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Study of Preoperative Pregabalin on Acute Post Operative Pain Relief in Laparoscopic Cholecystectomy Patients: A Prospective Cohort Study

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ABSTRACT:-
Introduction-Although Lapcholecystectomy is a minimally invasive procedure it is associated with moderate to severe pain. Opioids given post operatively is associated with side effects. Now it can be managed with a multimodal approach using adjuvants like gabapentin and pregabalin. Pregabablin has anti hyperalgesic properties which is superior to gabapentin.
Aim- To study the effect of preop pregabalin as an adjuvant to morphine on postop pain relief and post op opioid consumption in lap cholecystectomy patients, time needed for rescue analgesia by the patients and the overall opiod consumption during a six hour period after surgery.
Materials and methods- This was a prospective cohort study with 100 patients of ASA I and II undergoing lap cholecystectomy. They were divided into 2 groups (A and B) of 50 each by random table distribution. Group A received pregabalin while group B received placebo one hour before surgery. Morphine was given to both groups during induction. Patients post op pain perception was assessed using Verbal numerical scale at hourly intervals upto 6 hrs. A VNS score of 4 or above was given rescue analgesic (intravenous Tramadol). The time duration from end of surgery to first analgesic demand was recorded. The total analgesic requirement was also noted. Sideeffects if any was also noted.
Results- the pain scores were comparably less in group A
than B with p value less than 0.05. The duration to request for analgesia was more for group A than group B. The prolongation of duration of analgesiawas statistically significant (p value 0.000).
Conclusion- Preoppregabalin is highly effective in providing post op analgesia after lap cholecystectomy with longer duration, reduced pain scores, less post op opioid requirements with less side effects.

Keywords:- Lap cholecystectomy, pregabalin, postoperative analgesia, verbal numeric scale.

I. INTRODUCTION

Laparoscopic cholecystectomy is a common surgical procedure done for various gallbladder diseases.[1] It provides a safe and effective treatment for most patients with symptomatic gall stones and it has become the treatment of choice for many of these patient and now has been even considered as a day care surgery.[2]Compared to open cholecystectomy, laparoscopic method is associated with less postoperative pain, decreased post operativeanalgesic requirement, early recovery and return to normal physical activity, shorter hospital stay and thus less hospital expenses.[3,4,5]In addition it also provides improved cosmesis and improved patient satisfaction.

With recent developments in laparoscopic surgery and because of short duration of surgery, small incision and low rate of immediate complications, laparoscopic cholecystectomy can be done as a day care surgery.[,6,7] This warrants modification of anaesthetic techniques for early recovery and effective postoperative analgesia with minimal sedation and minimal respiratory depression, Although laparoscopic cholecystectomy is a minimally invasive surgery with less postoperative pain, many of the patients experience moderate to severe pain in early postoperativeperiod.[8]As in any abdominal surgery inadequate analgesia is associated with an increased pulmonary and cardiac complications, increased chance of deep vein thrombosis, delayed recovery and development of chronic neuropathic pain, increasing overall cost of treatment.[9]

Uncontrolled postoperative pain may activate sympathetic nervous system and thereby contribute to morbidity and mortality, which may be important in the

Development of myocardial ischemia and infarction and[10[11] may also delay return of postoperative gastrointestinal function.**[11]**

Postoperative respiratory function is markedly decreased, especially after upper abdominal and thoracic surgery.Patients with poor postoperative pain control may breathe lessdeeply, have an inadequate cough, and be more susceptible to development ofpostoperative pulmonary complications.[12]

Control of acute postoperative pain may improve long-term recovery or patient-reported outcomes (e.g., quality of life).[13]Optimizing treatment of acute postoperative pain can improve health-related quality of life (HRQL).[14]

Several analgesic interventions are investigated for their influence on early pain after laparoscopic cholecystectomy. They include use of intravenous opioids like morphine, non-steroidal anti- inflammatory drugs like diclofenac sodium , gabapentin , NMDA receptor antagonists like ketamine, port site infiltration with local anaesthetics, intraperitoneal instillation ofbupivacaine,Transversus Abdominal Plane (TAP) block and epidural analgesia.[15.]As the pain arising from laparoscopiccholecystectomy is complex in nature, none of the above methods alone is found to be fully effective in providing analgesia and this requires use of multimodal analgesia.

Opioids are an important component of analgesia for the surgical patient in PACU but can produce dose-dependent side effects, including pruritus, nausea vomiting, urinary retention,respiratory depression and opioid induced hyperalgia(OIH)[16]. Postoperative nausea and vomiting cause delayed PACU discharge. Multimodal postoperative analgesia including the gabapentinoids and other medications has shown promise in postoperative analgesia, possibly by synergistic mechanisms.[17]

Pregabalin has anti-hyperalgesicproperties similar or superior to gabapentin[18]

Gabapentinoids are anti-convulsants with membrane stabilizing and anti-nociceptive effects. These drugs bind to the presynaptic α2–§ subunit of voltage-dependent calcium channel. The anti-nociceptive effect is believed to be related to the reduction of the Ca2+ influx at presynaptic terminals in hyperexcitedneurones, which may lead to the reduction of release of several excitatory neurotransmitters, including glutamate, norepinephrine, substance P, and calcitonin generated peptide. Thus, gabapentinoids appear to reduce the hyperexcitability of dorsal horn neurones that is induced by tissue damage. [19]

These advantages of pregabalin made us to do this study and

II. AIM

1) Primary objective-To compare the efficacy of a single preoperative oral dose of Pregabalin as an adjuvant to morphine in providing post operative analgesia.

2) Secondary objectives- assessment of severity of post operative pain, mean du ration of analgesia, overall opioid consumption for 6 hrs post operatively and to observe any complications or adverse effects.

III. METHODOLOGY

This prospective observational cohort study was conducted in a tertiary referral institute and constituted of 100 patients of ASA I and II status aged between 20-60 years undergoing elective laparoscopic cholecystectomy under general anaesthesia, patients with history of drug allergy, those with chronic pain syndromes, pregnant patients, and those with renal and liver impairment were excluded from the study.

Approval from institutional ethics committee and research committee were obtained. Informed consent was also obtained from the patients in their own local language.

Sample size

A total of 100 patients undergoing laparoscopic cholecystectomy were divided into two groups of 50 each either to receive pregabalin and morphine or placebo and morphine. Sample size is calculated according to the formula

$$n = (Z_\alpha + Z_\beta)^2 SD^2 \times \frac{2}{d^2}$$

For a significant level of 0.05 and a power 85%

Z_α=1.96 Z_β=0.84 SD=standard deviation d= effectsize

SD = (SD1 + SD2)/2, d = (P1-P2)

In the study conducted by Agarwal A et al[80]SD is 25. When d is taken as 15 sample size will be 43.

IV. METHODS

The 100patiens were allotted to 2 groups by using a random number table and was administered by a resident who was unaware of the study.

The two groups were

1) Group A – received pregabalin 150mg orally one hour prior to surgery and I/V morphine 0.1mg/kg as premedication ontable.
2) Group B - received placebo one hour prior to surgery and I/V morphine 0.1mg/kg as premedication on table.

The drug was administered 1 hour prior to surgery. On arrival in the OT, the patient was monitored with pulse oximetry, electrocardiogram, noninvasive blood pressure measurement. Intravenous access was secured with 18G cannula under local anaesthesia and fluids administered as per Holliday Segar formula. Patient was premedicated with midazolam (0.05mg/kg), ondansetron (0.1mg/kg), glycopyrrolate (0.01mg/kg) and morphine (0.1 mg/kg). Patient was induced with Inj thiopentone (5mg/kg), preservative free Lignocaine (1.5 mg/kg) and intubated with succinylcholine (1.5 mg/kg). Anaesthesia was maintained with N_2O, O_2 and Isoflurane. Muscle relaxation was attained with Vecuronium (0.08 mg/kg) and supplemented with boluses of 1mg intraoperatively. On completion of the surgery patient was reversed with neostigmine (0.05mg/kg) and glycopyrrolate (0.01mg/kg). Patient was then monitored in the post anaesthesia care unit. The patient's postoperative pain perception was noted using verbal numerical rating scale at hourly intervals till the patient complained of pain or 6 hours post operatively whichever is earlier. A verbal numerical rating scale score of 4 or more was given rescue analgesic opiods intravenously (Injection tramadol 1.5mg /kg). The time duration from the end of surgery to the first analgesic dose (period of analgesia) was recorded and compared. The total opioid consumption during a six hour post operative period was measured .Total number of patients who received rescue dose analgesic were counted. The study also intended to observe the occurrence of post operative nausea or vomiting and to make a note of any other adverse effectsnoted.

STATISTICAL ANALYSIS

Statistical analysis was done using Statistical Package for Social Sciences(SPSS). Data were expressed as mean and standard deviation. Chi-square test or Fischers test were used for comparison. P-value of less than 0.05 was considered significant.

V. RESULTS

Statistical analysis

Quantitative data like NRS pain score and time were summarized as mean and Standard deviation (SD) while qualitative variables were summarized as frequency and percentages. Quantitative variables were compared using students't' test while qualitative variables were compared using the chi square test. A p value of < 0.05 was considered as statistically significant. All the analysis was carried out by PASW statistics software's for windows (PASW 18, IBM SPSS corp, US.

Table 1. Demographic parameters

Variables	Group A	Group B	P value
Age in years	40.8 (8.8)	39.5 (8.7)	0.44
Weight in Kg	56.7 (9.1)	57.3 (7.6)	0.71
Males, n(%)	6 (12)	9 (18)	0.40
Duration of surgery in Minutes	96.4 (25.9)	102.9 (27.2)	0.23

Total of 100 patients were included in the study, and divided into two groups of 50 each. Of the 50 patients in group A, 44(88%) were females and 6(12%) were males. In group B, 41(82%) were female and 9(18%) were males. The groups were comparable with respect to gender as the p value is 0.4. Both the groups were comparable with respect to age, weight and duration of surgery with no statistical significance.

Table 2. NRS PAIN SCORE

Pain by Numerical rating scale	Group A	Group B	P value
NRS -0	0.42 (0.73)	1.22 (1.31)	< 0.001
NRS -1	0.56 (0.81)	1.80 (1.20)	< 0.001
NRS -2	1.26 (1.34)	2.24 (1.12)	< 0.001
NRS -3	1.52 (1.13)	2.86 (1.36)	< 0.001
NRS -4	1.90 (1.40)	2.92 (0.99)	< 0.001
NRS -5	2.38 (1.23)	2.92 (0.940	0.02
NRS -6	2.30 (1.11)	2.76 (0.74)	0.02

The pain scores were analysed using Numerical Rating Scale (NRS) scale every hour for 6 hrs. It was found that the mean pain scores were significantly lower at all time intervals in group A than B and was statistically significant, p value less than 0.05.

Table 3 . Rescue analgesia duration and total analgesic requirement

Variables	Group A	Group B	P value
Duration to rescue analgesia in minutes	333.6 (60.5)	260.6 (104.4)	< 0.001
Total tramadol requirement in mg	23.0 (40.7)	34.0 (35.6)	0.15

The analysis of results show that the duration to request of rescue analgesia is more in Group A(333.64± 60.494 minutes) when compared to Group B
(260.6±104.395 minutes)

The total analgesic requirement in first 6 hours in both groups was calculated. Mean tramadol requirement in group A (Pregabalin) was 23.00±40.670 mg and in group B was 34.00±35.628 mg Figure 14). Average number of bolus in Group A is 0.44 and Group B is 0.66. There is a difference in tramadol requirement although it is not
Statistically significant (P value is 0.153) and the number of boluses of rescue analgesic given between these groups are insignificant as the p value 0.154.

Table 4 . Adverse effects

	Group		Total
	A	B	
No adverse effects	**39**	**46**	**85**
Somnolence	**10**	**0**	**10**
Nausea and vomiting	**1**	**4**	**5**
Total	**50**	**50**	**100**

10 patients in group A experienced sedation. There is significant sedation in group A compared to group B with less nausea and vomiting in group A.

VI. DISCUSSION

The observational study was done with the objective of investigating the efficacy of single preoperative dose of oral pregabalin as an adjuvant to morphine in providing post operative analgesia. Other objectives included comparing the severity of pain experienced by the patient during a 6 hour post operative period expressed in terms of verbal numerical rating scale and the time till the request of rescue analgesia which was defined as a pain score greater than or equal to 4 among the two groups. The study also observed the number of doses of rescue analgesics consumed during a six hour post operativeperiod and any adverse effects occurred.

Pregabalin binds to the α2δ-1 subunit of presynaptic voltage-gated calcium channels in the CNS. The analgesic effects may be related to calcium influx inhibition as well as inhibition of the release of excitatory neurotransmitters in spinal and supraspinal pathways. It was hypothesized that its use as an adjuvant to an opioid (morphine) could bring about better pain relief and thereby decrease postoperative opioid consumption.

Clearance from institutional research committee and ethics committee was obtained. Sample size calculated after discussion with the statistician.Of 100 patients 50(groupA) received oral pregabalin 1 hour before surgery and remaining 50(group B) received placebo. A time period of 1 hour prior tosurgery was chosen as pregabalin is rapidly absorbed after oral administrationwith 90% bioavailability and peak plasma concentrations seen after just 1 hour as per literature. The groups were comparable with respect to sex ,age, weight , ASA status and mean duration of surgery. The dose of 150 mg was chosen for Pregabalin as it was the dose used most frequently in studies. Administration of higher doses was associated with adverse effects like somnolence, dizziness, ataxia, blurred vision[20,21]

The NRS pain score were significantly different between the groups at all time frames and the pain scores were significantly less in Group A(P value<0.05)[Table4,Figure12].This finding is in concordance with that of Gianesello L and colleagues.[22]They found out that during the first 8 postoperative hours, VAS scores at rest were significantly lower in the pregabalin group than in the placebogroup.

Agarwal A and et al,in his study,concluded that oral pregabalin 150 mg administered before operation was effective in reducing postoperative pain and postoperative patient-controlled fentanyl requirement in patients undergoing laparoscopic cholecystectomy.[23]. Our study also showed reduced requirement for analgesics in the post operative period.

In the study by Reuben and colleagues, pregabalin 150 mg was found to be as effective as celecoxib in reducing post operative pain and morphine consumption.[24] This supports our study in the aspect that pregabalin can reduce post operative pain and opioid consumption

Jokela and colleagues observed that analgesia was better after premedication with pregabalin 150 mg with lesser side effects than a dose of 300mg.[25] A dose of 300 mg pregabalin is associated with increased incidence of side effects which made us to do our study with 150 mg dose.

Paech and colleagues found out that 100 mg pregabalin was ineffective in reducing post op pain after hysterectomy. It could be due to reduced recommended dose of pregabalin .[26]

Meta analysis of RCT's done previously to prove the efficacy of pregabalin in management of acute post operative pain done by Zhang and colleagues showsthat opioid consumption during the first 24 hours after surgery was significantly reduced by pregabalin and reduced opiod induced nausea and vomiting.[27]

Sarakatsianou and et-al obtained similar result from their study using 600 mg pregabalin(2 divided dose) in laparoscopic cholecystectomy patients.They concluded that administration of oral pregabalin in two divided dose pre operatively significantly reduced post operative pain as well as opiod consumption at the cost of increased incidence of dizziness.[28] In our study we gave pregabalin as a single dose and was associated with lesser opioid requirement.

P. W. H. Peng and et al found that low dose pregabalin (75mg) provided limited analgesic benefit in patients undergoing laparoscopic cholecystectomy.[29]. Low dose pregabalin does not have good analgesic effect as a dose if 150-300 mg .This made us to give 150 mg of pregabalin and has shown to have analgesic effect.

Thus the study is in accordance with many of previous studies in literatures that suggest oral pregabalin is an effective adjuvant to morphine in reducing postoperative pain and opioid related side effects. The study also observed that the number of additional boluses of rescue analgesia requested by the group A(pregabalin) was lesser than that of group B. This fact points to an opioid sparing effect but a statistically significant association could not be proved. Findings of this study suggest that oral pregabalin is a good option as an adjuvant medication to morphine to reduce opioid consumption post operatively. This in turn can facilitate faster discharge from post anesthesia care units and faster rehabilitation.

Adverse event observed was somnolence. Somnolence was observed in 10 patients out of the 50 patients, but they were easily woken up by calling their names. But none of the patients was so deeply sedated that they could not maintain airway after extubation. No cases of aspiration or hypoxia occurred. Nausea and vomiting were less in group A(pregabalin) compared to Group B.

Limitations of the study:

The dose of pregabalin used is in accordance with what is used by investigators in various studies as per literature. There are no RCTs suggesting a definite mg/kg dose for pregabalin. Using a fixed dose 150 mg for a wide range of patient weights can cause different effect site concentration of the drug in patients with different weights that can affect the drug effect and hence the study.

The pain scale used is numerical rating score, pain perception and tolerance may vary from patient to patient. Visual analogue scale (VAS) should have been used instead of Numercal Rating Scale (NRS) even though technically difficult. Also in our study only rest pain after laparoscopic

cholecystectomy was assessed, dynamic pain assessment is more important than static pain to facilitate early mobilization.

VII. CONCLUSION

Preoperative oral pregabalin when administered with opioids decreases the severity of acute post operative pain in laparoscopic cholecystectomy patients, prolongs the period of analgesia, reduces opiod consumption in the post op period and thereby reduces the opioid related side effects.

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Conflicts of interest- Nil

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