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Role of intra operative esmolol infusion in post operative pain relief after laparoscopic cholecystectomy.

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Abstract: *Postoperative pain following laparoscopic cholecystectomy is one of the main causes for lengthening the period of hospitalization. In an attempt to decrease this early postoperative complication, esmolol infusion was administered during general anaesthesia to patients undergoing laparoscopic cholecystectomy. Sixty patients ASA class I undergoing laparoscopic cholecystectomy were randomly assigned to two groups, esmolol group (Group E, n=30) and placebo group (Group P, n=30). In group E, patients received 1mg/kg esmolol bolus dose i.v immediately before induction while as group P received same volume of inj. Ringer Lactate as placebo. In group E, immediately after intubation, esmolol infusion was started at the rate of 5-10 µg/kg/min. The rate was titrated to maintain heart rate between 65-75 beats per min. Patients in group P received 100 ml of Ringer Lactate infusion. The incidence of PONV and pain were assessed after surgery. Incidence of postoperative analgesia requirement was significantly less in esmolol group. 50% of patients required analgesia in group E, while 83.33% required analgesia in group P (p=0.006). Post operative antiemetic requirements were also significantly less in group E. It was concluded that incidence of postoperative analgesia requirements over first 24 hours after laparoscopic cholecystectomy was found to be less in esmolol group as compared to placebo group.*

Key words: *Esmolol, Laparoscopic cholecystectomy, Ringer lactate*

I. Introduction

Diminished surgical trauma and associated morbidity have made laparoscopic cholecystectomy a standard technique for removal of diseased gallbladder. In spite of the high success rate of ambulatory laparoscopic cholecystectomy, the most common side effects reported with this surgery are postoperative nausea and vomiting (PONV), pain, medical complications, and urinary retention, leading to an unanticipated admission rate of approximately 5% [1].

One of the major challenges of ambulatory anaesthesia is the ability to provide effective post operative analgesia and hemodynamic stability, thus allowing patients to be safely discharged [2].Postoperative pain is less after laparoscopic cholecystectomy compared to open cholecystectomy [3] but effective analgesic treatment after laparoscopic cholecystectomy has remained a challenge.[4] In 17-41% of patients, pain is main reason for staying overnight in hospital on the day of surgery.[5]

Adrenergic receptor antagonist have been used during surgery with intention to attenuate the stress response and decrease unwanted peri-operative hemodynamic changes.[6] Esmolol, an ultra–short-acting cardioselective β-adrenergic receptor antagonist, has been proposed as an alternative to intra operative use of opioids, and found to facilitate the fast-tracking process and speed home-readiness of patients undergoing outpatient surgery .[7,8,9]

The present prospective, randomized study was designed to compare the effect of intra-operative i.v esmolol vs. placebo on incidence of post-operative pain in patients scheduled for laparoscopic cholecystectomy.

II. Patients and Methods

This randomized, prospective, double blind study included 60 patients of either gender, aged 18 and above, ASA 1, undergoing laparoscopic cholecystectomy under general anaesthesia. A proper approval from the local ethics committee and informed consent was taken from the patients included in the study. During pre-anaesthetic visit, all patients were clinically evaluated, assessed and investigated. Patients were instructed before surgery about the use of the visual analogue scale (VAS). Exclusion criteria were: ASA II, concurrent treatment with a β-blocker or a calcium channel blocker, chronic use of an opioid analgesic, history of asthma or reactive airway disease, diabetes mellitus, allergy to any drug used in study, obesity or cachexia, severe hemorrhage during surgery, conversion to open cholecystectomy or inability to comprehend pain assessment.

An anaesthetist not involved in the care of the patient prepared esmolol and placebo solution & held the randomization cards until the end of the study. Both patient and the anaesthetist in charge were blinded to group allocation for the duration of study. The patients were shifted to the operating room, intravenous line established

and patients were connected to Datex monitor for continuous monitoring of ECG, heart rate, non invasive blood pressure (NIBP), and oxygen saturation. All the patients received 10ml/kg ringer lactate (RL) before induction. Patients were randomly allocated to two groups:

GROUP E--- Esmolol group (n = 30)

GROUP P ---Placebo group (n = 30)

In both the groups, anaesthesia was induced in an identical manner with Inj. propofol 2-3mg/kg body weight and Inj. fentanyl 2 µg/kg. Intubation was facilitated with atracurium 0.5-0.75mg/kg.

In group E, patients received 1mg/kg esmolol (prepared to make a total volume of 5 ml) bolus dose i.v immediately before induction while as group P received same volume of inj. Ringer Lactate as placebo. In group E, immediately after intubation, esmolol infusion was started at the rate of 5-10 µg/kg/min. The esmolol infusion was prepared as 100 ml solution and was administered through a chamber set. The rate was titrated to maintain heart rate between 65-75 beats per min. Patients in group P received 100 ml of Ringer Lactate infusion which was also prepared as a 100 ml solution and was administered through the chamber set.

In both groups, controlled ventilation was performed. Maintenance of anaesthesia was done with isoflurane 0.4 -1 % in an inhaled mixture of 66% N_20 and 33% 0_2. Supplementary neuromuscular block was provided with bolus doses of atracurium. Isoflurane and N_2O were discontinued when laparoscope was withdrawn and the effects of neuromuscular blocking agents were reversed at the end of the procedure. Patients in both groups received inj. ondansetron 4mg and inj. Diclofenac sodium 50 mg i.m before extubation. Patients were extubated on the operating table and then transferred to the post anesthesia care unit (PACU).Whenever patients complained of pain during 24 hours post operatively, they were assessed using visual analogue scale (VAS) and patients with a VAS score of > 3 were administered analgesics in the form of lnj Diclofenac 50 mg i.m. Data collected was statistically evaluated and analyzed. Parametric data was expressed as mean ± SD, thereby the inter group comparisons were made by student's t-test .The test was two sided and referred for p-value for its significance. P-value less than 0.05 ($p< 0.05$) was taken to be statistically significant. The analysis was performed on SSPS version 11.3, statistical software for social sciences, Chicago, U.S.A for windows.

III. Results

The study recruited 60 patients with ASA status I . There were no significant group differences found in age, gender, previous history of PONV, history of smoking and motion sickness, duration of surgery and anaesthesia. (TABLE 1)

Table 1: Comparison between demographic details & other characteristics in two groups.

CHARACTERISTICS	GROUP-E	GROUP-P	p Value
Number of patients	30	30	
Mean age in years(± S.D)	40.17± 6.10	41.7±3.5	p=0.240
Gender (F/M)	21/09	23/07	p=0.559
Previous PONV	1	1	p=1
History of smoking	5	4	p=1
History of motion sickness	1	0	p=1
Duration of surgery (min)	69	60	p=0.074
Duration of anesthesia (min)	87	80	p=0.101

The mean value of mean heart rate (bpm) for group E and group P was 70.138 and 78.350 respectively. When these two values were compared, p value was 0.001 i.e. statistically significant. The mean heart rate did not decrease below 60 beats per minute in any patient. In addition, the MABP of group P and E was not significantly different at any point before, during or after the procedure.

Incidence of postoperative analgesia requirement was significantly less in esmolol group. 50% of patients required analgesia in group E, while 83.33% required analgesia in group P (*p=0.006*). (TABLE 2)

Table 2: Comparison of incidence of postoperative analgesia requirement (inj Diclofenac) in two groups.

	GROUP E	GROUP P	TOTAL	p VALUE
Number of patients who received post operative analgesia	15 (50%)	25 (83.33%)	40 (66.7%)	p= 0.006
Number of patients who did not receive post operative analgesia	15 (50%)	5 (16.77%)	20 (33.3%)	
TOTAL	**30**	**30**	**60**	

IV. Discussion

Cholecystectomy is one of the most commonly performed abdominal operations, and the laparoscopic approach has become the standard of care. Although the minimally invasive approach allows for rapid discharge home, the recovery process can be further accelerated by modifications in other aspects of perioperative care. Despite all the benefits that have emerged with the introduction of laparoscopic cholecystectomy, post-operative pain remains an issue. Ineffectively treated post-operative pain is still one of the common surgical complications, and this medical problem may result in clinical and psychological changes that may increase morbidity and mortality as well as costs and may decrease the quality of life.[10]

The introduction of rapid and short-acting opioids, anesthetics, and neuromuscular blockers have facilitated the implementation of fast-track surgery [2], but side effects associated with opioids, such as PONV, can still occur. Infact, pain, and PONV are the most common causes for unexpected hospital admission [1]. Anesthetic and analgesic techniques that avoid or minimize opioid use may therefore be beneficial.

Esmolol is β adrenergic receptor antagonist that selectively affects the cardiovascular system. Its effect is rapid and it has a short half life. It is used as a supplement to reduce the hemodynamic responses to surgical stimulations. This β adrenergic receptor antagonist has a sympathetic nerve blocking effect on PONV and pain ,the benefits of β adrenergic antagonists in patients with cardiovascular diseases are well established [6]. Stressful interventions that cause intense activation of the sympathetic nervous system can result in cardiovascular consequences. Thus, β adrenergic antagonists can be targeted to attenuate this unwanted response [11]

Functional magnetic resonance imaging studies in humans have also demonstrated hippocampal activation during emotional distress [12], fear [13], and anxiety [14].This hippocampal activation results, in part, from the activity of stress-related factors, including norepinephrine, which enhances the excitability of hippocampal principal neurons via an interaction with hippocampal *n*-methyl-d-aspartate subtype glutamate receptors [15]. It then seems possible that the activation of hippocampal β adrenergic receptors might play a role in nociceptive processes. If so, then blockade of these receptors should blunt the contribution of such β-adrenergic activation to the nociceptive process, thereby resulting in the attenuation of perceived pain intensity.

We used esmolol in a dose of 1mg/kg bolus followed by an infusion at the rate of 5 to 10 μg/kg/min in our study and compared the incidence of postoperative analgesic requirements between two groups in first 24hours. In group E only 15 (50%) patients received post operative analgesics in the form of inj Diclofenac 50mg i/m as against 25 (83.33%) patents in group P.

Our study is consistent with the study don e by YE Moon et al [16] in which they concluded that intra operative esmolol infusion decreased both the requirement for sevoflurane and post operative administration of fentanyl.

Our study is showing similar results as obtained in a study done by Chai et al [9] in which they found that morphine consumption for first three post operative days was significantly reduced in esmolol group in women undergoing abdominal hysterectomy. Vincent Collard et al [17] found that amount of fentanyl required in post anaesthesia care unit was significantly less in esmolol group as compared to remifentanil and control group.

Our study is also consistent with the study done by Sang Jun Lee et al [18] in which they concluded that perioperative esmolol infusion contributes to significant decrease in PONV and post operative pain and facilitates early discharge. White et al.[8] using the gynecologic surgical model, administered 1.5 μg/kg of fentanyl at induction, followed by an infusion of esmolol, and found that this group required less postoperative opioids.

Secondary observations drawn from the study include mean heart rate which was compared between two groups and found to be statistically significant. It confirms that β blockade was achieved intraoperatively using esmolol infusion at the rate of 5-10 μg/kg. The mean value of mean heart rate (bpm) for group E and group P was 70.138 and 78.350 respectively. This is consistent with the study done by Ebert J P et al [19] as they concluded that esmolol blunted the heart rate response effectively in patients receiving esmolol infusion intraoperatively. The esmolol group also had the lowest incidence of post operative nausea and vomiting and received less antiemetics post operatively.

Limitations of our study include a small patient population. These beneficial results should be sought in studies with larger group of patients.

V. Conclusion

Our study suggests that, incidence of postoperative analgesia requirement over first 24 hours after laparoscopic cholecystectomy is less in esmolol group as compared to placebo group.

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