The VAS scale used to measure pain in this study was previously validated and used to measure pain among patients with acute and postoperative pain in different health conditions

including cholecystectomy (Asakuma et al., 2011; Bisgaard, Klarskov, Rosenberg, & Kehlet, 2001; Fredman, Jedeikin, Olsfanger, Flor, & Gruzman, 1994; Gallagher et al., 2002; Myles et al., 2017). These studies have shown that the VAS scale was reliable and valid (Gallagher et al., 2002).

The patients in the esmolol group were essentially similar to those in the control group in terms of demographic characteristics. When gender, age group, occupation, educational level, marital status, and economic status distribution between the two groups were compared using Chi-squared test, differences were not statistically significant (*P*-value > 0.05). These similarities should have promoted assessing the effects of the intervention and should have eliminated any selection bias that could have influenced the findings of this study (Berger & Exner, 1999; Eduafo et al., 2020; Jager et al., 2020).

Interpretation of the findings and their implications for practice

Effect on operation duration

Findings of this study showed that continuous intraoperative infusion of esmolol had no effects on the average operation duration. In this study, the average operation duration was not significantly different between the intervention and control groups (*P*-value = 0.143). Findings of this study were consistent with those previously reported on surgical and anesthesia durations in cholecystectomies in which esmolol was infused intraoperatively (Bajracharya et al., 2019; V. Collard et al., 2007; Dereli et al., 2015; Dogan et al., 2016a; Ozturk, Kaya, Aran, Aksun, & Savaci, 2007).

This could be explained by the fact that infusion of esmolol does not interfere with the surgical procedure and operating the laparoscope by the surgeon. Therefore, removal of the gallbladder from patients in the intervention and control groups was carried out using the same procedure and therefore has taken the same amount of time. Taken together, these findings might not discourage surgeons, anesthetists, and other healthcare providers involved in perioperative care from infusing esmolol to reduce postoperative pain in patients scheduled for laparoscopic cholecystectomy.

Effect on hemodynamic parameters

In this study, continuous intraoperative infusion of esmolol had no effects on preoperative hemodynamic parameters like SBP, DBP, HR, and SpO2. So there were no statistically significant differences in the preoperative SBP, DBP, HR, and SpO2 values between patients in the two groups (*P*-values were in the range of 0.741 to 0.931). Similarly, continuous intraoperative infusion of esmolol had no effects on postoperative hemodynamic parameters like SBP, DBP, HR, and SpO2.

In this study, there were no statistically significant differences in the postoperative SBP, DBP, HR, and SpO2 values between patients in the two groups (*P*-values were in the range of 0.103 to 0.913). Findings of this study were consistent with those reported in previous studies in which esmolol was infused intraoperatively to patients who underwent laparoscopic cholecystectomy under general anesthesia (Bajracharya et al., 2019; V. Collard et al., 2007; Dereli et al., 2015; Dogan et al., 2016a; López-Álvarez et al., 2012).

In Turkey, Dereli et al showed that intraoperative infusion of esmolol in patients who underwent laparoscopic cholecystectomy had no significant effects on the average intraoperative BP, heart rate in PACU, and average BP in PACU compared to patients who did not receive an intraoperative infusion of esmolol (Dereli et al., 2015). On the other hand, intraoperative infusion of esmolol was shown to slightly reduce the intraoperative HR. This reduction in HR could be explained by the fact that esmolol belongs to beta-blockers with known HR reducing actions (Liu, Gatt, Gugino, Mallampati, & Covino, 1986; Ozturk, Kaya, Aran, Aksun, & Savaci, 2008). The effects of esmolol on HR were shown to be dose-dependent (Liu et al., 1986).

While findings of this study were consistent with those reported in the study of Dogan et al in terms of no differences in HR of patients who received an intraoperative infusion of esmolol and those who did not, the average intraoperative BP and SBP after induction were significantly lower in the esmolol group (Dogan et al., 2016a). On the other hand, findings of Dogan et al were consistent with the findings of this study on the absence of significant effects of esmolol on intraoperative and postoperative DBP and SpO2 values (Dogan et al., 2016a). It was shown that intraoperative bradycardia and hypotension caused by esmolol were responsive to atropine and ephedrine

(Bajracharya et al., 2019; V. Collard et al., 2007; Dogan et al., 2016a; López-Álvarez et al., 2012).

Taken together, these findings might indicate that intraoperative infusion of esmolol had no serious threats to the hemodynamic parameters. Incidence of bradycardia and hypotension can be easily managed using atropine and ephedrine. These findings might not discourage surgeons, anesthetists, and other healthcare providers involved in the perioperative care of patients scheduled for laparoscopic cholecystectomy.

Effect on postoperative pain

The data generated in this study showed that continuous intraoperative infusion of esmolol significantly reduced postoperative pain.

The average pain scores measured using the VAS for the patients in the intervention group were generally lower than those in the control group. The pain scores for the patients in the intervention group were significantly lower compared to those for patients in the control group when the patients were admitted to the PACU (*P*-value < 0.001), at 5 min (*P*-value < 0.001), 15 min (*P*-value < 0.001), 30 min (*P*-value < 0.004), and 1 h (*P*-value < 0.008). Postoperative pain scores measured at 4 h and 1 day postoperatively were not significantly different (*P*-value > 0.05). Dereli et al reported that intraoperative infusion of esmolol reduced postoperative pain in patients who underwent laparoscopic cholecystectomy compared to patients who did not receive esmolol in PACU, at 12 h, and at 24 h postoperatively (Dereli et al., 2015). Recently, Bajracharya et al showed in a randomized controlled trial that esmolol was equivalent to lidocaine in reducing the severity of pain in the first 24 h postoperatively in patients who underwent laparoscopic cholecystectomy (Bajracharya et al., 2019).

Similarly, Dogan et al reported lower postoperative VAS scores among patients who received esmolol compared to patients who received lidocaine during laparoscopic cholecystectomies at 10 and 20 min post extubation (Dogan et al., 2016a). In another study, López-Álvarez et al showed that patients who received esmolol reported significantly lower postoperative VAS scores compared to those who received remifentanil-ketamine combination for laparoscopic cholecystectomy (López-Álvarez et al., 2012). Results obtained in this study confirmed previous findings reported in the

literature and may suggest that esmolol could be beneficial in reducing postoperative pain among patients who undergo laparoscopic cholecystectomy.

Effect on require rescue analgesia postoperatively

The average time to require the first dose of rescue analgesia was slightly longer in the esmolol group compared to the control group but the difference between the two groups was not statistically significant. Findings of this study contradicted with what was reported in the literature. Dereli et al reported that patients who received an intraoperative infusion of esmolol required significantly less remifentanil, propofol, and desflurane compared to the patients in the control group (Dereli et al., 2015). Bajracharya et al reported that the time to first perception of pain was significantly different between patients who received esmolol and those who received lidocaine (Bajracharya et al., 2019). However, the morphine equivalents consumed in 24h were not significantly different between the two groups.

In the study of López-Álvarez et al, patients who received remifentanil-ketamine combination required doses of morphine while patients who received esmolol did not require morphine (López-Álvarez et al., 2012). From the same side, Ozturk et al reported that patients who received esmolol required significantly less analgesics compared to patients in the placebo group (Ozturk et al., 2007). Similarly, Dogan et al reported that patients who received lidocaine required additional analgesics compared to patients in the esmolol group (Dogan et al., 2016a).

Effect on incidence of postoperative nausea and vomiting

There were no significant differences in the incidence of postoperative nausea and vomiting in the patients in the two groups. Additionally, the incidence of postoperative nausea and vomiting was not different between patients from both genders, different age groups, occupations, educational levels, marital status, and economic classes (*P*-value > 0.05).

Findings of this study were contradictory to those reported by Dereli et al in which esmolol was shown to significantly reduce postoperative nausea and vomiting (Dereli et al., 2015). Bajracharya et al reported that there were no significant differences between the scores of postoperative nausea and vomiting among patients who received lidocaine

and those who received esmolol (Bajracharya et al., 2019). Ozturk et al reported that patients who received esmolol required significantly less antiemetic drugs compared to patients in the placebo group (Ozturk et al., 2007). Dogan et al reported that a similar number of patients in lidocaine and esmolol groups reported nausea and vomiting and were managed with metoclopramide (Dogan et al., 2016a).

Although the literature suggested that continuous intraoperative infusion of esmolol could reduce the incidence of postoperative nausea and vomiting among patients, findings of this study should not discourage surgeons, anesthetists, and other healthcare providers of perioperative care from considering esmolol for patients scheduled for laparoscopic cholecystectomy.

Strengths and limitations of the study

- First, investigate the effects of continuous intraoperative infusion of esmolol among patients who underwent laparoscopic cholecystectomy in a major hospital in Palestine.

- Second, this study was conducted in a double-blind randomized controlled trial design. Double-blind randomized controlled trial designs are robust in producing findings with a low risk of bias.

- Third, valid and assessment tools were used to collect the data used in this study. This should have provided reliable data.

- Fourth, the two groups compared in this study were similar in terms of demographic characteristics. This should have allowed an unbiased assessment of the effects of the intervention.

On the other hand, the study has the following limitations.

- First, the amount of anesthetics required for each patient were not collected in this study. This precluded comparing anesthetic requirements between both groups. Second, the bispectral index (BIS) values were not collected in this study.

- Collection of BIS values could have allowed additional comparison of the patients.

- Third, the amount of analgesics administered to the patients were not collected. Collection of such information should have strengthened the data collected on the postoperative pain.

- Fourth, the amount of antiemetics administered to patients in this study were not collected. Collection of this information should have strengthened the data collected on the postoperative nausea and vomiting.

Recommendations

Based on the findings of this study, the following recommendations can be made:

- Surgeons, anesthetics, and other healthcare providers of perioperative care might consider intraoperative infusion esmolol to reduce postoperative pain among patients undergoing laparoscopic cholecystectomy.

- Continuous intraoperative infusion of esmolol during maintenance anesthesia could significantly reduce postoperative pain in patients undergoing laparoscopic cholecystectomy.

- Infusion of esmolol is not without risks, therefore, the decision to infuse esmolol intraoperatively should be made after considering the risks of bradycardia and hypotension.

- Atropine and ephedrine should be made handy when deciding to infuse esmolol intraoperatively to manage potential episodes of bradycardia and hypotension.

Future directions

Considering the design and findings of this study, future double-blind randomized controlled trials might be conducted considering a larger sample size, collection of more hemodynamic and clinical parameters like BIS, quantification of the amounts of anesthetics, analgesics, and antiemetics administered to each patient. Additionally, planning should consider recording the incidence of episodes of bradycardia and hypotension. Amounts of drugs administered to manage these episodes should also be quantified.

Conclusions

Postoperative pain continues to present a heavy burden on patients who undergo surgical interventions, notably, laparoscopic cholecystectomy. In conclusion, continuous intraoperative infusion of esmolol during maintenance anesthesia of patients undergoing laparoscopic cholecystectomy was shown to significantly reduce postoperative pain without destabilizing the hemodynamic parameters. farther more, rescue analgesia was less frequently needed in the esmolol group, nausea and vomiting were not reduced by esmolol and are still a major concern. Results of this study might be used to improve future perioperative care of patients scheduled for laparoscopic cholecystectomies. Larger double-blind randomized controlled trials are still needed to investigate the effects of different doses of esmolol on postoperative pain, nausea and vomiting, consumption of analgesics and antiemetics, the incidence of bradycardia and hypotension among patients undergoing laparoscopic cholecystectomy.

List of abbreviations

Abbreviations	Meaning
Group E	Esmolol
group C	Control group
PONV	Postoperative nausea and vomiting
HR	heart rate
BP	blood pressure
SBP	systolic blood pressure
DBP	diastolic blood pressure
SPSS	Statistical Package for the Social Sciences
SPO2	Non- Invasive Oxygen saturation
lab chole	laparoscopic cholecystectomy
LC	laparoscopic cholecystectomy
ASA	American Society of Anesthesiologists
RCT	randomized clinical trials
MAP	mean arterial pressure
FiO2	fraction of inspired oxygen
PACU	Post-Anaesthesia Care Unit
VS.	Versus
BIS	Bispectral index
ECG	Electrocardiogram
Kg	Kilogram(s)
Min	Minute

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Appendices

Appendix A

Questionnaire

An-Najah National University

Faculty of Medicine & Health Sciences Department of Nursing & Midwifery Department

Faculty of Graduate Studies

Assessment sheet to evaluate:

The effect of intraoperative continuous infusion of esmolol on pain reduction, vomiting and hemodynamics stability post operation on laparoscopic cholecystectomy patients

prepared by:

Ahmad Mohammad Ahmad Bast

Supervisor

Dr Jamal Qaddumi

Patient signature :……..

Demographic data

1 . Gender : male □ female □

2 . Age: less than 20 □ from 20 to less than 35 □ From 35 to less than 50 □ more than 50

3 . occupation : Governmental sector □ private sector □ other □

4 . city :…….

5 . Educational level : Not educated □ basic level□ high level □ Diploma□ Bachelor's degree□ Postgraduate□

6. social status : single □ married □ widow □ divorced□

7. Economic status:

□ Less than 1500

□ 1500 _ 2499

□ 2500 _ 3499

□ more than 3500

Vital signs: pre-operative

Bb

HR

SPO2

Vital signs: on zero minute

Bb

HR

SPO2

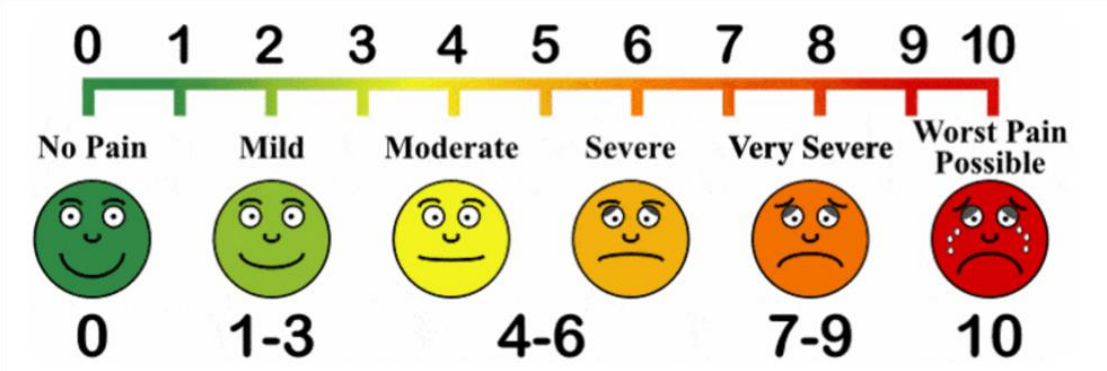
Vomiting episodes during the first 24h post-operative:

.....

Duration of the operation:

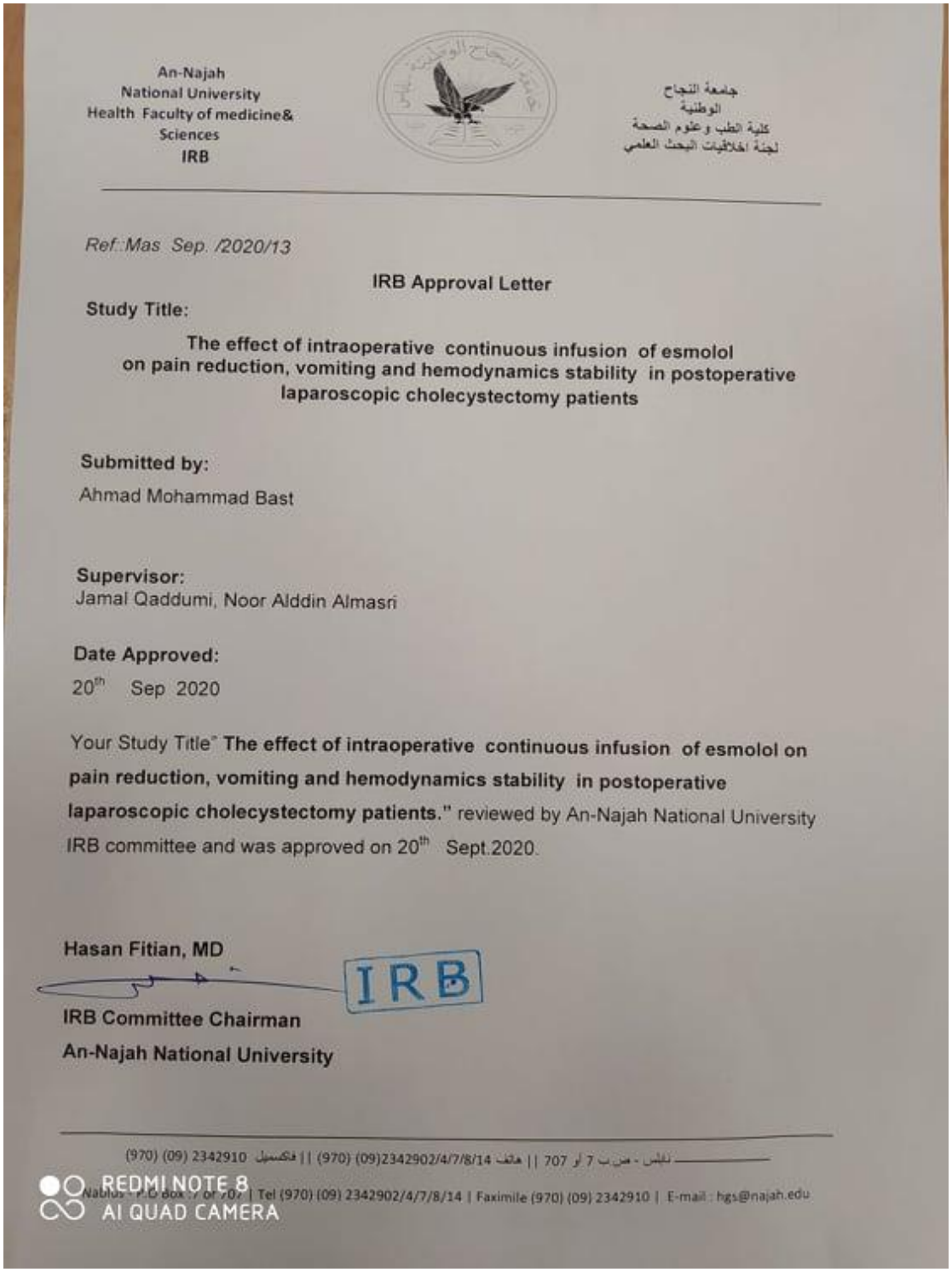
Pain measurement via VAS at
0 min :
5 min :
15 min :
30 min :
1 h:
4 h :
24h :

rescue analgesia ……..



Appendix (B)

IRB Approval Letter



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

جامعة النجاح
الوطنية
كلية الطب وعلوم الصحة
لجنة اخلاقيات البحث العلمي

Ref: Mas Sep. /2020/13

IRB Approval Letter

Study Title:

The effect of intraoperative continuous infusion of esmolol on pain reduction, vomiting and hemodynamics stability in postoperative laparoscopic cholecystectomy patients

Submitted by:
Ahmad Mohammad Bast

Supervisor:
Jamal Qaddumi, Noor Alddin Almasri

Date Approved:
20th Sep 2020

Your Study Title" **The effect of intraoperative continuous infusion of esmolol on pain reduction, vomiting and hemodynamics stability in postoperative laparoscopic cholecystectomy patients.**" reviewed by An-Najah National University IRB committee and was approved on 20th Sept.2020.

Hasan Fitian, MD

IRB

IRB Committee Chairman
An-Najah National University

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State of Palestine
Ministry of Health - Nablus
General Directorate of Education in Health

دولة فلسطين
وزارة الصحة- نابلس
الإدارة العامة للتعليم الصحي

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

الرقـــم: ت.ت/١٧٧٧/١٦٥
التـاريخ: ت.ت/١٩/١٠/٢٠١٧

الأخ مدير عام الادارة العامة للمستشفيات المحترم ،،،

تحية واحترام،،،

الموضـــوع: تسهيل مهمة بحث

لاحقاً لموافقة معالي وزيرة الصحة، يرجى تسهيل مهمة الطالب: **أحمد محمد احمد بسط،**

ماجستير تمريض التخدير، جامعة النجاح، لاجراء بحث التخرج بعنوان:

" The effect of intraoperative continuous infusion of esmolol on pain reduction, vomiting and hemodynamics stability postoperative on laparoscopic cholecystectomy patients "

حيث سيقوم الطالب بجمع المعلومات عن طريق تعبئة استبانة الدراسة من المرضى عينة الدراسة (بعد اخذ موافقتهم)، مع العلم ان مشرف الدراسة: د. جمال قدومي، وذلك في:

- **مستشفى رفيديا**

حيث سيتم الالتزام باساليب واخلاقيات البحث العلمي.

وتقبلوا فائق الاحترام،،،

دولة فلسطين وزارة الصحة الإدارة العامة للتعليم الصحي

د. أمل ابو عوض
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جـامعـــة النجاح الوطنية

كليـــة الدراســـات العليـــا

تأثير دواء الايزميلول على تقليل مستوى الألم والغثيان وثبات العلامات الحيوية بعد العملية للمرضى الذين يستأصلون المرارة عن طريق المنظار

إعداد

احمد محمد احمد بسط

إشراف

د . جمال القدومي

د. نور المصري

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

2022

تأثير دواء الايزميلول على تقليل مستوى الألم والغثيان وثبات العلامات الحيوية بعد العملية للمرضى الذين يستأصلون المرارة عن طريق المنظار

إعداد

احمد محمد احمد بسط

إشراف

د . جمال القدومي

د. نور المصري

الملخص

الخلفية: غالبًا ما يتطلب التخفيف من آلام ما بعد العمليات الجراحية إعطاء مسكنات قوية مثل المواد المخدرة. حيث ان تقليل جرعات المسكنات الأفيونية (المخدرة)، وتواترها، وشدتها يمكن ان يؤدي إلى تحسين نتائج المرضى.

الهدف: أجريت هذه الدراسة لتقييم آثار الحقن المستمر لدواء الايسميلول وريديا أثناء العملية على تقليل آلام ما بعد الجراحة بين المرضى الذين خضعوا لعملية استئصال المرارة بالمنظار تحت التخدير العام. قيمت الدراسة أيضًا آثار الحقن المستمر الايسميلول أثناء العملية على تقليل الغثيان، القيء وثبات العلامات الحيوية بين المرضى المنضمين. كما تم فحص الارتباط بين الخصائص الديموغرافية للمرضى وتأثير الحقن المستمر أثناء العملية على تقليل الألم بعد العملية الجراحية، ومدة عملية استئصال المرارة بالمنظار، ودرجة الألم بعد الجراحة.

الطريقة: أجريت هذه الدراسة باستخدام تصميم تجربة سريريه عمليه عشوائية مزدوجة التعمية. كان المرضى في كل من مجموعتي التحكم والتدخل من البالغين (> 18 عامًا) الذين تم انضمامهم من مستشفى رفيديا. تلقى المرضى في مجموعة التدخل الحقن المستمر 5–10 ميكروغرام لكل/كيلوغرام

من دواء الايسميلول أثناء العملية حتى الانتهاء من الجراحة. تلقى المرضى في مجموعة التحكم المحلول الوريدي الملحي المتعادل 0.9% نفس المعدل. تم قياس الالم ما بعد الجراحة باستخدام مقياس تناظري بصري وتم جمع المتغيرات الديموغرافية والعلامات الحيوية للمرضى في ورقة التقييم التي تم تطويرها لهذه الدراسة.

النتائج: تم اختيار ما مجموعه 65 مريضا بصورة عشوائية في مجموعة التحكم (ن = 36) والتدخل (ن = 29). لم تكن هناك فروق ذات دلالة إحصائية في المتغيرات الديموغرافية والعلامات الحيوية قبل الجراحة للمرضى في كلا المجموعتين قبل أن يدار التدخل. في هذه الدراسة، تبين أن الحقن المستمر للايسميلول أثناء العملية يحافظ على معايير العلامات الحيوية.

في غرفة الافاقة ويقلل بشكل كبير من آلام ما بعد الجراحة (حتى ساعة واحدة بعد الجراحة) بين المرضى الذين خضعوا لعملية استئصال المرارة بالمنظار. كان متوسط الوقت المطلوب للحصول على جرعة أولى من التسكين أطول في مجموعة الايسميلول مقارنة بمجموعة التحم ،ومع ذلك كان هذا الفرق لا يعتد به إحصائيا.

الخلاصة: لا تزال آلام ما بعد الجراحة تشكل عبئًا ثقيلًا على المرضى الذين يخضعون لتدخلات جراحية، ولا سيما استئصال المرارة بالمنظار. في الختام، تبين أن الحقن المستمر للإيسميلول خلال العملية الجراحية وأثناء التخدير للمرضى الذين يخضعون لاستئصال المرارة بالمنظار يقلل بشكل كبير من الألم بعد الجراحة دون زعزعة استقرار العلامات الحيوية. وكان هناك حاجة أقل لتسكين الالم في مجموعة الايسيميلول لكن الغثيان والقيء لم يتم تقليله بواسطة الايسيملول ولا يزال مصدر قلق كبير. يمكن استخدام نتائج هذه الدراسة لتحسين الرعاية المحيطة بالجراحة في المستقبل للمرضى المقرر لهم استئصال المرارة بالمنظار.

الكلمات المفتاحية: مسكنات الالم، الايسميلول، استئصال المرارة بالمنظار، تقليل المواد الافيونية المخدرة، آلام ما بعد الجراحة، التعافي.