An-Najah National University

Faculty of Graduate Studies

Comparison of Intra-Peritoneal Instillation of Bupivacaine and Morphine Hydrochloride versus Bupivacaine and Magnesium Sulfate for Post-Operative Pain Relief after Laparoscopic Cholecystectomy A Randomized Double-Blind Comparison Study

By

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Dedication

To my dear parents, wife, lovely son, sisters, brothers,

Teachers, friends and all members of my family with love and respect.

Acknowledgments

It is my pleasure to thank all patients who were participate in this study, and I would like to express my thanks to my supervisor Dr. Wael Sadqa for his encouragement, assistance and supervision during this work.

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الإقرار

نا الموقع أدناه، مقدم الرسالة التي تحمل العنوان:

Comparison of Intra-Peritoneal Instillation of Bupivacaine and Morphine Hydrochloride versus Bupivacaine and Magnesium Sulfate for Post-Operative Pain Relief after Laparoscopic Cholecystectomy, A Randomized Double-Blind Comparison Study.

أقر بأن ما اشتملت عليه هذه الرسالة أن ما هو نتاج جهدي الخاص، باستثناء ما تمت الاشاره إليه حيثما ورد، وان هذه الرسالة ككل، أو أي جزء منها لم يقدم من قبل لنيل أيّ درجة أو لقب علميّ لدى أي مؤسسة تعليمية أو بحثية أخرى.

Declaration

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

Student`s name: **اسم الطالب:**

Signature: **التوقيع:**

Date: **التاريخ:**

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List of Abbreviations

ANOVA	Analysis of variance
ASA	American society of anesthesiologist
BMI	Body mass index
BP	Blood pressure
CO2	Carbon dioxide
DBP	Diastolic blood pressure
ECG	Electrocardiogram
ETCO2	End tidal CO2
g	Gram
HR	Heart rate
Hrs.	Hours
IRB	Institutional review board
IPLA	Intraperitoneal local anesthesia
IV	Intra venous
LC	Laparoscopic cholecystectomy
LIA	Local Instillation anesthesia
MANE	Morrow assessment of nausea and emesis
mg	Milligram
Mg	Bupivacaine plus Magnesium sulfate
min	Minutes
ml	Milliliter
mmHg	Millimeter of mercury

Mo	Bupivacaine plus morphine hydrochloride
Na	Sodium
NIBP	Noninvasive blood pressure
NMDA	N-Methyl-D-Aspartate
NSAIDs	Non-steroidal anti- inflammatory drugs
PACU	Post anesthetic care unite
p-value	Probability value
RA	Rescue analgesia
SpO2	blood oxygen saturation
SBP	Systolic blood pressure
SD	Standard deviation
VAS	Visual analogue scale
VRS	Visual rating prince Henry scale
%	Percent

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Abstract

Background

Surgical and laparoscopic techniques are two different methods for the removal of gall bladder. Today, laparoscopic cholecystectomy is a preferred method for short-term hospitalization and early return to function related to minimal invasive surgical technique. However, patients still complain of significant postoperative pain, secondary inflammation of the diaphragm and the nociceptive genus of the annoying membrane's peritoneum

Multimodal analgesia is necessary for managing pain after laparoscopic cholecystectomy. Magnesium sulfate is a new emerging medication for the management of acute pain. There are no previous reports to compare the analgesic effect of intraperitoneal instillation of bupivacaine plus morphine hydrochloride and bupivacaine plus magnesium sulfate for postoperative pain after laparoscopic cholecystectomy.

Aims

The purpose of this study is to compare the analgesic effect of intraperitoneal instillation of bupivacaine plus morphine hydrochloride versus bupivacaine

plus magnesium sulfate in patients undergoing laparoscopic cholecystectomy under general anesthesia for better pain relief and less opioid consumption during the first 24 hours.

Methods

Following the approval of the Institutional Review Board of An-Najah National University and written informed consent from patients undergoing laparoscopic cholecystectomy, hundred patients between 18 and 60 years old, American Society of Anesthesiologist (ASA) Grades I and II, were randomized to one of the following groups by the sealed envelope: : (Mo group) (n = 50) receiving intraperitoneal instillation of 30 ml 0.25% bupivacaine and 3 mg morphine and (Mg group) (n = 50) receiving intraperitoneal instillation of 0.25% bupivacaine plus 50 mg / kg magnesium sulfate to a total volume of 30 ml. Medications were given after peritoneal wash and suctioning through intraperitoneal instillation. A drug solution is prepared by a doctor who does not participate in the study. All patients received the same anesthesia method, general anesthesia was administered. The induction protocol was standard for all patients. Patients were monitored for electrocardiogram (ECG), heart rate, blood oxygenation (SpO2%) and noninvasive blood pressure (NIBP). Postoperative pain was evaluated using visual analog scale (pain score of 0-10). The participants were evaluated for 24 hours after the operation with the registration of abdominal pain. The postoperative pain outcome was reported at 0 and 30 min, 1, 4, 8, 12, 16 and 24 hours. The cut-off value for VAS is 4 for indication of rescue medication. At VAS $\geq$ 4, rescue analgesics were administered on request (20 mg of

pethidine) intravenously in Post Anesthetic Care Unit (PACU) and 50 mg intramuscularly in the surgical ward.

Results

Patients' characteristics of age, gender and BMI were comparable in the two groups. There was no significant difference between the groups regarding the duration of the surgery. The demographic parameters (age, gender and BMI) have no effect on the mean of VAS (p-value> 0.05). There are significant differences between Mo and Mg groups in the total VAS score (P value <0.05). In the Mo group, the mean of total VAS (2.09) was significantly lower than the mean of total VAS in the Mg group (2.71); which means that patients in the Mo group had significantly less intensity of pain than patients in the Mg group (p = 0.006).

There is a significant difference between the number (percent) of patients complaining of moderate to severe postoperative pain in Mo group 15/50 (30%) compared to Mg group 25/50 (50%) (p = 0.0423). When Estimating the size of the treatment effect of morphine hydrochloride plus bupivacaine, found that the relative risk reduction of moderate to severe pain postoperatively is 0.40. There is also a significant difference between the number (percent) of patients complained of drowsiness in Mo Group 7/50 (14%) compared to Mg group 18/50 (36%) (p =0.0115). There are no significant differences between the two study groups regarding nausea, vomiting, dizziness and urinary retention.

Patients in Mo group consume less rescue analgesic dose M (± SD) (64.29 mg + 22.04) compared to patients in Mg group M (± SD) (74.40 mg + 25.67)

without significant relationship between both doses (p-value = 0.163). Blood pressure, heart rate and oxygen saturation were examined as hemodynamic parameters. The result showed that no significant relationship between these parameters and VAS (p-value> 0.05).

Conclusion

Intraperitoneal instillation of combination of bupivacaine with morphine hydrochloride is superior to bupivacaine plus magnesium sulfate to reduce the intensity and incidence of postoperative pain in patients undergoing laparoscopic cholecystectomy surgery without significant increase of side effects. This peripheral effect of opioid provides a new approach to pain relief that can have major clinical benefits.

Recommendation

Based on the results of this study, it is recommended to consider the intraperitoneal instillation of morphine hydrochloride with bupivacaine as a standard application for laparoscopic cholecystectomy surgery to reduce postoperative pain

Keywords: Bupivacaine, Intra-peritoneal instillation, Laparoscopic cholecystectomy, Magnesium sulfate, Morphine hydrochloride, Rescue analgesia.

Chapter One

Introduction

1.1 Introduction

A symptomatic gallstone disease is one of the prevailing problems seen in clinical practice (Ahmad et al., 2015). Surgical removal of the gall bladder can be done laparoscopic or open cholecystectomy (Simpson et al., 1999). Laparoscopic cholecystectomy (LC) affords different accomplishment compared to open cholecystectomy, and it is the accepted gallstone treatment approach, as it contributes minimum bowel guidance, culminating in hasty return to function and reduce the length of stay at the hospital (Kum et al., 1994).

Similar to all surgical procedures, patients have compelling postoperative pain; The patients experience severe abdominal and throat pain at the start of the postoperative period and crave pain relief after laparoscopic surgery (Karadeniz et al, 2000; Memedov et al., 2008; Ng et al, 2004; Elhakim et al, 2000 Dath et al., 2000; 1999).

progressive manner to further reduce this pain are the subject of many ongoing studies. Intraoperative and postoperative techniques for diminishing postoperative pain have been expressed (Ahmad et al, 2015). Better control of postoperative pain can benefit L.C. as a procedure for day care and avert further complications. Ongoing practice for many institutions, including ours, is to release the patient on the first postoperative day (Ahmad et al, 2015).

In the United States, over 73 million surgical procedures are executed on patients annually. Up to 75% of these patients struggle with postoperative pain, which may have a decisive effect on rehabilitation time (Kessler et al,

2013). Acute postoperative pain alleviation is important for patient satisfaction and time for discharge, which will promote results and lower healthcare expenditure (LeBlanc, 2014).

Pain can be visceral due to peritoneal irritability induced by floating carbon dioxide in the abdomen, chest pain due to irritation of diaphragm and lesser oftentimes parietal abdominal pain can evolve when disturb the abdominal wall (Wills et al, 2000).

Different treatments have been proposed to treat pain after laparoscopy. The note of peritoneal inflammation after carbon dioxide, pneumoperitoneum, contribute to a legitimate framework for the practice of non-steroidal anti-inflammatory drugs (NSAIDs) (Comyn, 1988; Comfort et al, 1992; Edwards et al., 1991; Rosenblum et al., 1991; Cracker et al., 1992; Liu et al., 1993), nonetheless, treatment of post laparoscopic pain with NSAID revenues questionable outcomes. Presently, the common treatment for acute postoperative pain is the practice of systemic opioids (LeBlanc, 2014). Opioids are not apart from complications: (Brennan, 1999; Sherwinter et al., 2008) Drowsiness, nausea, vomiting, urinary retention, are all side effects of opioids. These side effects can preeminent to longer stays and deprived patient outcomes (Brennan, 1999).

Alternately, the handling of IV-acetaminophen is postoperatively expanding (Arslan et al., 2013; Pasero et al., 2012). This practice restraints post-operative usage of opioids and lessens opioid produced side effects (Macarioet al, 2011). Bringing up rear, the usage of IV-acetaminophen should be utilized with discretion in some patients, such as hypovolemia

pertinent to dehydration or blood loss, chronic malnutrition and severe renal deterioration. Further, IV acetaminophen is inconsistent in patients with severe hepatic devastation (Arslan et al., 2013; Paseroet, 2012).

The performance of injecting local anesthetics into the different layers of the surgical section (sore) is a familiar practice in general anesthesia of surgical cases (Scott, 2010). Operations with local anesthetics has continued to increase in popularity since the mid 1990's (Johnson et al, 1999). It is legitimately inexpensive, technically uncomplicated, and may probably diminish postoperative embarrassment (Brower et al., 2003). Perioperative localization anesthesia (LIA) is one of the ultimate techniques for accomplish these scopes (Hofstad et al., 2015; Andersen et al., 2007; Parvataneni et al., 2007). LIA to the surgery site is a simple way and has demonstrated an immense impact on the abdomen, chest and plastic surgical setting. Literally, it is an extensively used analgesic technique in the last years. In this technique, a solution is used that encompasses long-term local anesthesia in combination with opioids, NSAIDs or steroids (Parvatanen et al., 2007; Andersen et al., 2008). The effects of LIA may differ depending on the type of surgical procedure, type and dosage of local anesthesia, ancillary addition to local anesthesia, injection in the incision or whole wound (Shin et al., 2012).

There are two fundamental methods of local anesthetic wound setting: The first is a precautionary model that administers anesthesia pre-operatively. The second model administers anesthetics immediately before surgical termination at the end of surgery (LeBlanc, 2014).

Currently, peripheral usage of local anesthetics for postoperative pain administration has become a favored method of laparoscopic surgery. Many reports are accessible on the impact of intraperitoneal local anesthesia for pain alleviation after laparoscopic surgery. Combinations of intraperitoneal bupivacaine with morphine have been studied formerly (Bina et al., 2013). The results were demonstrated that patients with combinations of intraperitoneal bupivacaine and morphine may promote pain relief and fewer opioid consumption during the first 24 hours, compared with only the bupivacaine group.

Combinations of intraperitoneal bupivacaine with magnesium sulfate have been examined for the treatment of acute pain in L.C. (Maharjan & Shrestha, 2012). The results exhibited that intraperitoneal instillation of bupivacaine plus magnesium sulfate grants excellent analgesia in the immediate postoperative period after laparoscopic surgery.

There are no prior reports to compare the analgesic effect of intraperitoneal instillation of bupivacaine plus morphine hydrochloride and bupivacaine plus magnesium sulfate for postoperative pain after laparoscopic cholecystectomy. The purpose of this study is therefore to compare the analgesic effect of intraperitoneal instillation of bupivacaine plus morphine hydrochloride versus bupivacaine plus magnesium sulfate to provide effective postoperative pain relief in patients undergoing L.C. under general anesthesia.

1.2. Background

1.2.1. Chronological development of surgical technique of cholecystectomy:

Jean-Louis Petit, inventor of gallbladder surgery in 1733, proposed ousting gallbladder and drainage of the gall bladder, thus creating fistula in patients with empyema, which he profitably implemented in 1743 (Beal, 1984).

Marion Simms operated the first cholecystectomy of a 45-year-old woman with obstructive jaundice 1878 (Servetus, 1989). Mouret from France performed the first human L.C. On the day of March 1987, when he concluded a gynecological laparoscopy on a woman who also complained from symptomatic gallstones, he shifted his laparoscope to the sub-hepatic area. When he found a somewhat free and smooth gall bladder, he determined to remove the laparoscopic instead of opening. He implemented the procedure profitably and the patient recovered without complexity (Mouret, 1991).

There are three components of pain after laparoscopic surgery:

1. Visceral pain trunks from the expanding of the intra- abdominal cavity and peritoneal inflammation.
2. Shoulder pain is the consequence of phrenic nerve irritation precipitated by enduring carbon dioxide in the abdominal cavity
3. Parietal pain as a result of surgical incision which is lower in intensity by cause of its small size (Hernández-Palazón et al, 2003).

1.2.2. Pain

1.2.2.1. Definition of pain

Pain after laparoscopy can be moderate or severe for part of patients. progressively, the nature of pain after laparoscopy diverges significantly from that observed after laparotomy. In fact, laparotomy primarily results in parietal pain (abdominal wall), patients ascribe more of visceral pain after operative laparoscopy (Joris et al, 1992). Shoulder pain attributes to diaphragmatic irritability subsequently of carbon dioxide, pneumoperitoneum is a usual postoperative observation after laparoscopy (35% to 60%) (Collins et al., 1984; Edwards et al., 1991).

Visceral pain tales for the greater dislike experienced in the recent postoperative period. Intensity diminishes quickly after the first 24 hours postoperatively. Although visceral pain progresses after L.C. is not impressed by mobilization, cough increments its intensity. Indeed, the mobilization test only enforced the contraction of the abdominal muscles, and did not comprise the movement of the intra-abdominal viscera. In opposition, cough harvest a brusque displacement of the liver, and hence results in stimulation of the inflamed cholecystectomy wound. Parietal pain is lesser intense than visceral pain, by cause of the small abdominal cuts and the bordered damage to the abdominal wall. For the same apprehension, and in contrast to pain after laparotomy, parietal pain after L.C. requires intense abdominal muscle contraction to be incremented and consequently aggravated only by cough but not bygone mobilization. Shoulder pain,

insignificant during the first postoperative hours, then increases to develop into the main trouble on the second day post-operatively (Joris et al, 1995). Shoulder pain that is contingent to the diaphragm's irritation is the major trouble in patients undergoing gynecological laparoscopy. It is reasonable to propose that bupivacaine conducted in the sub-diaphragmatic area blocks nociceptive input engendered in the inflamed diaphragmatic peritoneum. After L.C. Visceral pain is prevalent, while shoulder pain is imperceptible. An anatomic intraperitoneal flow (or flux) advance local anesthesia to the sub-membrane area (Zinsser et al., 1952; Autio et al., 1964) and aside from the cholecystectomy wound. Therefore, pain convinced in this wound is not blocked, although local anesthesia is conducted in its immediate proximity. correspondingly, local anesthesia after intraperitoneal administration may not accomplish adequate local concentration to block nociceptive entrance from the abdominal wall. Finally, shoulder pain, ignored in early postoperative period, can be actually ignored by patients who, consequently, will not observe any reduction after intraperitoneal bupivacaine (Joris et al, 1995).

1.2.2.2. Pathophysiology of post-operative pain

Promptly enlarge gastrointestinal tract can be accompanied with damage of blood vessels, traumatic clench of nerves and discharge of inflammatory mediators. The lengthened exist of shoulder pain (Dobbs et al, 1987; Joris et al, 1992; Riedel et al, 1980) suggest agitation of the phrenic nerve. This pain is most common after laparotomy (McMahon et al, 1994) and both

laparotomy and laparoscopy are accompanied with constant pneumoperitoneum, sometimes for 3 days. There is a statistically significant relationship between the width of the gas bubble and pain score (Jackson et al, 1996), and this pain can be diminished by aspiration of the gas under the diaphragm (Riedel et al, 1980), with "active aspiration", is reduplicated suction and manipulation (Fredman et al, 1994), using a gas discharge or by applying local anesthesia under the diaphragm under direct vision (Narchi et al., 1992; Narchi et al., 1991) or by a sub-frenic catheter (Goegler et al., 1993). Peritoneal inflammation or the existence of gas is perhaps also the root of the upper abdominal pain after lower abdominal surgery or after diagnostic laparoscopy. This may also ending for a minimum 3 days (Dobbs et al., 1987). The usage of nitrous oxide instead of carbon dioxide for peritoneal insufflation cannot be pledged for the intraabdominal explosions reported (Hunter et al, 1995), but it negatively reversal the incidence and severity of postoperative pain or nausea and vomiting (Jensen et al., 1993; Lipscomb et al., 1993).

1.2.3.Pharmacodynamic and pharmacokinetic of the study drugs

The justification for choosing the intraperitoneal route is to block the visceral afference signal and possibly adjust visceral nociception and give analgesia. Local anesthetics hinder nociception by influencing nerve membrane associated proteins and by hindering the discharge and action of prostaglandins and other agents that animate or stimulate the nociceptors and devote to inflammation (Liu et al, 2001). Nonetheless, absorption from large

peritoneal surface may happen, which may be another analgesic mechanism (Bina et al, 2013). Bupivacaine is preferred in the current study because of its efficiency and long-term efficacy activity. The half-life of bupivacaine is between 5 and 16 hrs (Bina et al., 2013).

By employing intraperitoneal local anesthesia (IPLA) it may be conceivable to regulate peritoneal and visceral signaling to the brain, by that alleviate the metabolic effect of visceral surgery. There is a barricade of free afferent nerve endings in the abdomen. Systemic penetration of local anesthesia from the abdominal cavity can also play a role in diminished nociception. Local anesthetics have anti-inflammatory impacts and the mechanism of these impacts can be prostaglandin antagonism, hinder of leukocyte migration and lysosomal enzyme discharge (Bina et al, 2013).

Morphine hydrochloride

Morphine is a definite mu receptor agonist and the most hydrophilic opioid in clinical usage. The hydrophilic quality concludes in reluctant passage athwart membranes like the intestinal mucosa and the blood brain barrier. The analgesic reaction is quiet even if given intravenously. Bio-availability is largely decreased when given orally or rectally and with a relevant individual variance (Lundeberg, 2012). Morphine is metabolized in the liver by unification to morphine 3- and morphine-6-glucuronide (Choonara et al., 1989; Choonara et al., 1992; Svensson et al., 1982). Metabolites are eliminated through the kidneys (Gong et al., 1992; Osborne et al., 1988).

Common side effects associated with use of morphine use include:

Gastrointestinal side effects - These include nausea, vomiting, stomach cramps and constipation. Shrink pupils - Morphine can account pupils to compress and emerge pointed in size. Respiratory depression - The breathing mechanism can be depressed due to limited blood oxygen levels. In healthy people, when blood oxygen declines and blood carbon dioxide goes up, respiratory drive increment. However, morphine debilitate this drive in the brain (Mandal, 2016)

Start doses advance to euphoria but at larger doses unpleasant symptoms such as hallucinations, delirium, dizziness and confusion appear. There may be some headache and memory loss. Biliary colic and consequent severe abdominal pain are common in the overdose of morphine. With high doses, muscle rigidity and abnormal movement of limbs and muscles called myoclonus can confessed (Mandal, 2016)

Magnesium sulfate

Magnesium is the fourth most familiar cation in the body. It has relevant physiological roles in enzymatic activation of energy metabolism and protein synthesis (James, 1992). Magnesium has also been demonstrated to have anti-nociceptive effects in animals and human models of chronic pain (Feria et al., 1993; Tramer et al., 1996). The analgesic tracts of magnesium are basically regarded to the antagonism of the N-methyl-D-aspartate (NMDA) receptor and the control of calcium influx in cells (Feria et al., 1993; Iseri et al., 1984; Woolf et al., 1991). This analgesic effect was first demonstrated in humans in 1996 when magnesium was given intravenously during the

perioperative period (Tramer et al, 1996). It has been suggested to reduce post-operative analgesic needs (Levaux et al, 2003; Koinig et al, 1998).

Bupivacain

Bupivacaine is the determined local anesthetic in caudal, epidural and vertebral anesthesia and is most often used clinically to handle with acute and chronic pain (Meaghan et al, 2015).

Further to blocking Na- channels, bupivacaine influences the activity of many other channels, counting NMDA receptors. It is crusial that bupivacaine hinders NMDA receptor-mediated synaptic transmission in spinal dorsal horns, an area gravely involved in centralized sensitization (Meaghan et al, 2015). Rising concentrations of bupivacaine decreased GluN2 subunit channel transparency and pH-independent ways by incrementing the average period of closures and diminishing median time for openings (Meaghan et al, 2015).

1.3. Aim and objectives

The purpose of this study is to compare the analgesic effect of intraperitoneal instillation of bupivacaine plus morphine hydrochloride versus bupivacaine plus magnesium sulfate to provide effective postoperative pain relief in patients undergoing L.C. under general anesthesia.

1.4. Problem statement

- Postoperative pain is one of the greater prevalent problems after L.C. Diminishing of postoperative pain increases functional recovery, decreased hospitalization and postoperative morbidity.
- There are three sorts of pain after L.C: Incisional, visceral and shoulder pain. The pain is caused by many factors and is a multimodal pathways, so pain relief is important (Alexander, 1997).
- The pain of laparoscopic procedures is basically visceral in its origin. Factors that are extensive for this pain may be regarded to surgical procedures, CO2 insufflation and intra-abdominal pressure cultivate during laparoscopic procedure. Higher insufflation pressure should be prevented as they can significantly increment the severity of postoperative pain (Alexander, 1997).
- Sub-phrenic and shoulder pain after laparoscopic procedures debut to derive from diaphragmatic and phrenic nerve irritation due to insufflated CO2. This pain contributes to aggravate by ambulation and may end many days after surgery. Remaining insufflating gas can also increment the intensity of post-laparoscopic pain. Accordingly, the abdomen should be actively vented at the end of the laparoscopic procedure (Alexander J, 1997).
- Opioids are the groundwork of post-operative pain monitoring, high dose opioids have many side effects such as respiratory depression, ileus, nausea and vomiting. Any other way the devaluation of opioid dose would increments the degree of postoperative pain in patients.

- Some complications can be prevented when diminishing postoperative pain in L.C, for example limited respiratory effort and inability to adequately cure secretion, leading to a reduction in functional residual capacity, early airway closure, segment or lobar collapse, retention of secretion which can generate bronchopneumonia (Egan et al, 1988).

1.5. Significance of the study

Surgical procedures are accompanied with tissue destruction and the majority of patients treated will experience some degree of pain after surgery. Many patients complain from moderate or severe pain after surgery. Research has demonstrated that poorly handled pain management can have both acute and chronic adverse effects. Peripheral action of opioid especially in inflamed tissue administer support for the existence of peripheral opioid receptors and provides a new accession to pain management that can have major clinical advantages. Yet there is static argument and local anesthesia instillation has not proved to be an ultimate method (Tong et al, 2014).

Magnesium sulfate is adjuvant that antagonizes calcium similar to the NMDA receptor antagonists (Koinig et al., 1998; Kara et al, 2002). Magnesium and Bupivacaine award both safe and cheap medicines to decrease postoperative pain and analgesic consumption and have been used as effective adjuvants for postoperative pain handled (Bhatia et al, 2004). Postoperative recovery may be protracted by postoperative pain and complications may happen more periodically (Spreng, 2011).

According to our knowledge, no data have been published about the incidence of postoperative pain or the effect of post-operative pain management in Palestine. The ultimate vision is to improve postoperative pain management to the point where pain after surgery can be prevented and surgery becomes "painless".

1.6. Literature review

Postoperative pain management planning should begin during the preoperative period. There are several studies that deal with the monitoring and control of pain after L.C. and compare the effect of wound setting with marcaine and opioids, such as morphine, as compared to magnesium sulphate for postoperative analgesia (Razavi et al., 2015)

Addition of opioid to local anesthetics results in better postoperative analgesia and reduces opioid demand after surgery as described in a study by Chander et al. (2011). The same study shows that unbearable cut pain decreased when adding fentanyl as opioid to bupivacaine and decreased analgesic postoperative consumption (Chander et al, 2011).

Tverosky et al. (1990) determined that wound adjustment provides good postoperative analgesia, which facilitates a fast and even recovery. Local anesthetics are potent long-term and act through several mechanisms including inhibition of the effects of prostaglandins, inhibition of migration of leukocytes and reduce of vascular permeability.

The results of the study conducted by Upadya et al (2015) included a total of 60 patients ASA I and II planned for L.C. included, group I received 2 mg /

kg 0.5% bupivacaine as a local intraperitoneal application and group II patients received 1 g of paracetamol every 6 hours. Postoperatively, patients were assessed for pain using Visual Analog Scale (VAS), Visual Rating Scale (VRS), Shoulder pain. The total number of patients required to save analgesia (R.A.) and possible side effects was noted, the authors show that intraperitoneal and intra-incisional instillation of 0.5% bupivacaine gives lower visual analogue scale up to 4 hours postoperatively.

On the other hand, Eldaba et al. (2013) studied local anesthesia with magnesium sulfate after caesarean section, a total of 120 patients, ASA I-II were recruited for Caesarean section. At the end of the operation, the wound was infiltrated continuously at a rate of 5 ml / h for 24 hours postoperatively with one of the following solutions: 0.25% bupivacaine, a mixture of 0.125% bupivacaine and 5% magnesium sulfate or normal saline (0.9%). Total opioid consumption, VAS in rest and movement, the occurrence of opioid adverse events and signs of ulceration were evaluated during the study period (24 hours after surgery). Remaining pain, surgical wound infection, need for additional antibiotic treatment and wound healing failed, and showed that the continuous wound infusion with local anesthesia alone reduced opioid needs by approximately 37%. At the same time, continuous wound infusion with a mixture of local anesthesia and magnesium sulphate reduces opioid demand by approximately 75% compared to placebo. Opioid-saving effect reduced postoperative nausea and vomiting, sedation and urinary retention.

1.7. Research question

Is there a preference for a group of drugs on the other, which is intraperitoneal instillation of bupivacaine plus morphine hydrochloride and bupivacaine plus magnesium sulfate to reduce postoperative pain in patients undergoing laparoscopic surgery?

1.8. Research Hypothesis

There is a significant difference at a level of 0.05 related to the intensity of post-operative pain between intraperitoneal instillation of bupivacaine (marcaine®) plus magnesium sulfate group and bupivacaine (marcaine®) plus morphine hydrochloride group in patients undergoing laparoscopic surgery.

There is a significant difference at a level of 0.05 related to the consumption of rescue medication that is Pethidine between intraperitoneal instillation of bupivacaine (marcaine®) plus magnesium sulfate group and bupivacaine (marcaine®) plus morphine group in patients undergoing laparoscopic surgery.

Chapter Two

Materials and Methods

2.1. Study design

A Prospective, Randomized, Double blind Comparison Study

- Allocation: Randomized.
- Endpoint Classification: Safety/Efficacy Study.
- Primary Purpose: Observetion.

2.2. Sites and Settings

The participants were taken from AN- Najah national university Hospital, Nablus, Palestine. AN- Najah national university Hospital was selected due to availability of high quality technologies, which not available in any other hospital in west bank of Palestine, and because of the An- Najah national university Hospital is a central high advance hospital and covers the North region of West bank, Palestine. The other hospital was Al Istishari Arab hospital in Ramallah city, which is high level of technological progress.

2.3. Sample and sampling

The sample of the study was clients from the settings which are determined, the participants were chosen randomly, after having the permissions to conduct the study and assuring confidentiality.

2.4. The inclusion subjects:

- ages 18 and 60 years
- Male and female
- ASA I-II

2.5. The exclusion subjects:

- Patient with hepatic or renal dysfunction.
- use of opioid during 24 hrs prior to the study
- treatment with steroids prior to surgery.
- drug or alcohol abuse
- allergy to any of the study drug,
- chronic pain syndrome as a result of neurological disease

2.6. Sample size calculation

A formula (i.e. Pocock's sample size formula) was used

Sample size was predefined by power analysis depending on the likelihood that the decision rule would lead to the conclusion that the pain occurred in the control group (these data were taken from the previous study) (Eldaba et al. 2013) The incidence of pain in the treatment groups would differ. The error (a) was set to 0.05 which is the risk of making Type I errors, and (b) Power (1-type II error) was set to 0.85. Minimum standard error = 1. According to the efficacy analysis, 50 patients were recommended in each group**.**

A formula (i.e. Pocock's sample size formula) that can be directly applied for comparison of proportions P_1 and P_2 in two equally sized groups:

$$n = \frac{[P_1 (1-P_1) + P_2 (1-P_2)]}{(P_1-P_2)^2} (Z_{\alpha/2} + Z_{\beta})^2$$

Where:

n: required sample size

P_1: estimated proportion of study outcome in the exposed group (i.e. combination therapy) ($P_1 = 0.30$).

P_2: estimated proportion of study outcome in the unexposed group (placebo therapy) ($P_2 = 0.70$).

α: level of statistical significance

$Z_{\alpha/2}$: Represents the desired level of statistical significance (typically 1.96 for $\alpha = 0.05$)

Z_{β}: Represents the desired power (typically 0.84 for 80% power)

$$n = \frac{[0.30(1-0.30) + 0.70 (1-0.70)]}{(0.30-0.70)^2} (1.96+ 0.84)^2$$

$$n = \frac{[0.30 (0.70) + 0.70(0.30)]}{(0.40)^2} (2.8)^2$$

$$n = \frac{[0.21 + 0.21]}{0.16} (7.84)$$

$$n = \frac{[0.42]}{0.16} (7.84)$$

$n \approx 50$ patients

Thus, a total of 100 patients (50 for each group) should be targeted for recruitment into the study

2.7. Randomization and blindness

Randomization was done through opaque and well-sealed envelopes. The sequence generation was done with a computer. The number was printed on

envelopes and the group was written on the card together with the serial number. When the patients arrived opened envelopes to see the group that would be assigned.

Blindness

Patients, healthcare providers included in patient care, as collected and analyzed data, were not aware of the distribution of the treatment group.

2.8. Methods and intervention plan

o A total of 100 patients, ASA I and II between the ages of 18 and 60, planned for laparoscopic surgery were included in a randomized prospective double-blind study after approval by the IRB and written informed consent.

o The study inclusion criteria included the use of opioid for 24 hours. pre-study, drug or alcohol abuse and allergy to any of the study medications, chronic pain syndrome where pain evaluation was assessed unreliable due to neurological disease or treatment with steroids prior to surgery.

o All patients received the same anesthetic technique. General anesthesia is administered. The induction protocol was standard for all patients. Patients are monitored for electrocardiogram (ECG), heart rate (H.R.), oxygen saturation (Sa O2), noninvasive blood pressure (NIBP) and end-tidal CO2 (ETCO2). 18-gauge intravenous cannula was inserted into a suitable vein on the dorsum of non-dominant hand, during the intraoperative period.

o All patients receive ring lactate at a rate of 7 ml / kg / h. The patients are pre-oxygenated at 5 liters / min 100% O2 for 3 to 5 minutes. Anesthesia is induced by intravenous administration of fentanyl (2 μg / kg), propofol (2

mg / kg) and to facilitate the endotracheal intubation recuronium (1 mg / kg). Anesthesia is maintained with a mixture of air and oxygen 50% / 50%, sevoflurane 1-2% and recuronium supplementation is recorded. The ventilation is adjusted to maintain ETCO2 between 35 and 40 mmHg. Patients are placed in trendelenburg position during laparoscopy, intra-abdominal pressure maintained between 12 and 14 mmHg.

o Standard laparoscopic cholecystectomy with 4-port technique was performed. All operations were performed by a team of surgeons who have experience of laparoscopic surgery.

o Randomization was done through opaque and well-sealed envelopes. The sequence generation was done with a computer. The number was printed on envelopes and the group was written on the card together with the serial number. When the patients arrived opened envelopes to see the group that would be assigned. A drug solution is prepared by a doctor who did not participate in the study, and drugs are filled in pre-coded syringes and given to the surgeon.

o Patients were also blinded for the administered drug. The drugs were delivered in the same size syringe and the same color by the surgeon. Nurses evaluating patients for parameters in the post-anesthesia Care Unit (PACU) and at the surgical ward are not aware of the treatment where the patient was randomized

o_Mo group, 30 ml 0.25% bupivacaine and 3 mg morphine intraperitoneal were received at the site of surgery via the navel port with patient in a trendelenburg position (after peritoneal washing and suction).

o_Mg group, 30ml 0.25% bupivacaine was received and 50 mg / kg magnesium sulfate was introduced in the same pattern as in the Mo group.

o CO2 was then evacuated from the peritoneal cavity and skin incision was sutured.

2.9. Variable definitions

Dependent variable:

- Dose of rescue analgesic in PACU and in the surgical ward as continuous variable.
- VAS degree in the PACU as continuous variable.
- VAS degree in the surgical ward as continuous variable.
- Adverse events (nausea, vomiting, drowsiness, dizziness, urine retention).

Independent variable:

1. Intra-Peritoneal Instillation of Bupivacaine and Morphine Hydrochloride
2. Intra-Peritoneal Instillation Bupivacaine and Magnesium Sulfate
3. Age.
4. Gender.
5. Duration of surgery.

2.10. Follow up of the patient

- Usually the cut off value of VAS is 4 for rescue medication indication. when VAS $\geq$ 4, rescue analgesic was administered. Before induction of anesthesia patients are instructed how to use a 10 cm VAS (VAS-0 with

end-point labeled “no pain” and 10 to “worst conceivable pain”). The degree of postoperative pain is assessed at 0, 1/2, 1, 4, 8, 12, 16, 24 hrs. using the VAS score.

- R.A. was administered on request, 20 mg of pethidine intravenously in the recovery room and 50 mg intramuscularly in the ward if needed. The number of patients requiring rescue analgesia was recorded in each group.
- Patients evaluated for 24 hours post-operatively with recording of abdominal pain using the standard 10 cm VAS. The post-operative pain score reported at 0 and 30 minutes, then at 1, 4, 8, 12,16 and 24 hours using the VAS score.
- The time of arrival in the post-operative recovery room is defined as zero hr. post-operatively. Postoperatively, A trained nurse assessed pain and analgesic consumption. If VAS is ≥ 4, 20 mg pethidine is administered as R.A. until patient felt comfortable or VAS < 3. All adverse effects including nausea vomiting and dizziness are recorded during 24 hours postoperatively.
- Total dose of pethidine requirement measured and recorded in specified data sheet during next 24 hrs.
- Postoperative monitoring included noninvasive BP, HR and pulse and respiration were recorded.
- The following parameters are evaluated in all study groups:

(1) The incidence and severity of postoperative pain for 24 hrs (the severity of postoperative pain measured at 0. 0.5, 1, 2, 4, 6, 8, 12, 16, and 24 hrs. postoperatively, using VAS pain score.

(2) Total dose of analgesia.

(3) Postoperative complications (nausea, vomiting, urine retention, drowsiness, dizziness).

(4) Postoperative hemodynamics (HR, BP).

❖ Nausea is treated with metoclopramide (10 mg) i.v.

2.10.1. Morrow Assessment of Nausea and Emesis

If the vomiting frequency is twice or higher and / or the patient did his nausea ≥ on Likert type scale (0-6), it is an indication to give antiemetic (Pramin ® 10 mg i.v.). Nausea was scored by a Lickert-type scale, which is called MANE(Morrow Assessment of Nausea and Emesis*)* (Morrow 1984) . This scale (0-6) was used in daily clinical practice on the post anesthetic care unit(PACU) at our hospital. Symptom severity is rated on the scale (0-6) to answer the question “how would you describe your nausea at its worst” from 0= none, 1= very mild, 2= mild, 3= moderate, 4= severe, 5= very severe and, 6= intolerable. MANE has been clinically validated and a test-retest reliability coefficient has been determined (Morrow 1984).

2.10.2. Rescue Analgesia

Pethidine, like R.A., was administered on request, 20 mg I.V. in PACU and 50 mg I.M. in the surgical ward as needed. The number of patients requiring rescue analgesia was recorded in each group.

2.11. Statistical analysis

For statistical analysis, SPSS version 20.0 is used. The parametric variables are presented as mean±SD or frequency (%) and analyzed by student t-test;. Statistical analysis is performed with an ANOVA test. Non-parametric variables are analyzed by Chi-Square. $P < 0.05$ was considered as statistically significant. Pearson Correlation between Age and total VAS in Mo and Mg groups was used.

2.12. Ethical consideration

This study was conducted in accordance with the Helsinki Declaration. Individual consent forms were obtained for all participants.

- Institutional Review Board (IRB) approval of An-Najah National University is obtained.
- Consent was obtained from the patient prior to participation.
- Confidentiality and voluntary participation to all participants were insured
- A detailed explanation of the purpose and objectives of the study was given to all patients.

Chapter Three

Results

3.1. Results

The purpose of the current study was to compare intraperitoneal instillation of bupivacaine and morphine hydrochloride versus bupivacaine and magnesium sulfate for postoperative pain relief after L.C. 100 patients, ASA I & II, 18-60 years old were recruited in the study.

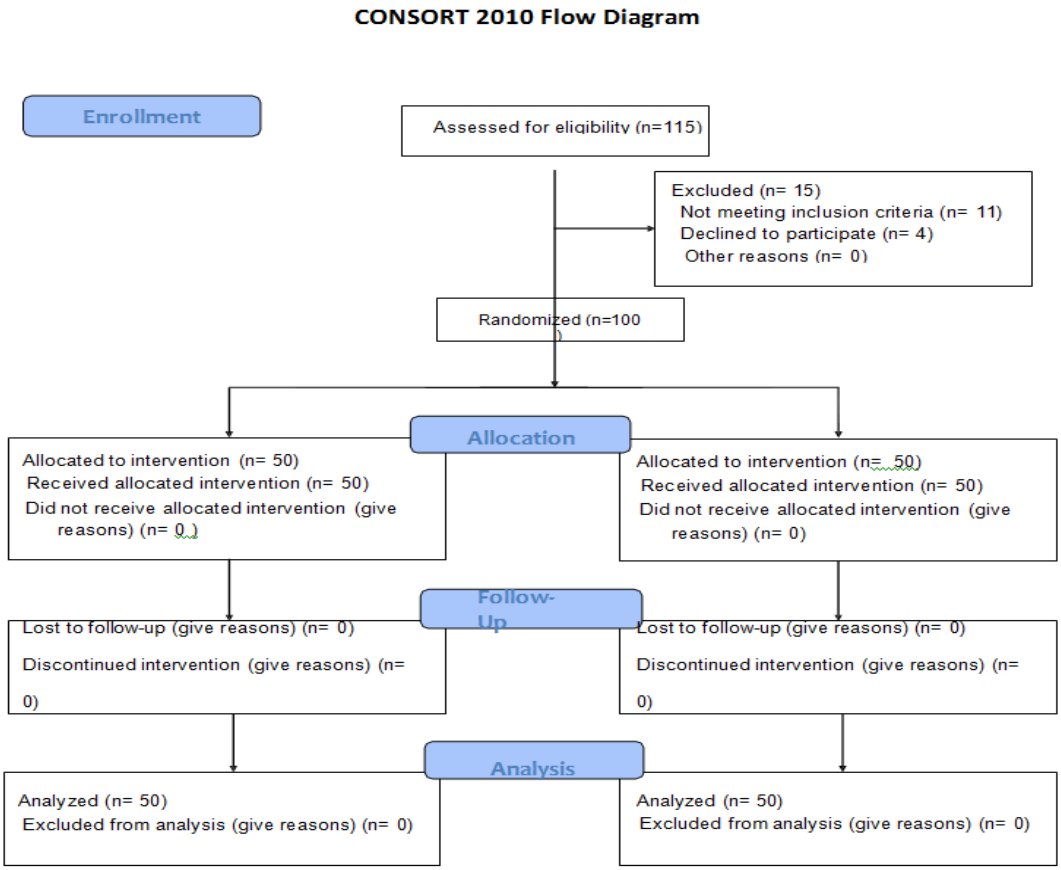

Figure (1): Consort Flow Diagram

Table (1) Patients' demographic characteristics and duration of surgery in Mo & Mg groups

variable	Morphine group	Magnesium group
	n=50	n=50
	M(SD)	M(SD)
Age (years)	41.96 + 11.5	43.12 + 6.9
Gender		
Male n(%)	16(32%)	14(28%)
Female n(%)	34(68%)	36(72%)
BMI (kg/m2)		
<=24.9n(%)	6(12%)	6(12%)
25-29.9n(%)	20(40%)	22(44%)
30-34.9n(%)	14(28%)	18(36%)
35-39.9n(%)	10(20%)	4(8%)
Duration of surgery (min)	55.18 + 7.20	54.44 + 7.15

Patient characteristics regarding age, gender and BMI were comparable in the two groups. There was no significant difference between the groups regarding duration of surgery (table 1).

Table (2): Pearson Correlation between Age and Total VAS in Mo and Mg groups

Age and Total VAS	Mo	Mg
Pearson Correlation	-0.112	-0.052
Sig. (2-tailed)	0.602	0.807

The results in table (2) show that there are no significant relationships between the age and the total VAS in both study Mo and Mg groups (P values > 0.05). The Pearson correlation coefficient in Mo group was (-0.112) and (-0.052) in Mg group.

Table (3): Independent Samples t- test Results between Gender and Total VAS in Mo and Mg groups

Total VAS	Mo		Mg	
Gender	M±S.D	t(P-value)	M±S.D	t(P-value)
Male	1.86±0.75	-0.893(0.382)	2.45±0.81	-1.172(0.253)
Female	2.18±0.83		2.81±+0.66	

The results in table (3) show that there are no significant differences between Males and Females in the Total VAS score in both study Mo and Mg groups (P values > 0.05). In Mo group, the mean of total VAS was (1.86) for males and (2.18) for females (p=0.328). In Mg group, the mean of total VAS was (2.45) for males and (2.81) for females (p=0.253).

Table (4): One Way ANOVA test Results between BMI and Total VAS in Mo and Mg groups

Total VAS	Mo		Mg	
BMI	M±S.D	F(P-value)	M±S.D	F(P-value)
<=24.9	2.13±1.94	0.423(0.738)	3.06±0.44	1.871(0.167)
25-29.9	1.98±0.75		2.72±0.7	
30-34.9	1.83±0.36		2.43±0.53	
35-39.9	2.38±0.92		3.63±1.41	
Total	2.04±0.79		2.71±0.72	

The results in table (4) show that there are no significant differences between BMI groups in the Total VAS score in both study Mo and Mg groups (P values > 0.05). In Mo group, the mean of total VAS was (2.38) for BMI group (35-39.9), (2.13) for BMI group (<=24.9), (1.98) for BMI group (25-29.9), (1.83) for BMI group (30-34.9) (p=0.738. In Mg group, the mean of total VAS was (3.63) for BMI group (35-39.9), (3.06) for BMI group (<=24.9), (2.72) for BMI group (25-29.9), (2.43) for BMI group(30-34.9) (p=0.167).

Table (5): Independent Samples t-test Results between type of instillation and Total VAS in Mo and Mg groups

Total VAS type of Instillation	M±S.D	t(P-value)
Mo	2.09±0.81	-2.882(0.006)
Mg	2.71±0.71	

The results in table (5) show that there are significant differences between Mo and Mg groups in the total VAS score (P value <0.05). In Mo group, the mean of total VAS was (2.09) which is significantly lower than the mean of total VAS in Mg group (2.71); which means that patients in Mo group significantly had less intensity of pain than patients in Mg group (p=0.006).

Table(6):VAS score in different time intervals in the two groups (mean ±standard deviation).

type of Instillation	Mo	Mg	t(P-value)
VAS(hr)	M+S.D	M+S.D	
0	3.33±1.58	4.08±1.85	-1.518(0.136)
1/2	1.78±1.28	2.8±1.53	-2.491(0.016)*
1	1.78±1.57	2.24±1.42	-1.061(0.294)
4	1.79±1.18	2.56±1.76	-1.789(0.08)
8	2.48±1.47	3.36±2.1	-1.671(0.102)
12	2.26±1.89	2.56±1.19	-0.662(0.511)
16	1.65±1.43	2.48±1.66	-1.841(0.072)
24	1.33±0.7	1.6±0.76	-1.271(0.21)

* p < 0.05- Significant, By Independent ‘t’ test

The results in table (6) show that there are significant differences between Mo and Mg groups in the VAS score only at the first (1/2 hr.) In Mg group, the mean of VAS at (1/2 hr.) was (2.8) which is significantly higher than the mean VAS at (1/2 hr.) in Mo group (1.78) (p=0.016) Figure 1.

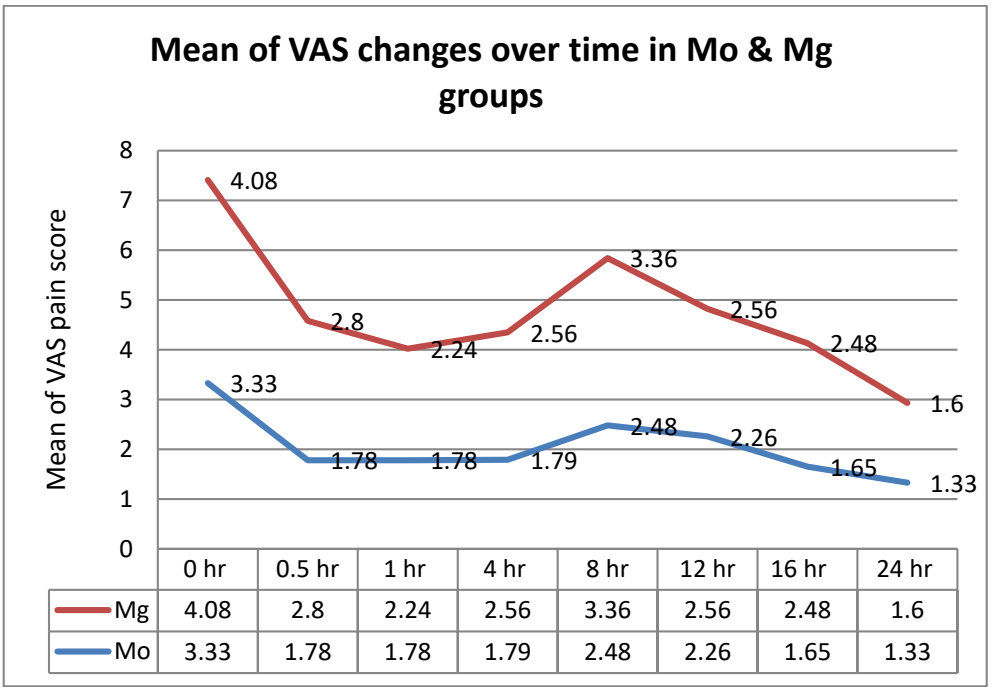

Figure (2): Mean of VAS changes over time in Mo and Mg groups.

Table (7): The mean of total Rescue Analgesia within 24 hours

Total Rescue Analgesia type of Instillation	M+S.D	t(P-value)
Mo	64.29 mg±22.04	-1.419(0.163)
Mg	74.40 mg±25.67	

The results in table (7) show that there is no significant difference between Mo and Mg groups in the total R.A. (P value >0.05). In Mo group, the mean of total R.A. was (64.29) which is not significantly differ from the mean of total R.A.in Mg group (74.40) (p=0.163).

Table (8): Frequencies (%) of patients with Total Rescue Analgesia in Mo and Mg groups at different times through 24 hours

Total Rescue Analgesia (hr)	Mo Frequency no. of patient (%) n=50	Mg Frequency no. of patient (%) n=50	P-value
1/2	0	2(4%)	0.1552
1	2(4%)	6(12%)	0.1424
4	4(8%)	10(20%)	0.0853
8	16(32%)	18(36%)	0.6744
12	14(28%)	10(20%)	0.3514
16	2(4%)	12(24%)	0.0041
24	0	0	

The results in table (8) show that there are no significant differences between the number of patients in Mo and Mg groups in the Total R.A. at different times 30 min, 1, 4, 8, 12, and 24 hours (P value >0.05). The number of patients who were requested rescue medication in Mo group at 16 hr. 2(4%) is significantly less than in Mo group 12(24%) (p=0.0041)

Table (9): Independent Samples t-test Results between Mo and Mg groups at different times through 24 hours and Total SBP through time

Values are presented as Mean ±SD

Hemodynamic Systolic Blood Pressure	Mo	Mg	t(P-value)
	M+S.D	M+S.D	
0	125.64±13.6	127.12±13.74	-0.383(0.704)
1/2	124.32±12.96	125.72±10.71	-0.416(0.679)
1	121.8±11.82	121.72±10.93	0.025(0.98)
4	124.8±10.32	123.16±11.33	0.535(0.595)
8	122.96±10.91	124.28±11.47	-0.417(0.679)
12	122.64±11.28	123.32±9.88	-0.227(0.822)
16	123±9.93	121.4±11.84	0.518(0.607)
24	121.56±9.06	120.84±10.98	0.253(0.802)
Total	123.34±10.21	123.45±10.45	-0.036(0.971)

The results in table (9) show that there are no significant differences between Mo and Mg groups in the SBP through time (all P values >0.05). In Mo group, the mean of total SBP was (123.34) which is not significantly differ from the mean of total SBP in Mg group (123.45) (p=0.971).

Table (10): Independent Samples t-test Results between Mo and Mg groups at different times through 24 hours and Total DBP through time.

Values are presented as Mean ±SD

Hemodynamic Diastolic Blood Pressure (hr)	Mo	Mg	t(P-value)
	M+S.D	M+S.D	
0	78.72±8.34	80.04±9.34	-0.527(0.601)
1/2	78.88±7.13	79.48±8.03	-0.28(0.781)
1	77.28+6.83	77.92±7.99	-0.304(0.762)
4	78.76±7.15	79.2±8.33	-0.2(0.842)
8	78.52±7.7	78.64±8.84	-0.051(0.959)
12	77.6±7.82	78.12±8.25	-0.229(0.82)
16	77.84±6.16	77.4±9.44	0.195(0.846)
24	76.68±6.33	77.84±8.71	-0.539(0.593)
Tot	78.04±6.52	78.58±7.82	-0.268(0.79)

The results in table (10) show that there are no significant differences between Mo and Mg groups in the DBP through time (all P values >0.05). In Mo group, the mean of total DBP was (78.04) which is not significantly differ from the mean of total DBP in Mg group (78.58) (p=0.79).

Table (11): Independent Samples t-test Results between Mo and Mg groups at different times through 24 hours and Total HR through time. Values are presented as Mean ±SD

Hemodynamic Heart Rate (hr)	Mo	mg	t(P-value)
	M+S.D	M+S.D	
0	82.8±9.62	84.88±10.1	-0.745(0.46)
1/2	81.88±9.76	82.92±11.78	-0.34(0.735)
1	80.64±9.7	84.6±9.55	-1.454(0.152)
4	82.04±7.93	84.2±10.5	-0.82(0.416)
4	80.08±7.71	82.92±10.69	-1.077(0.287)
12	81.92±7.69	83.76±9	-0.777(0.441)
16	81.16±9.81	82.72±9.9	-0.56(0.578)
24	80.24±8.48	82.08±9.74	-0.712(0.48)
Tot	81.35±7.61	83.51±8.91	-0.924(0.36)

The results in table (11) show that there are no significant differences between Mo and Mg groups in the HR through time (all P values >0.05). In Mo group, the mean of total HR was (81.35) which is not significantly differ from the mean of total HR in Mg group (83.51) (p=0.36).

Table (12): Independent Samples t-test Results between Mo and Mg groups at different times through 24 hours and Total SaO2. Values are presented as Mean ±SD

Hemodynamic SpO2	Mo	Mg	t(P-value)
	M+S.D	M+S.D	
0	97.4±1.71	97.48±2.73	-0.124(0.902)
1/2	97.24±1.61	97.68±0.99	-1.162(0.251)
1	98±1.85	97.88±1.2	0.272(0.787)
4	98±1.71	98.52±1.16	-1.26(0.214)
8	98.08+1.66	98.56±1.33	-1.131(0.264)
12	98±1.71	98.16±1.11	-0.393(0.696)
16	98±2.02	98.08±1.63	-0.154(0.878)
24	98.08±1.61	98.04±1.21	0.1(0.921)
Tot	97.85±1.42	98.05±0.88	-0.597(0.553)

The results in table (12) show that there are no significant differences between Mo and Mg groups in the SpO2 through time (all P values >0.05). Mo group, the mean of total SpO2 was (97.85) which is not significantly differ from the mean of total SaO2 in Mg group (98.05) (p=0.553).

Table (13): Pearson Correlation between Postoperative Hemodynamic variables (SBP, DBP, Heart Rate and SaO2) and Total VAS in Mo and Mg groups

	Total VAS	Mo	Mg
Tot SBP	Pearson Correlation	0.247	-0.335
	Sig. (2-tailed)	0.245	0.101
Tot DBP	Pearson Correlation	0.236	-0.428
	Sig. (2-tailed)	0.267	0.033
Tot HR	Pearson Correlation	-0.025	0.055
	Sig. (2-tailed)	0.908	0.792
Tot SaO2	Pearson Correlation	-0.518	-0.204
	Sig. (2-tailed)	0.009	0.328

The results in table (13) show that there is significant negative relationship between DBP and total VAS in Mg group (P value=0.033< 0.05), the Pearson correlation coefficient was (-0.428). In Mo group, there is no significant relationship.

The results also show that there is significant negative relationship between SaO2 saturation and total VAS in Mo group (P value=0.009 < 0.05), the Pearson correlation coefficient was (-0.518). In mg group, there is no significant relationship.

From the other hand, the results show that there are no significant relationships between both SBP, HR and the Total VAS in both study Mo and Mg groups (P values > 0.05).

Table (14): Independent Samples t-test Results between Postoperative Complications and Total Rescue Analgesia in Mo and Mg groups

Tot RA	Mo		Mg	
variable(n1,n2)	M (mg)+S.D	t(P-value)	M(mg)+S.D	t(P-value)
nausea				
No (33, 28)	70±35.36	0.655(0.521)	53.33±28.87	-1.56(0.132)
Yes (17, 22)	62.5±17.32		77.27±24.53	
vomiting				
No (41,36)	61.67±28.87	-0.619(0.543)	72.73±32.89	-0.283(0.78)
Yes (9,14)	67.78±6.67		75.71±19.5	
urine retention				
No (49,49)	64.29±22.04	-----	74.58±26.21	0.171(0.865)
Yes (1,1)	-----		70+0	
drowsiness				
No (43,32)	61.43±26.85	-0.834(0.415)	67.14±23.6	-0.877(0.389)
Yes (7,18)	70±0		77.22±26.53	
dizziness				
No (50,50)	64.29±22.04	-----	74.4±25.67	-----
Yes (0,0)	-----		-----	
others				
No (50,50)	64.29±22.04	-----	74.4±25.67	-----
Yes (0,0)	-----		-----	

The results in table (14) show that there are no significant relationships between Postoperative complications and total R.A. in both study Mo and Mg groups (all P values> 0.05).

Regarding nausea, in Mo group, the mean of total rescue analgesia was (70) for patients who had not nausea and (62.5) for patients who had nausea (p=0.521). In Mg group, the mean of total R.A. was (53.33) for patients who hadn't nausea and (77.27) for patients who had Nausea (p=0.132).

Regarding vomiting, in Mo group, the mean of total R.A. was (61.67) for patients who hadn't vomiting and (67.78) for patients who had vomiting

(p=0.543). In Mg group, the mean of total R.A. was (72.73) for patients who hadn't vomiting and (75.71) for patients who had vomiting (0.78).

Regarding urine retention, in Mo group, the mean of total R.A. was (64.29) for patients who hadn't urine retention and there were no patients who had urine retention (p= >0.05). In Mg group, the mean of total R.A. was (74.58) for patients who hadn't urine retention and (70) for patients who had urine retention (p=0.865).

Regarding drowsiness, in Mo group, the mean of total R.A. was (61.43) for patients who hadn't drowsiness and (70) for patients who had drowsiness (p=0.415). In Mg group, the mean of total R.A. was (67.14) for patients who hadn't drowsiness and (77.22) for patients who had drowsiness (p=0.389).

Finally, there were no patients who had dizziness or other postoperative complications in both groups.

Table (15): Number of patients (%) with postoperative symptoms including pain in Mo and Mg groups. Values are presented as frequency (%)

	MO	Mg	P value
Pain ≥4 moderate to severe pain	15 (30%)	25 (50%)	0.0423*
Nausea≥3 Moderate to severe nausea	10(20%)	12(24%)	0.6310
Vomiting	9 (18%)	14 (28%)	0.2371
drowsiness	7(14%)	18 (36%)	0.0115*
dizziness	0	0	-
Urine retention	1 (2%)	1(2%)	-

*P < 0.05 when Mo group is compared to Mg group

The results in the table (15) show that there is a significant difference between the number (percent) of patients complaining of moderate to severe postoperative pain in Mo group 15/50 (30%) compared to Mg group 25/50 (50%) (p = 0.0423). There is also a significant difference between the number (percent) of patients who complained of drowsiness in Mo Group 7/50 (14%) compared to 18/50 (36%) in Mg group (p = 0.0115). There are no significant differences between the two study groups regarding nausea, vomiting, dizziness and urinary retention Figure 2.

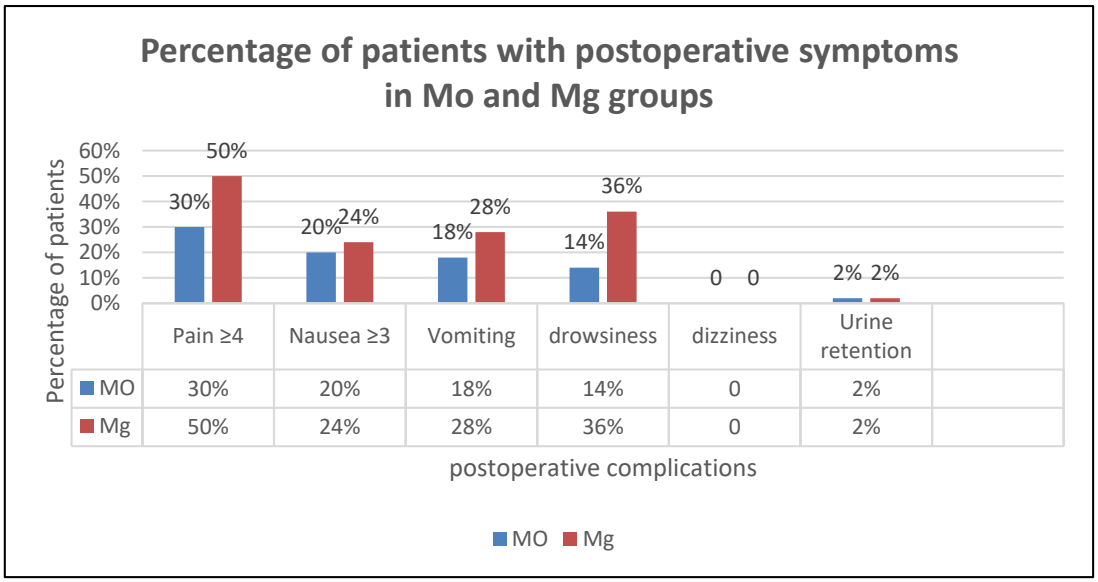

Figure (3): Graphical probability of postoperative symptoms for Mo and Mg groups

Table (16): Pearson Correlation between Duration of Surgery and Total VAS in Mo and Mg groups

	Total VAS	Mo	Mg
Duration of Surgery	Pearson Correlation	0.202	-0.140
	Sig. (2-tailed)	0.368	0.506

The results of the table above show that there are no significant relationships between duration of surgery and the total VAS in both study groups (P values> 0.05).

Chapter Four

Discussion

Incidence and intensity of Post- operative pain

As the cause of postoperative pain in patients undergoing laparoscopic surgery is multifactorial, multimodal analgesia is necessary to counter postoperative pain. In the current study, at the end of laparoscopic cholecystectomy surgery, 100 patients were randomized to one of the following groups: Mo group receiving intraperitoneal instillation of 30 ml 0.25% bupivacaine plus 3 mg morphine hydrochloride and MG group receiving intraperitoneal instillation of 30 ml 0.25% bupivacaine plus 50 mg / kg magnesium sulfate. The results in the current study show that morphine hydrochloride plus bupivacaine significantly reduces the incidence and intensity of postoperative pain compared to magnesium sulfate plus bupivacaine. The results show that there are significant differences between Mo and Mg groups in the total VAS score (P value <0.05). In the Mo group, the mean of total VAS (2.09) was significantly lower than the mean of total VAS in the Mg group (2.71); which means that patients in the Mo group significantly had less intensity of pain than patients in the Mg group (p = 0.006). This means that bupivacaine plus morphine hydrochloride is more effective in reducing the intensity of postoperative pain than magnesium sulfate plus bupivacaine. The rationale for selecting the intraperitoneal pathway is to block the visceral afference signal and potentially modifying visceral nociception. Local anesthetics inhibit nociception by affecting nerve membrane associated proteins and by inhibiting the release and action of prostaglandins and other agents that sensitize or stimulate nociceptors and contribute to inflammation (Liu & Hodgson, 2001). However, absorption

from large peritoneal surface can also occur, which may be a further mechanism of analgesia. We chose bupivacaine for our study because of its long-term effectivity. The half-life of bupivacaine is between 5 and 16 hours. The result of the current study is in accordance with the study by Bena et al. Showed that addition of 3 mg of morphine to 30 ml of 0.25% bupivacaine further enhanced the effectiveness of intraperitoneal bupivacaine in the reduction of postoperative pain after laparoscopic cholecystectomy surgery (Bina et al., 2013). On the other hand, the result of the current study is in violation of Shoebi et al. study that shown when magnesium sulfate is added to bupivacaine, improves intraperitoneal analgesic effect in postoperative period without any unwanted effects (Shoebi, et al., 2007).

Magnesium sulfate is used in most studies to improve pain relief quality with fewer demands on post-operative analgesics (Mentes & Harlak, 2008; Saadwy & Khaki, 2010; Bhatia, 2004; Kesavan et al., 2010). Since magnesium reduces intracellular calcium influx and also antagonizes the N-methyl-D-aspartate (NMDA) receptor, which reduces postoperative pain, it is useful for reducing somatic and visceral pain and also reducing the opioid analgesic requirements (Lee & Kwon, 2009; Ray & Bhattacharjee 2010 Scheinin et al., 1995).

For the incidence of postoperative pain, there were significantly fewer frequency (percentage) of patients in Mo group 15 (30%) complaining of moderate to severe pain postoperatively compared to 25 (50%) patients in the Mg group ($p = 0.0423$). This result is consistent with the study performed by Bina et al. As shown, the group of bupivacaine plus morphine

hydrochloride had better pain relief than the control group at all time intervals and this difference was also statistically significant (P <0.05 (Bina et al., 2013). The study clarifies that morphine hydrochloride with bupivacaine reduces the incidence of postoperative pain. The result of this study complies with the study conducted by Hernandez et al (2003), examined intraperitoneal application of bupivacaine plus morphine for pain relief after laparoscopic surgery and reported that the combination is effective in reducing pain during the first 6 hours. In our study when calculating the size of the treatment effect of morphine hydrochloride plus bupivacaine, it was found that the relative risk reduction of moderate to severe pain postoperatively is 0.40.

On the other hand, a study on the effect of intraperitoneal instillation of opioid showed that morphine was ineffective when given as analgesia. The authors speculated that this may be because the intact peritoneum prevents the entry of hydrophilic morphine molecules and blocks their access to the neural receptors. Inflammation interferes with the peritoneal barrier and, consequently, the access of opioid agonists to the sensory neurons is facilitated to produce only analgesia in swelling tissue (Liu & Hodgson, 2001).

The results of the current study are not in line with Maharjan & Shrestha (2012) study conducted in 60 patients undergoing laparoscopic cholecystectomy. Patients were randomized to one of the following groups: the bupivacaine group received intraperitoneal instillation of 30 ml 0.25% bupivacaine and magnesium sulfate group receiving intraperitoneal

instillation or 0.25% bupivacaine plus 50 mg / kg magnesium sulfate to a total volume of 30 ml. Postoperative pain was evaluated using visual analog scale. The time period for the first analgesia required was noted and rescue analgesics were given as tramadol 50 mg intravenously and as needed. Patients receiving intraperitoneal bupivacaine plus magnesium sulfate at the end of surgery had better pain relief during the first 24 hours. The authors concluded that the combination of bupivacaine and magnesium sulfate in abdominal cavity by laparoscopic surgery gives patients better analgesics and less analgesics during the first 24 hours compared to the bupivacaine group alone.

The requirements for analgesic rescue medication

The results in the current study show that there is no significant difference between Mo and Mg groups in Total Rescue Analyze. (P-value> 0.05). In the Mo group, the mean of total R.A. was (64.29 mg) which does not differ significantly from the mean of total rescue analgesia in the Mg group (74.40 mg). There is only a significant difference between the Mo and Mg groups at 16 hours postoperatively in favor of the Mo group. Compared to a previous study by Bina et al. (2013). Comparison of the analgesic requirements showed that a number of patients receiving rescue analgesia were significantly lower in bupivacaine and morphine groups compared to bupivacaine and placebo group.

Adverse effects

Regarding adverse effects, there were no significant differences between the study groups regarding nausea, vomiting, dizziness, urinary retention and were distributed equally in both groups but there is a significant difference between the groups associated with drowsiness. There are significantly lower number of drowsiness in the Mo group 7/50 (14%) compared with the Mg group 18/50 (36%) (p = 0.0115). The authors of the current study speculated that increased number of patients with drowsiness in the Mg group could be as a result of the mean (SD) of rescue medication, which is pethidine 74.40 mg ± 25.67 which is higher than in Mo group 64, 29 mg ±22.04, This may have caused drowsiness in the Mg group. The current results are consistent with Bina et al (2013) results regarding adverse effects, only nausea and / or vomiting was present in 10 of 90 patients and were distributed equally in all groups. Bina et al. also explained that there was no itching, excessive sedation or dryness of the bupivacaine plus morphine group. The authors speculated that this could be explained because the dose of morphine used in the intraperitoneal instillation was significantly less to cause systemic side effects. The dose of morphine used was 2 mg morphine added to 0.25% bupivacaine 30 ml.

Hemodynamic parameters

Regarding hemodynamic parameters, the results in the current study show that there is significant negative correlation between DBP and total VAS in the Mg group (P = 0.033). In the Mo Group there is no significant relationship. And the results also show that there is a significant negative

correlation between SPO2 and total VAS in Mo group (P value = 0.009). In the Mg group there is no significant relationship. These results were not clinically significant. On the other hand, the results show that there are no significant relationships between both SBP, HR and total VAS in both study Mo and Mg groups (P-values> 0.05) . Compared to Bina et al (2013), important parameters such as HR, BP and SPO2 were identified as important patient comfort indicators as the values correlated well with VAS scores.

Conclusion

Intraperitoneal instillation of combination of bupivacaine with morphine hydrochloride is superior to bupivacaine plus magnesium sulfate to reduce the intensity and incidence of postoperative pain in patients undergoing laparoscopic cholecystectomy surgery without significant increase of side effects. This peripheral effect of opioid provides a new approach to pain relief that can have major clinical benefits.

Recommendations

Based on the results of this study, it is recommended to consider the intraperitoneal instillation of morphine hydrochloride with bupivacaine as a standard application for laparoscopic cholecystectomy surgery to reduce postoperative pain.

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Appendixes

Appendix A: Data Collection Form

Hospital Name _____

Age: _____ Gender: Male □ Female □

Current Admission Date: __ /__ /__

Operation Date: __ /__ /__

ASA:____

Pre-operative data

1. Body mass index (BMI):

<17.9 □ 18.0 – 24.9 □ 25.0 – 29.9 □

30.0-34.9 □ 35.0 - 39.9 □ >40.0 □

2. Elective □ Acute □

3. Primary indication:

Biliary colic □ Cholecystitis □

Gallstone pancreatitis □ Others □

4. Number of surgical admissions with biliary symptoms in the previous 12 months:

0 1 2 3 4 5 >6

5. Use of opioid during 24 hours prior to the study : Yes □ No □

6. Drug or alcohol abuse : Yes □ No □

7. Allergy to any of the study drug :Yes □ No □

8. Type of Instillation : group A □ group B □

Intra-operative data

- Method of operation:

Laparoscopic □ Open □ Laparoscopic -> Open □

Follow up of the patient

(VAS-0 with end-point labeled "no pain" and 10 to "worst conceivable pain"). The degree of postoperative pain.

VAS score	0 hr	1/2 hr	1 hr	4 hr	8 hr	12 hr	16 hr	24 hr
degree								

Pethidine, as rescue analgesia, will be administered on request 10 to 20 mg intravenously in the recovery room and 50 mg intramuscularly in the ward if needed. The number of patients requiring rescue analgesia will be recorded in each group.

Dose of rescue analgesic in PACU and in the surgical ward as continuous variable.

rescue analgesia	zero hr	1/2 hr	1 hr	4 hr	8 hr	12 hr	16 hr	24 hr
Pethidine Dose								

Postoperative hemodynamic in PACU and in the surgical ward as continuous variable.

Hemodynamic	zero hr	1/2 hr	1 hr	4 hr	8 hr	12 hr	16 hr	24 hr
blood pressure								
heart rate								
respiration								

- Postoperative complications :

nausea□ vomiting□ urine retention□ drowsiness□ dizziness□ others

If frequency of vomiting is two times and above, it is an indication for giving antiemetic (Pramine10mg i.v.) and it will be evaluated by a Lickert-type scale.

Lickert-type scale:

MANE*	None	Very mild	Mild	Moderate	Severe	Very severe	Intolerable
Score							

* MANE (Morrow Assessment of Nausea and Emesis)

- Abdominal drain left at the end: Yes □ No □

- Duration of Surgery: _____ (*in minutes*)

Appendix B

INFORMED CONSENT

You have been invited, because you recently had surgery to remove your gallbladder, to participate in a research project being conducted in the Department of Operation,Your participation is entirely voluntary. It is up to you to decide whether or not to take part in this study.

Before you decide, it is important for you to understand what the research involves. This consent form will tell you about the study, why the research is being done and the possible benefits, risks and discomforts.

If you wish to participate, you will be asked to sign this form. If you decide to take part in

this study, you are still free to withdraw at any time and without giving any reasons for your

decision.

If you do not wish to participate, you do not have to provide any reason for your

decision. You will not lose the benefit of any medical care to which you are entitled or are

presently receiving.

Please read this form carefully and feel free to discuss it with your family, friends and
doctor before you decide.

Benefits:

There will be no direct benefits to you for participating in this study. We hope that the
information gained from this study can be used in the future to benefit other people with a similar
condition.

Risks and discomforts:

There are no physical risks associated with this study.

Costs and reimbursements:

There is no cost to you for participating in this study. You will not be paid for your
participation.

Who to contact for questions about this study:

If you have any questions about this study, you can contact The Principal Investigators,
Obaida Weld Ali (0598323573)

Consent:

I, _____, have read and understand the above information and agree to participate in the study entitled:

Comparison of intra-peritoneal instillation of bupivacaine and Morphine hydrochloride versus bupivacaine and magnesium sulfate for post operative pain relief after laproscopic cholecystectomy .

I understand that my participation is voluntary andthat all the information collected will be kept confidential and used only for scientific objectives.

I am not waiving any of my legal rights by signing this consent form. I freely consent to

participate in this study.

Signature_____

Date_____

نموذج موافقة

لقد تمت دعوتك للمشاركة في البحث كونك ستقوم بعملية جراحية لإزالة المرارة بالمنظار ,بحيث ستكون مشاركتك في البحث الذي سيقام في قسم العمليات الجراحية, وهذه المشاركة تعتبر طواعية ولك الحق في القبول أو الرفض, وقبل أن تقرر المشاركة في البحث يجب أن تدرك مضمون هذا البحث .

نموذج الموافقة هذا سيوضح لك أهمية إجراء البحث وما هي المنافع المنتظرة وهل سيكون هناك خطورة أو أي إزعاج يترتب على مشاركتك .

إذا أحببت المشاركة سيكون أمامك المقدرة على ترك البحث والانسحاب في أي وقت ودون إبداء الأسباب ,وفي حال انسحابك من المشاركة في البحث , لن تفقد أي رعاية طبية أو اهتمام .

رجاء اقرأ نموذج الموافقة هذا جيدا وبأريحية مطلقة , وناقش الأمر مع العائلة والأصدقاء أو الطبيب الخاص بك قبل اتخاذ القرار

المنفعة من المشاركة في البحث

ليس هناك منفعة مرتقبة , وأنا أرجو أن تكون المعلومات المستفادة من البحث بعد إتمامه مفيدة لأشخاص آخرين سيخضعون لمثل هذه العملية الجراحية .

المخاطر

لا يوجد مخاطر أو مضاعفات مرتبطة بهذه الدراسة

التكلفة

لا يوجد تكلفه مترتبة على المشاركة في البحث

جهة الاتصال عند الحاجة

عند وجود أي استفسار أو توضيح بالإمكان الاتصال مباشرة بالباحث الرئيسي في البحث (عبيدة ولدعلي)

على الرقم 0598323573

نموذج الموافقة

أنا _____ قرأت وفهمت كل ما جاء من معلومات وأوافق على المشاركة في البحث , وقد فهمت أن مشاركتي في البحث بإرادتي وجميع المعلومات التي أصرح بها والتي يتم جمعها سيتم الاحتفاظ بسريتها , واستعمالها للأهداف العلمية فقط , وعليه أوقع.

توقيع المريض: _____ التاريخ :_____

Appendix C

An-Najah
National University
Faculty of Graduate Studies
Dean's Office

جامعة
النجـــاح الوطنية
كلية الدراسات العليا
مكتب العميد

التاريخ، 2017/6/5

حضرة الدكتورة عائدة القيسي المحترمة
منسقة برنامج ماجستير تمريض التخدير

تحية طيبة وبعد،

الموضوع: الموافقة على عنوان الاطروحة وتحديد المشرف

قرر مجلس كلية الدراسات العليا في جلسته رقم (339)، المنعقدة بتاريخ 2017/5/28، الموافقة على مشروع الأطروحة المقدم من الطالب/ة عبيدة نصفت عبد الرؤوف ولد علي، رقم تسجيل 11356930، تخصص ماجستير تمريض التخدير، عنوان الأطروحة:

(مقارنة بين الحقن البرتوني (الصفاقي الداخلي) لمادة الباقيين مع المورفين هايدروكلوريد، وبين الحقن البرتوني (الصفاقي الداخلي) لباقيين مع المغنيسيوم سلفيت، لتقليل الألم بعد عملية إزالة المرارة بالمنظار الجراحي)

(Comparison between Intra-Peritoneal Instillation of Bupivacaine with Morphine Hydrochloride Versus Bupivacaine with Magnesium Sulfate for Post-Operative Pain Relief after Laparoscopic Cholecystectomy)

بإشراف: 1- د. وائل صدقة 2- د. عائدة القيسي

يرجى اعلام المشرف والطالب بضرورة تسجيل الاطروحة خلال اسبوعين من تاريخ اصدار الكتاب. وفي حال عدم تسجيل الطالب/ة للاطروحة في الفترة المحددة له/ا ستقوم كلية الدراسات العليا بإلغاء اعتماد العنوان والمشرف

وتفضلوا بقبول وافر الاحترام ،،،

عميد كلية الدراسات العليا
د. محمد سليمان

نسخة: د. رئيس قسم الدراسات العليا للعلوم الطبية والصحية المحترم
ق.أ. ع القبول والتسجيل المحترم
مشرف الطالب
ملف الطالب

ملاحظة: على الطالب/ة مراجعة الدائرة المالية (محاسبة الطلبة) قبل دفع رسوم تسجيل الاطروحة للضرورة

فلسطين، نابلس، ص.ب 7707 هاتف 2345115/ 2345114 2345113 (09)(972)* فاكسميل 2342907(09)(972)
3200 (5) هاتف داخلي Nablus, P. O. Box (7) *Tel. 972 9 2345113, 2345114, 2345115
* Facsimile 972 92342907 *www.najah.edu - email fgs@najah.edu

Appendix D

*ASA Physical Status (PS) Classification System**		
ASA PS Category	**Peroperative Health Status**	**Comments, Examples**
ASA PS 1	Normal healthy patient	No organic, physiologic, or psychiatric disturbance; excludes the very young and very old; healthy with good exercise tolerance
ASA PS 2	Patients with mild systemic disease	No functional limitations; has a well-controlled disease of one body system; controlled hypertension or diabetes without systemic effects, cigarette smoking without chronic obstructive pulmonary disease (COPD); mild obesity, pregnancy
ASA PS 3	Patients with severe systemic disease	Some functional limitation; has a controlled disease of more than one body system or one major system; no immediate danger of death; controlled congestive heart failure (CHF), stable angina, old heart attack, poorly controlled hypertension, morbid obesity, chronic renal failure; bronchospastic disease with intermittent symptoms
ASA PS 4	Patients with severe systemic disease that is a constant threat to life	Has at least one severe disease that is poorly controlled or at end stage; possible risk of death; unstable angina, symptomatic COPD, symptomatic CHF, hepatorenal failure
ASA PS 5	Moribund patients who are not expected to survive without the operation	Not expected to survive > 24 hours without surgery; imminent risk of death; multiorgan failure, sepsis syndrome with hemodynamic instability, hypothermia, poorly controlled coagulopathy
ASA PS 6	A declared brain-dead patient who organs are being removed for donor purposes	

*ASA PS classifications from the American Society of Anesthesiologists

جامعة النجاح الوطنية
كلية الدراسات العليا

مقارنة بين الحقن البرتوني (الصفاقي الداخلي) لمادة البافكيين مع المورفين هايدروكلورايد، وبين الحقن البرتوني للبافكيين مع المغنيسيوم سلفيت، لتقليل الألم بعد عملية ازالة المرارة بالمنظار الجراحي

اعداد
عبيدة نصفت عبد الرؤوف ولد علي

اشراف
د. وائل صدقة
د. عائدة القيسي

قدمت هذه الأطروحة استكمالا لمتطلبات الحصول على درجة الماجستير في تمريض التخدير بكلية الدراسات العليا في جامعة النجاح الوطنية، نابلس- فلسطين
2018

مقارنة بين الحقن البرتوني (الصفاقي الداخلي) لمادة البافكيين مع المورفين هايدروكلورايد، وبين الحقن البرتوني للبافكيين مع المغنيسيوم سلفيت، لتقليل الألم بعد عملية ازالة المرارة بالمنظار الجراحي

اعداد

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اشراف

د. وائل صدقة

د. عائدة القيسي

الملخص

المقدمة

هناك طريقتين متبعات لإزالة المرارة , حيث يتم إزالة المرارة بشكل جراحي أو بالمنظار , وهذه الأيام يتم تفضيل إجراء العملية بالمنظار , لكون المريض يحتاج لمدة اقل للمتابعة في المستشفى بعد العملية , وتعود الوظائف الجسدية بشكل أسرع بسبب محدودية الإجراء الجراحي المتداخل .

وعلى الرغم من ذلك, يبقى المريض يعاني من الألم بعد العملية , بسبب التهيج الحاصل على الحجاب الحاجز بعد إطلاق nociceptive input .

يعتبر استعمال مسكن للألم متعدد التركيب للسيطر على الألم بعد عملية المنظار لإزالة المرارة من الأساليب الجديدة هذه الأيام للتقليل من المضاعفات المترافقة مع الجرعات العالية في حالة إستعمال مسكن واحد , ومن الأدوية التي تبين لها دور فعال في الحد من الألم (المغنيسيوم سلفيت), حيث لاتوجد دراسات للمقارنة بين الحقن البرتوني (الصفاقي الداخلي) لمادة البافكيين مع المورفين هايدروكلورايد، وبين الحقن البرتوني للبافكيين مع المغنيسيوم سلفيت، لتقليل الألم بعد عملية ازالة المرارة بالمنظار الجراحي

الأهداف

هذه الدراسة هدفها مقارنة تأثير المسكن الذي يتم حقنه في الجدار البرتوني (الصفاقي الداخلي) لمادة البافكيين مع المورفين هايدروكلورايد، وبين الحقن البرتوني للبافكيين مع المغنيسيوم سلفيت، لتقليل

الألم بعد عملية ازالة المرارة بالمنظار الجراحي, لمن يتم إخضاعهم لتخدير كامل , للوصول بالمريض لأقل مستوى للألم , وللتقليل من الحاجة لاستعمال المسكنات ما بعد العملية خلال الأربعة وعشرون ساعة اللاحقة للعملية.

تصميم الدراسة

بعد خضوع البحث لموافقة لجنة أخلاقيات البحث العلمي في جامعة النجاح الوطنية وكتابة نموذج موافقة لإخضاع المريض للبحث بعد عملية إزالة المرارة بالمنظار , خضع للتجربة 100 حالة تتراوح أعمارهم بين عمر 18 و 60 عاما , وبدرجة أولى وثانية حسب تصنيف جمعية أطباء التخدير الأمريكية .

وبشكل عشوائي تم تقسيم المرضى لمجموعتين , تم إعطاء المجموعة الأول مادة البافكيين 30 مل 0.25 % , مع المورفين هايدروكلورايد 3 ملغم , بالمقابل تم إعطاء المجموعة الثانية والتي احتوت 50 حالة أيضا , مادة البافكيين 30 مل 0.25 % مع المغنيسيوم سلفيت(50 ملغم / كيلو),اعطاء الدواء تم بعد غسل وسحب السوائل من الجدار البرتوني (الصفاقي الداخلي) ,تم تحضير الدواء من طبيب غير مشارك بالدراسة , وجميع المرضى تم تخديرهم للعملية بنفس البروتوكول , ومن ثم مراقبة تخطيط القلب , النبض , ضغط الدم , ونسبة إشباع الدم بالأكسجين لجميع المرضى , وتم مراقبة المشاركين في البحث لفترة 24 ساعة بعد الانتهاء من العملية لضبط مستوى الألم لديهم .

باستعمال مقياس الألم , حيث يتضمن 10 مستويات , تم اعتبار المستوى 4 من مقياس الألم , الحد الفاصل للتدخل وإعطاء المريض جرعة المسكن التي تم اعتمادها من مادة المخدر البيثادين 20 ملغم، عن طريق الوريد, في غرفة متابعة المريض والمراقبة في قسم العمليات وفي حال حاجة المريض لجرعة اضافية للمسكن يتم اعطائه 50 ملغم عن طريق العضل خلال تواجد المريض في قسم الجراحة في حال وجود الألم .

النتائج

كانت خصائص المرضى من العمر والجنس ومؤشر كتلة الجسم قابلة للمقارنة في المجموعتين. لم يكن هناك فرق كبير بين المجموعتين فيما يتعلق مدة الجراحة. المعلمات الديموغرافية (العمر، الجنس

وBMI) ليس لها أي تأثير على متوسط من VAS (ف قيمة> 0.05). هناك فروق ذات دلالة إحصائية بين مجموعات من مو والمغنيسيوم في الدرجة الكلية VAS (قيمة 0.05> P).

في المجموعة مو، يعني من إجمالي VAS (2:09) كان أقل بكثير من متوسط مجموع المغنيسيوم VAS في مجموعة (2.71)؛ ما يعني مو في المجموعة المريض كان أقل بكثير من شدة الألم في المجموعة المغنيسيوم المريض (ع = 0.006).

هناك فرق كبير بين عدد (في المائة) من يشكو المريض من الآلام المتوسطة والشديدة بعد العملية الجراحية في مجموعة مو 50/15 (30٪) بالمقارنة مع مجموعة المغنيسيوم 50/25 (50٪) (ع = 0.0423). عندما تقدير حجم تأثير العلاج من المورفين بالإضافة إلى هيدروكلوريد بوبيفاكايين، وجدت أن الحد من المخاطر النسبية من الآلام المتوسطة والشديدة بعد العمل الجراحي هو 00:40. هو أيضا هناك فرق كبير بين عدد (في المائة) من المريض يشكو من الخمول في المجموعة مو 50/7 (14٪) بالمقارنة مع مجموعة المغنيسيوم 50/18 (36٪) (ع = 0.0115). لا توجد فروق ذات دلالة إحصائية بين مجموعتي الدراسة فيما يتعلق الغثيان والتقيؤ والدوار واحتباس البول.

المرضى في المجموعة مو تستهلك أقل الإنقاذ جرعة مسكن (± SD) M (64.29 ملغم + 22.04) بالمقارنة مع المريض في مجموعة المغنيسيوم (± SD) M (74.40 ملغم + 25.67) دون علاقة ذات دلالة إحصائية بين الجرعات عناء (قيمة ص = 0.163) . تم فحص ضغط الدم ومعدل ضربات القلب وتشبع الأكسجين كمعلمات الدورة الدموية. أظهرت النتيجة عدم وجود علاقة ذات دلالة إحصائية بين هذه المعلمات و VAS (قيمة 0.05 <p).

الاستنتاج

تقطير داخل الصفاق من مزيج من بوبيفاكايين مع هيدروكلوريد المورفين متفوقة على بوبيفاكايين بالإضافة إلى المغنيسيوم سلفات للحد من شدة وحدوث آلام ما بعد الجراحة في المستشفى خضع لجراحة استئصال المرارة بالمنظار دون زيادة كبيرة من الآثار الجانبية. يوفر هذا التأثير المحيطي للأفيونيات نهجًا جديدًا لتخفيف الآلام يمكن أن يكون له فوائد سريرية كبيرة.

توصية

وبناء على نتائج هذه الدراسة، فمن المستحسن للنظر في تقطير داخل الصفاق من هيدروكلوريد المورفين مع بوبيفاكايين كتطبيق افتراضي لجراحة استئصال المرارة بالمنظار للحد من الألم بعد العملية الجراحية لإزالة المرارة بالمنظار