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AIM: *The purpose of this study is to evaluate three different analgesic procedures after laparoscopic cholecystectomy for pain control.*
MATERIAL OF STUDY: *The study involved 183 patients who underwent laparoscopic cholecystectomy with the same technique for the induction and maintenance of the general anesthesia. They were divided into three different postoperative pain treatment groups: continuous infusion of Tramadol and Ketorolac with elastomeric pump, intraperitoneal topical instillation of Levobupivacaine, and intraperitoneal aerosolization of Levobupivacaine.*
RESULTS: *No differences were found in the demographics. shorter operating time was observed in group 1. Eight hours after surgery in groups 2 and 3, there was an increase in pain compared to patients in the first group. The request for postoperative analgesic assistance was lower in groups 1 and 2.*
DISCUSSION: *Various topical and intravenous ways for analgesic actions have been used to improve the pain control after laparoscopic procedures, individually and in comparison between them. The main result of our research is that the use of levobupivacaine employed in the topical intraperitoneal application anesthesia by instillation and nebulization, do not improve the postoperative pain in the first 24 hours after LC, compared with intravenous analgesic elastomeric pump.*
CONCLUSIONS: *Despite the positive data found in the literature, our observations have not shown a better pain control after laparoscopic cholecystectomy with the use of intraperitoneal analgesia compared to intravenous.*

KEY WORDS: Gallstone disease, Gallbladder bladder, Laparoscopic cholecystectomy, Postoperative pain, Stones

Introduction

Gallstone disease represents one of the major causes of abdominal morbidity and mortality through the world [1,2]. This pathology is a frequent problem in developed countries, representing a major health problem [3]. Laparoscopic approach, from the last two decades, is stably the gold standard in the treatment of benign gallbladder diseases. Some advantages, in comparison to open approach, characterize the postoperative period of mini-invasive procedures: shorter recovery time and hospital stay, better cosmetic results and sensible reduction of postoperative pain and discomfort. To complete the clinical scenario of a postoperative recovery, the optimal control of the pain after laparoscopic cholecystectomy (LC) remains essential, required objective for the researchers [4-6], in fact, some patients still complain of postoperative pain, which can be represented by superficial incisional wound pain, deep visceral pain and/or post-laparoscopy shoulder pain, all of which may require additional analgesia and result in delayed hospital discharge [7]. The exact etiology of postoperative pain remains unclear. However, it appears to be multifactorial, and treatment of any one factor in isolation will not achieve the desired outcome. The causes include initiation of pneumoperitoneum, type of insufflated gas and

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intraabdominal pH, residual intraperitoneal gas, gas temperature, humidity, and the use of certain anesthetic and anti-inflammatory drugs. Additional contributing factors include access-related pain, sociocultural status, and individual factors [8-12]. The aim of this prospective observational study was to evaluate three different analgesic procedures after laparoscopic cholecystectomy: continuous infusion of Tramadol and Ketorolac with elastomeric pump, intraperitoneal local instillation of Levobupivacaine, intraperitoneal aerosolization of Levobupivacaine, and on the basis of our experience to define the most effective.

Material and Method

This one-year experience was conducted from July 2018 to July 2019 at the Department of Medical and Surgical Sciences of the University of Foggia (Italy). The study specimen regarded 183 patients, scheduled for elective laparoscopic cholecystectomy (LC) performed by our standardized antegrade technique [13]. The indications for LC were symptomatic gallstones; other inclusion criteria were: the patients aged over 18 years and ASA risk 1-2. Exclusion criteria were emergency LC for cholecystitis, gallstone pancreatitis [14] and patients undergone to endoscopic retrograde cholangiopancreatography (ERCP) before the operation and additional procedures during the intervention. The preoperative evaluation was completed by ECG, chest-x-ray, liver function tests, blood panel, coagulation [15]. Written informed consent was obtained from every patient prior the surgical procedure. In all patients we used the Hasson open entry technique to perform laparoscopy. The cholecystectomy was carried out with two 10 mm trocars and two 5 mm trocars and following the antegrade dissection of gallbladder prior the recognition of cystic duct and cystic artery [16,17]. During the procedures there were no bile leaks, bile duct injuries, retained stones, allergic reactions to local intraperitoneal anesthesia, other postoperative complications requiring reoperation or prolonged hospital stay. In these groups of patients there was not any deviations from the normal postoperative course. All the patients underwent standard induction of anesthesia with propofol 2 mg/kg, fentanyl 1mcg/Kg, cisatracurium 0,1mg/kg or rocuronium 0,6mg/kg. After tracheal intubation, anesthesia was maintained with a mixture of oxygen and air and sevoflurane at MAC 0,8%, cisatracurium 2 mg or rocuronium 10 mg were administered respectively after 45 or 30 minutes after induction. Intraoperative analgesia was maintained using remifentanyl 0,05-0,1 mcg/Kg/min. A bolus of ranitidine 50mg, ketorolac 30mg, ondansetron 4mg and tramadol 100mg was also administered 30 minutes before the end of the intervention. The patients have been subdivided in three groups, based on the different treatment of postoperative pain. The first group (group 1) consists of 60 patients treated with postoperative intravenous analgesia administered by elastomeric pump. The solution consisted in a mixture containing tramadol 200mg, ketorolac 180mg, ranitidine 200mg, ondansetron 8 mg and NaCl 0,9% in a total volume of 100 ml with an infusion rate of 2 ml/h. In the second group 60 patients have been submitted intraoperatively at the end of intervention, to intraperitoneal topical instillation of levobupivacaine. Finally in the third group 63 patients have been treated with the intraperitoneal nebulization of the levobupivacaine. In the topical instillation (groups 2) a total of 40 ml of levobupivacaine 0,125% was administrated topically using a Nelaton catheter inserted via epigastric port over the anterior surface of the liver (20 ml) and on the lower surface of the liver (20 ml). In the group 3 the solution has been dispensed in peritoneal cavity by nebulization. The postoperative pain of the patients has been evaluated by visual analogue scale (VAS) pain score on 4, 8 and 24 hours after the end of intervention. Time of oral intake, postoperative ambulation and hospital stay were recorded. All the data were noted in Microsoft excel sheet (version 2010) and statistical analysis was done using SPSS software, version 16 (SPSS Inc., Chicago, IL, USA) for windows. Intergroup statistical significance was calculated using one-way analysis of variance (ANOVA) only gender was analyzed using chi-square test. A p value <0.05 was considered statistically significant.

Results

One hundred and eighty three patients were registered in this study, subdivided in three groups: the first group treated with postoperative elastomeric pump, topical intraperitoneal instillation in the second group and intraperitoneal nebulization in the third group. There was no significant difference between the three groups regarding the demographic data, age and sex, general state of health, BMI and past medical history, synthesized by ASA score. Patients demographic data are shown in Table I. There was a significant difference in the mean operating time (p = 0,000) which was shorter in the group 1 (Table II). The patients of the group 2 and 3, submitted to topical intraperitoneal instillation and nebulization of levobupivacaine respectively, showed a higher incidence of abdominal and shoulder pain than group 1, in particular 8 hours after the surgical procedure (statistically significant difference, p =0,008); there were also differences at 4 and 24 hours after the intervention but not statistically significant (Table II). The request for postoperative analgesic assistance, evaluated in milligrams of Paracetamol, was lower in groups 1 and 2, compared to group 3 (p = 0,000). On the contrary in the postoperative recovery there was not statistically significant differences regarding postoperative ambulation after surgery and hospital stay (Table II). All patients started to oral intake 24 hours after surgical procedure.

TABLE I - *Demographic data.*

Groups Variables	Group 1	Group 2	Group 3	p *value*
Gender	F 32/60 (53,3%) M 28/60 (46,7%)	F 29/60 (48,3%) M 31/60 (51,7%)	F 32/63 (50,8%) M 31/63 (49,2%)	0,861
Age				
Average (STD)	50.70 (16.91)	52.92 (12.59)	48.97 (13.93)	0,325
Median	48	53	48	
Range	25-89	32-78	26-72	
BMI				
Average (STD)	26.78 (2.87)	27.30 (2.63)	26.02 (6.22)	0,250
Median	26.4	27.7	26.5	
Range	23-33.2	23-32.49	20.08-32.01	
ASA				
Score	1.60 (0.49)	1.60 (0.49)	1.48 (0.50)	0,297
Average (STD)	2	2	1	
MedianRange	1-2	1-2	1-2	

Group 1: elastomeric pump; Group 2: local instillation; Group 3: intraperitoneal nebulization; Age: in years.

TABLE II - *Intraoperative and postoperative outcomes.*

Groups Variables	Group 1	Group 2	Group 3	p *value*
Operative time				
Average (STD)	76.42 (13.74)	83.58 (13.31)	86.67 (15.66)	0,000
Median	75	85	90	
Range	50-105	60-110	55-115	
VAS 4h				
Average (STD)	2.50 (1.37)	2.35 (1.02)	2.57 (0.80)	0,520
Median	2.5	2	2	
Range	1-7	1-5	1-4	
VAS 8h				
Average (STD)	2.95 (1.41)	3.55 (1.37)	3.71 (1.43)	0,008
Median	3	3.5	4	
Range	0-5	0-6	1-6	
VAS 24h				
Average (STD)	1.85 (1.07)	1.80 (0.94)	2 (1.12)	0,544
Median	2	2	2	
Range	0-4	0-3	0-4	
Postoperative ambulation				
Average (STD)	24.57 (2.36)	24.65 (1.92)	24.57 (2.50)	0,975
Median	24	24.5	24	
Range	20-30	20-28	20-30	
Postoperative hospitalization				
Average (STD)	2.75 (0.77)	2.75 (0.70)	3.05 (1.05)	0,082
Median	3	3	3	
Range	2-5	2-4	2-6	
Postoperative analgesia (paracetamol)				
Average (STD)	0.45 (0.50)	0.45 (0.50)	0.81 (0.67)	0,000
Median	0	0	1	
Range	0-1	0-1	0-2	

Operative time: in minutes; Postoperative ambulation: in hours; Postoperative hospitalization: in days; Postoperative analgesia: in milligram

Discussion and Comments

The origins of the postoperative pain are multifactorial, with parietal and visceral components. In addition right shoulder pain, secondary to diaphragmatic irritation as a result of carbon dioxide (Co_2) pneumoperitoneum effect, is frequent (35%-60%) after LC. The optimal control of the pain after LC remains an interesting theme for the researchers. The visceral component of post-cholecystectomy pain is caused (connected with) by dissected peritoneum surrounding the gallbladder. The source of somatic pain is more variable: distension of the parietal peritoneum by insufflation of Co^2, traumatic lesions of the parietal incisions for trocars accesses 18. The somatic component of postoperative pain is the major and more intense factor, compared with the visceral pain and more evident in the first 48 hours [19]. In the proposable grading of the intensity of the pain in the postoperative period of LC the most painful sites were the sites of parietal incisions: umbilical incision followed by the other trocar sites. Another characteristic site of postoperative pain is the shoulder tip, but in this area there was lower pain intensity. The pain referred to the shoulder tip can be due to diaphragmatic irritation by high intra-abdominal pressure of the pneumoperitoneum and by Co_2 absorption from the peritoneal serosa [20,21]. The involvement of peritoneal serosa underlies the pain after laparoscopic approach because the Co_2 insufflation and then elevated intra-abdominal pressure causes peritoneal inflammation and neuronal rupture with close connection between abdominal wall compliance to higher intraperitoneal pressure and the severity of postoperative pain [22]. In summary moderate/severe pain is common in the postoperative period of LC; many studies have been carried out with the purpose to reduce the frequency and severity of postoperative pain after LC. Various procedures have been employed: intravenous postoperative analgesic as Fentanyl, Ketoprofen, Morphine, Diclofenac sodium, local intraperitoneal anesthetic instillation or nebulization, sub-peritoneal diaphragm injections of local anesthetic, peritoneal washout with saline to remove of residual Co_2 at the end of intervention, ultrasound guided transverse abdominis plane block with local anesthetic. Nevertheless no one of these procedures obtained the results of complete analgesia. Probably should be useful the integration of ways of administration and of pharmacological drugs [8,23-25]. Moreover the difficult to treat post-laparoscopic pain lies on its findings: the pain usually can result from the interaction of several starting points, as the incisions on the abdominal wall, the dissection of liver bed, the irritation of peritoneum serosa and diaphragm by increased intra-abdominal pressure and absorption of Co_2. Ultimately a mixture of somatic and visceral pain [26]. The mechanism of action for systemic analgesia is not well defined. Lidocaine is active by sodium channel blockade [27]. Other hypothesized factors should develop action as direct or indirect interaction on various receptors and on ways of nociceptive transmission such as muscarinic antagonists, release of endogenous opioids, reduced neurokinin levels, etc. [28,29]. The therapy with opioids and FANS has played a preminent role in the postoperative analgesia and it's still administrated routinely, however their side effect and the increasing availability of suitable alternatives may limit their future use in some situations. Nevertheless several data from the literature support the use of perioperative analgesic intravenous infusion as part of a multimodal analgesic regimen for the management of postoperative pain. In particular the perioperative systemic intravenous use of lidocaine was reported and its results such as reduced postoperative pain after LC, fast recovery of bowel functions, fewer opioids required and fewer opioid-related side-effects [30,31]. The intraperitoneal use of local anesthetic to control the pain has been studied in a lot of randomized trials. These trials showed different results and used a variety of local anesthetics with different routes of administration. The analgesic effect of topical wash (instillation, nebulization, injection) is different, based on the site of application. The injection of local anesthetic in right subdiaphragmatic peritoneum was followed by evident decrease of postoperative pain for a long period and short recovery, compared with other sites application of topical anesthetic (liver surface, gallbladder bed). These particular research results showed that greater source of postoperative pain after LC comes from the irritation of diaphragm with transmission via the somatic pain fibers of the diaphragm rather than the pain transmitted via autonomic visceral pain fibers from the liver capsule and gallbladder peritoneum [32]. Various topical ways for analgesic actions have been used to improve the pain control after laparoscopic procedures: evacuation of the insufflated gas (Co_2), instillation or nebulization of local anesthetic in the site of surgery, infiltration of local anesthetic into the skin and muscle of the site of trocar accesse [33-35]. Despite the many studies, the choice of topical anesthetic is still debated in terms of efficacy. The use of lidocaine and bupivacaine has been shown to be effective in reducing post-cholecystectomy pain compared with a placebo. There are many advantageous effects from the intraperitoneal application of the bupivacaine on postoperative pain control, characterized of longer duration of analgesia after LC. In some researches, reported in the literature, the topical application of bupivacaine is associated with the buprenorphine, a semisynthetic opioid. This association is characterized by better analgesic results compared with bupivacaine alone [36-38].

The main result of our research is that the use of levobupivacaine employed in the topical intraperitoneal application anesthesia by instillation and nebulization, do not improve the postoperative pain in the first 24 hours after LC, compared with intravenous analgesic elastomeric pump. In addition, patients in groups 2 and 3 (intraperitoneal analgesia) required more postoperative

analgesia (paracetamol) at 8 hours than patients in group 1 (statistically significant result). This is the demonstration of longer and stable effect of intravenous analgesia. These results were confirmed by the VAS pain score. Nevertheless there is discussion about the analgesia results related the way of performance of the topical intraperitoneal anesthesia. The bupivacaine sprayed on the anterior surface of the liver and gallbladder showed lesser pain control, compared with the injection of local anesthetic in the right sub-peritoneal sub-diaphragmatic site that was followed by considerable pain control [31]. The use of local anesthetic soaking a tablet of regenerated oxidized cellulose (tabotamp) in the gallbladder bed can determine a valuable postoperative comfort [38].
Intraperitoneal local anesthetic nebulization of bupivacaine has been proposed based on the characteristics of this procedure which allows uniform dispersion of local anesthetic particles into the peritoneal cavity. The analgesic results of this procedure have been more valuable and for longer time, also compared with instillation of the drug [39-42].

Conclusions

Our observations have been inspired by previous data obtained by various authors with the use of bupivacaine for intraperitoneal analgesic drugs in the management of postoperative pain after LC. The outcomes of this study have shown that there is no improvement between intraperitoneal and classical intravenous analgesia with elastomeric pump. However, in light of the results of the literature, and with more numerous cases, more detailed studies could be conducted on the pathways of transmission of pain after laparoscopic cholecystectomy, thus being able to gather further research ideas.

Riassunto

Lo scopo di questo studio è di valutare tre diverse procedure analgesiche per il controllo del dolore dopo colecistectomia laparoscopica, ed ha coinvolto 183 pazienti sottoposti a colecistectomia laparoscopica con la stessa tecnica per l'induzione e il mantenimento dell'anestesia generale. I casi sono stati divisi in tre diversi gruppi di trattamento del dolore postoperatorio: infusione continua di tramadolo e ketorolac con pompa elastomerica, instillazione topica intraperitoneale di levobupivacaina e aerosolizzazione intraperitoneale di levobupivacaine.
Risultati: Nessuna differenza è stata riscontrata nei dati demografici. È stato osservato un tempo operatorio più breve nel gruppo 1. Otto ore dopo l'intervento chirurgico nei gruppi 2 e 3, c'è stato un aumento del dolore rispetto ai pazienti del primo gruppo. La richiesta di assistenza analgesica aggiuntiva postoperatoria è risultata inferiore nei gruppi 1 e 2.
Discussione: Varie tecniche analgesiche postoperatorie sono state proposte, sia per somministrazioni topiche che endovenose, per migliorare il controllo del dolore dopo procedure laparoscopiche, individualmente e in confronto tra loro. Il risultato principale della nostra ricerca è stato che l'uso della levobupivacaine, impiegata nell'anestesia topica intraperitoneale mediante instillazione e nebulizzazione, non migliora il controllo del dolore postoperatorio nelle prime 24 ore dopo LC, rispetto alla pompa elastomerica analgesica endovenosa.
Conclusioni: Nonostante i dati positivi riscontrati in letteratura, le nostre osservazioni non hanno mostrato un migliore controllo del dolore dopo colecistectomia laparoscopica con l'impiego dell'analgesia intraperitoneale rispetto a quella endovenosa.

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