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A Randomized Controlled Study for Comparative Evaluation of Pre-Emptive Single Dose Analgesia with Pregabalin Vs. Lumbar Epidural Analgesia Using Bupivacaine in Adult Patients Undergoing Laparoscopic Surgeries on Post Operative Pain and Haemodynamics.

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ABSTRACT: Background: Postoperative pain is the dominating complaint and the primary reason for prolonged convalescence after laparoscopic surgeries. We have evaluated the efficacy of preemptive single dose Pregabalin for attenuating postoperative pain after laparoscopic surgeries over invasive lumbar epidural analgesia using bupivacaine.

Method: 90 adults (18-68yr),ASA status I and II,of either sex undergoing elective laparoscopic surgeries were included in this randomized study. Subjects were divided in three groups of 30 each as C for control, E to receive lumbar epidural analgesia 10 ml of 0.25% bupivacaine given before premedication and induction of anesthesia and P to receive Pregabalin 150mg orally,1hr before surgery. Postoperative hemodynamics and pain were assessed by a 100 mm Visual Analogue Scale, where 0, no pain;100,worst pain. Results were analyzed by Chisquare test, one way ANOVA and multiple comparision:Tukey test.

Result: Postoperative pain, hemodynamic instability and PONV were reduced in Pregabalin group compared with lumbar epidural analgesia and control group.($p<0.005$)

Conclusion: Asingle preemptive oral dose of Pregabalin 150 mgis aneffective method for reducing postoperative pain.

I.INTRODUCTION:

Nowadays Laparoscopic surgery has gained popularity because it offers several advantages compared to traditional open surgical technique such as reduction in overall medical costs reduced bleeding, less post-operative surgical and pulmonary complications, and early recovery.Although the magnitude of pain can be expected to be reduced when compared to open procedures, pain may still be a significant factor during the postoperative recovery period following laparoscopic surgery.(1)

Preemptive analgesia is a protective analgesic modality that is initiated before and is operational during the surgical procedures in order to reduce the physiological consequences of nociceptive transmission provoked by the procedures. Its aim is to minimize sensitization induced by noxious stimuli arising throughout the perioperative period.

Pregabalin is a lipophilic gamma-amino-butyric acid (GABA) analog with anticonvulsant, anxiolytic and sleep-modulating properties. Recently pregabalin has demonstrated analgesic effects in various clinical trials as preemptive analgesic for acute post op pain management of laparoscopic surgeries.(2)

Epidural analgesia has emerged as very safe technique for abdominal surgeries also for post-operative analgesia. (3)

However, epidural analgesia though effective is an invasive, relatively expensive and demanding high degree of care from insertion to removal of catheter. Hence we decided to compare this method of pain relief with a single preemptive analgesic i.e. oral pregabalin which is easy to administer, cost effective and will not need too much of care as a method of analgesia.

II.MATERIAL AND METHODS

This randomized, prospective, controlled study was carried out in the department of anesthesiology, MGIMS, Sevagram Maharashtra after approval of Institutional Ethical Committee. 90 patients of ASA I-II grade between 18-65 yrs of either sex scheduled for elective surgery (non-cardiac) under general anesthesia requiring endotracheal intubation were included. Excluded patients were those who refused giving consent, patients with anticipated difficult intubation

(Mallampati grades III ,IV), or who were hypertensive or had respiratory, cardiovascular ,neurological, psychological, hepatic, renal and endocrinal disease or on any medication like sedatives or opioids, alcohol abuse history or drug allergy, lactating or pregnant patients. Study was carried out in period ranging between years 2018-2019 over 18months.

Informed written consent for study in patient's language was taken and patients were randomly allocated into 3 groups of 30 each by computer generated table. Group P (n=30)= pregabalin group received 150 mg oral pregabalin 1 hr prior to surgery; Group E(n=30)= Epidural group received 10 ml of 0.25% bupivacaine before premedication and induction of anesthesia; Group C (n=30) =control group neither received pre-emptive pregabalin nor epidural analgesia

On the day prior to surgery a thorough pre-operative assessment of the patient was performed including general physical & systemic examination. All patients were explained about anesthesia technique & written informed consent was taken. Patients were kept NBM for 6 hrs prior to surgery Patients premedicated with oral ranitidine 150 mg and Alprazolam (0.25 mg) on night before surgery.In group P(n=30), patients were given 150 mg tab pregabalin 1 hr prior to surgery and shifted to OT after 1 hr.

In the OT, standard monitors (ECG, Noninvasive blood pressure and pulse oximeter) were attached to the patient , and baseline vitals namely heart rate (HR),pulse oximetry (SPO2), blood pressure(BP), Mean Arterial Pressure (MAP), respiratory rate (RR) and Electrocardiogeram (ECG) were recorded.After securing an 18G IV line,patients were preloaded with 10 ml /kg ringer's lactate.In group E(n=30) patients, epidural catheters were placed at L1-L2 intervertebral space and 3 cc test dose with 2% lignocaine with adrenaline was given and 10 ml of 0.25% bupivacaine was given before premedication.

Anesthesia technique: Anesthesia machine and breathing circuits checked, resuscitation equipments were kept ready. Vital parameters were continuously monitored.Preoxygenation was done for 3 min with 100% oxygen. IV premedication on table- glycopyrolate 5 mcg/kg , midazolam 0.02mg/kg, fentanyl 2mcg/kg.IV infusion with crystalloid RL 6-8mL/kg/hr.

Induction of anaesthesia: IV propofol 2mg/kg, IV atracurium 0.6mg/kg to facilitate endotracheal intubation. The patients were ventilated through bag and mask with 100% oxygen with BAINS circuit for next 5 Minutes to maintain ETCO2 between 30-40 mmHg. Thereafter, laryngoscopy was performed by senior anesthesiologists with Macintosh laryngoscope and intubation done with a cuffed endotracheal tube of appropriate size within 30 seconds.Anaesthesiawas maintained with o2 +air+isoflurane and atracurium to maintain muscle relaxation and intraoperative analgesia. Patient was mechanically ventilated using circle system to keep EtCo2 between 35-45 mmHg and Tidal Volume of 6-7 ml/kg. Intraabdominal pressure was maintained at 12-14 mmHg throughout the laparoscopic procedure. Patients received inj Paracetamol 1gm IV (15mg/kg dose) and inj Diclofenac sodium 75 mg IM 30 min after induction and intubation.

All patients received local infiltration with 10ml of 0.25% bupivacaine in all laparoscopic ports at the time of closure of wound.

Intraoperative vital parameter recording was done for HR, SBP, DBP, SPO2 at following intervals:Baseline before pre medication, after induction (5min), after insufflation (5min),afterdesufflation (5min), after extubation (5 min)

After procedure, neuromuscular blockade was reversed using inj Neostigmine 0.05mg/kg and Inj Glycopyrrolate0.01mg/kg. After adequate return of tone and good breathing efforts of the patients, they were extubated and epidural catheters were removed from the group E patients.

In the recovery room , a senior resident who was not part of the anesthesia team recorded the HR, BP, SPo2, VAS score ,sedation status(Ramsay sedation score) at 0 hr,1hr, 2hr, 4hr and 6 hr. Any patient having PONV, bradycardia requiring atropine treatment , desaturation or requiring airway support were observed and noted. Recovery staff was instructed not to give any analgesia to the patient without informing the observing senior resident. Rescue analgesia was provided in the form of i.vDiclofenac 1.5mg/kg if VAS score was more than or equal to 4. Time of 1st rescue analgesia and duration of pain relief were noted. Rescue antiemetic was provided in the form of i.vondansetron 0.08mg/kg.

Statistical analysiswas done by using descriptive and inferential statistics using Chisquare test, one way ANOVA and Multiple Comparison: Tukey Test and software used in the analysis were EPI-INFO 6.0 version, STATA, SPSS 17.0 version and GraphPad Prism 6.0 version. EXCEL spreadsheet was used for electronic data entry. Descriptive data presented as mean +/- SD. The comparisons considered as not significant ($p > 0.05$),significant ($p < 0.05$) or highly significant ($p < 0.001$) . Using

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the results of previously conducted study and considering an α error of 0.001 and β error of 1.282, with power of 90 % and p1 as 98 and p2 as 90, in the below stated formula the sample size of 30 in each group wasderived.

$$n = \frac{2(Z\alpha+Z\beta)2\ (S1^2 + S2^2)}{(x1- x2)^2}$$

Zα=3.29 , Zβ=1.282 , power=90% , q=6
S1= standard deviation of Pregabalin group
S2= standard deviation of Epidural group

III.RESULTS:

The demographic profile of the patients in terms of age, body weight, male:female ratio, ASA status, Mallampati Class were comparable and no significant differences found among the three groups (P > 0.05).**(table 1)**

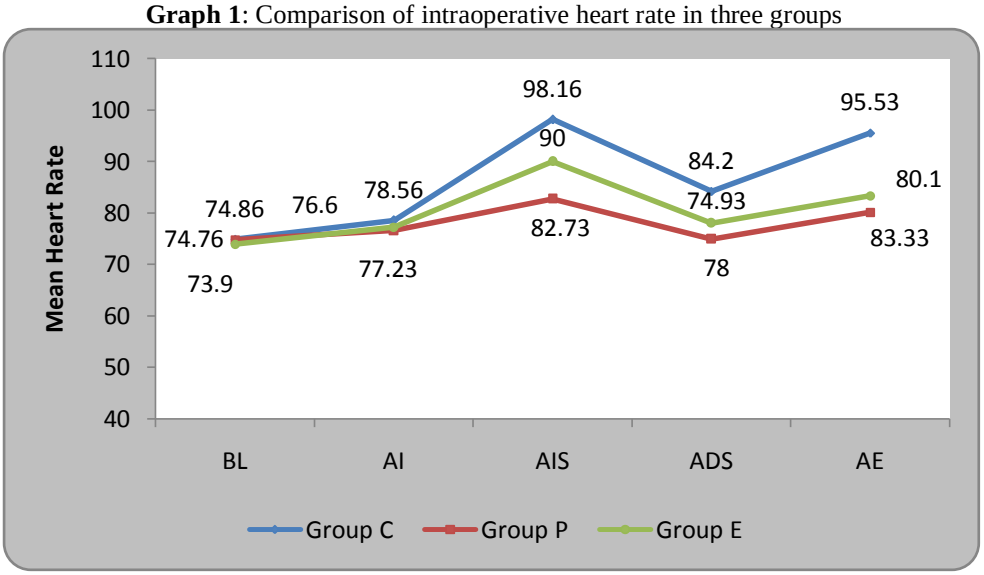
Table 1. Comparison of demographic data between 3 groups

Parameters	**Group C**	**Group P**	**Group E**	**p- value**
Age	36.9±16.38	41±15.37	40.53±13.84	0.23
Gender(m/f)	17/13	18/12	15/15	0.73
BMI(Body Mass Index)	22.36±2.52	21.96±2.89	22.46±1.42	0.89

A.Intraoperative Monitoring

1) HEART RATE

Graph 1: Comparison of intraoperative heart rate in three groups



As shown in graph no 1, the statistical evaluation of mean heart rate at the baseline before premedication and after Induction immediately after 5 minwas statistically non significant between all groups.5 min after insufflation of CO2,afterdesufflation of gas immediately after 5 min and after extubation (5min) the statistical evaluation of mean HR between group C and group P was significant (p=0.0001) and between group P and E was non-significant.

2) MEAN ARTERIAL PRESSURE(MAP)

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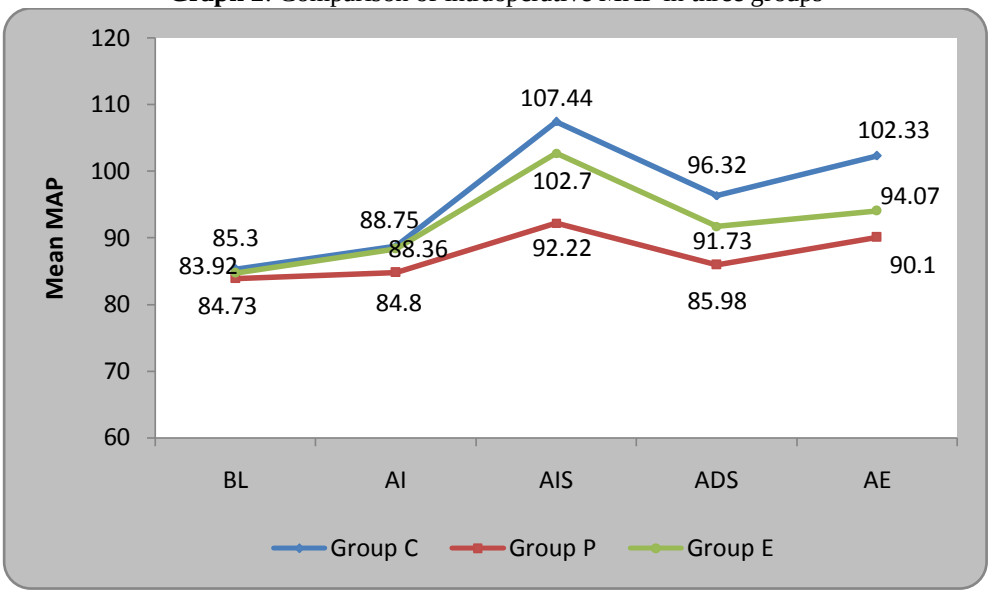
Graph 2: Comparison of intraoperative MAP in three groups

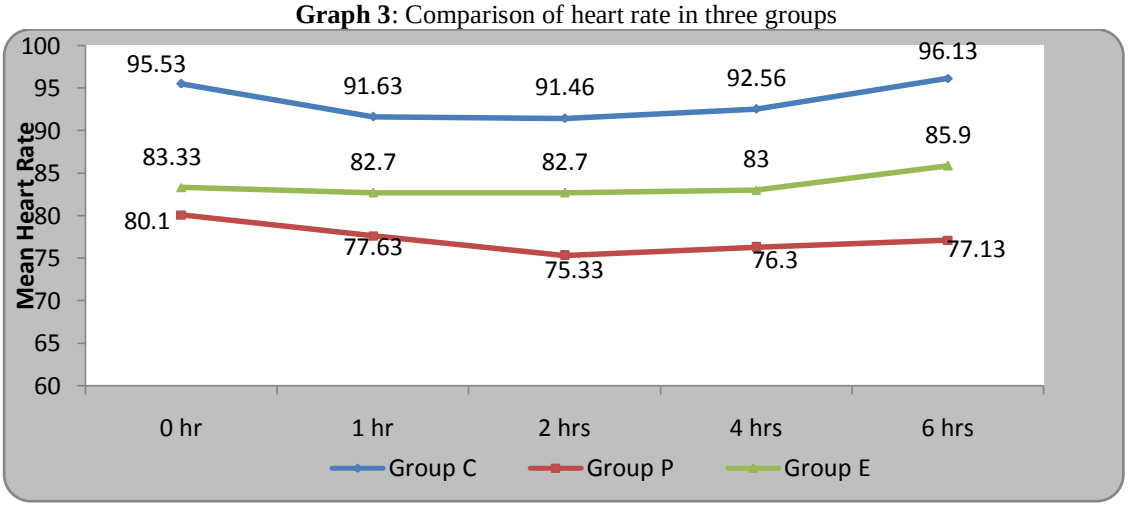


As shown in graph no 2, the statistical evaluation of MAP at the baseline before premedication andafter Induction immediately after 5 min was statistically non significant between all groups. 5 min after insufflation of CO2,after desufflation of gas immediately after 5 min and after extubation (5min) the statistical evaluation of MAP between group C and group P was significant (p=0.0001) and between group P and E was non-significant.

B.POSTOPERATIVE MONITORING:

1) HEART RATE

Graph 3: Comparison of heart rate in three groups



As shown in graph no 3 ,at 0, 1, 2 , 4 and 6 hr after extubation the HR changes were statistically highly significant (p=0.0001) throughout between group P and group C. Between group E and group C it was highly significant throughout (p=0.0001)

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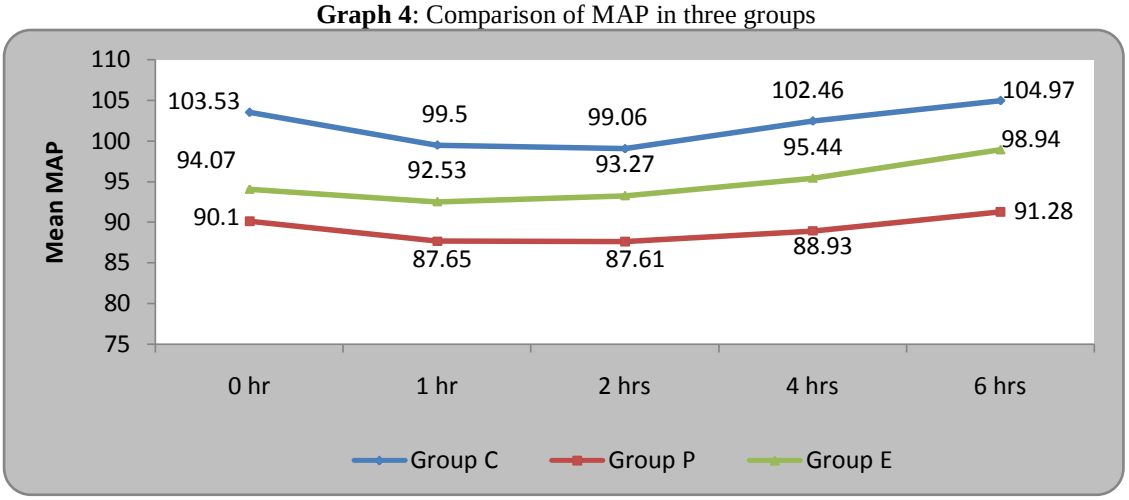
2)MEAN ARTERIAL BLOOD PRESSURE (MAP)

Graph 4: Comparison of MAP in three groups

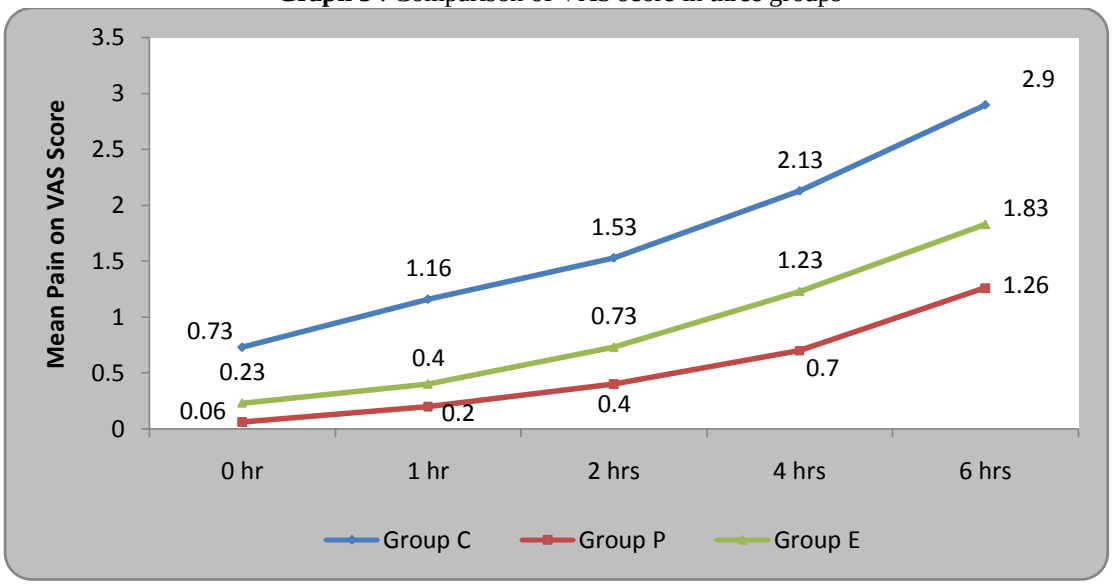


As shown in graph no 4 ,at 0, 1, 2 , 4 and 6 hr after extubation the MAP changes were statistically highly significant (p=0.0001) throughout between group P and group C also between group E and group C.

Between group P and group E the mean MAP changes at 0 hr and 1 hr were non- significant (p=0.403) and (p=0.094) respectively. At 2 hr, 4hr and 6 hr after extubation the mean MAP between group P and group E was statistically significant.(p<0.005)

2)VISUAL ANALOGUE SCORE (VAS)

Graph 5 : Comparison of VAS score in three groups



As seen in this graph no 5, the VAS score between group P and group C was statistically highly significant (p<0.01) at 0 hr, 1 hr , 2 hr, 4 hr and 6 hr after extubation. The VAS score between group E and group C was also statistically significant throughout the study.

The VAS score between group P and E was statistically non significant at 0 hr, 1 hr, 2 hr and 4thhr after extubation. At 6thhr the VAS score between groups P and E was significant.(p=0.044). This showed that the pain relief was better with pregabalin and epidural as compared to control group. And the pain relief was even better with pregabalin in post operative period as compared to epidural group.

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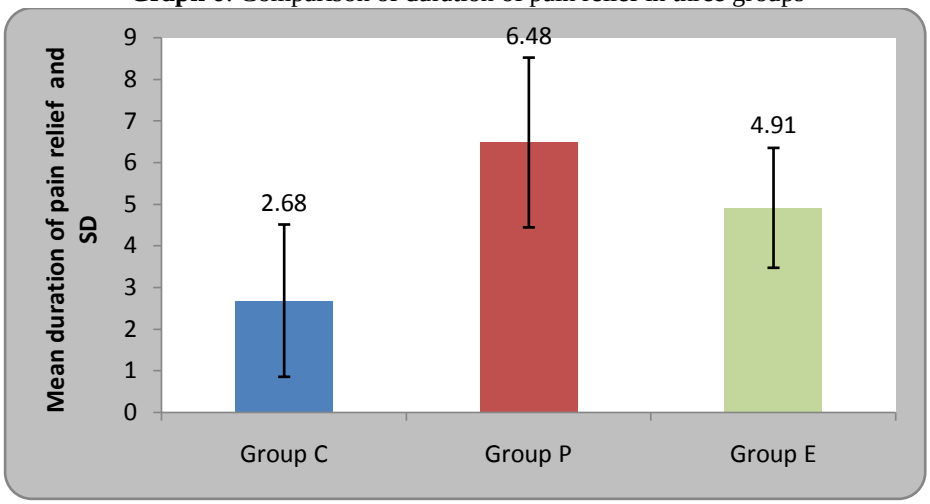
3)DURATION OF PAIN RELEIF

Graph 6: Comparison of duration of pain relief in three groups



As observed in the above graph no 6, the mean duration of pain relief in all three groups was statistically significant. The mean duration of pain relief in group P in post operative period was 6.48 hrs which was much higher than group E (4.91hrs) and group C (2.68 hrs)

The statistical evaluation of mean duration of pain relief between groups P and C; groups E and C; groups P and E was statistically highly significant.

4)RAMSAY SEDATION SCORE (RSS)

For assessing the sedation levels in the patients of all three groups, RSS was used which was found to be non significant between groups C, E and P.

C.COMPICATIONS

1)Post Operative Nausea and Vomiting (PONV)

Table 2: Distribution of patients in three groups according to PONV

PONV	Group C	Group P	Group E	⨯2-value
Present	6(20%)	0(0%)	1(3.33%)	9.60 p=0.008,S
Absent	24(80%)	30(100%)	29(96.67%)	
Total	30(100%)	30(100%)	30(100%)	

The statistical evaluation between these three groups was significant. (p=0.08)

Other complication that is bradycardia, patient requiring airway support, desaturation were also monitored for 6 hrspostoperativey and found to be non significant among all the three groups.

IV.DISCUSSION

Although, laparoscopic cholecystectomy is a minimally invasive procedure, it is associated with intraabdominal, incisional and shoulder pain after surgery. Postoperative abdominal and shoulder pain are the most common complaints after elective laparoscopic surgery.(4)

Joris and colleagues (5) reported that after laparoscopic cholecystectomy, visceral pain predominates in the first 24 h but subsides from a peak soon after operation, whereas shoulder pain, minor on the first day, increases and becomes significant on the following day.

Preemptive analgesia can improve patient comfort, decrease postoperative morbidity and have the potential to effect health care savings.(6)

Pregabalin is a newer Gabapentinoid with greater potency and a more favorable pharmacological profile than Gabapentin. (7) Epidural analgesia has emerged as a very safe technique for abdominal surgeries as well as for post-operative analgesia, with only occasional complications reported. (8)

In this study we have compared the two techniques of preemptive analgesia in laparoscopic surgeries; one of which is a single dose oral pregabalin 150 mg 1 hour before surgery and other one is preoperative lumbar epidural analgesia using 10 ml 0.25 % bupivacaine.

Dosages Of Drug Selected

A Agarwal(9) ,ZAsgari(10), Cabrera(11), Kumkum(12) have found that that 75 mg dose of pregabalin is less effective for attenuating

postoperative pain and 300 mg dose is associated with greater sedation score and hence 150 mg dose the most appreciated and safe. On the contrary, Paech reported that a single preoperative dose of 100 mg pregabalin was ineffective in reducing acute postoperative pain or improving recovery after minor surgery.13)

Since most of the authors found 150 mg dose safe and effective for perioperative hemodynamic stability and attenuation of postoperative pain, 150 mg dose was selected.

In this study, for group E, 10 ml 0.25 % bupivacaine was used for lumbar epidural analgesia. This concentration from 10 ml to max 20 ml volume is recommended by FDA for epidural analgesia to achieve sensory block. (14) Similar concentrations have been used in studies by VSuryavanshi(8), S.Ozcan(15)

HEAMODYNAMIC CHANGES

We observed that patients who had received 150 mg Pregabalin or epidural analgesia with 10 ml 0.25 % Bupivacaine had better hemodynamic stability in perioperative period.Similar to our study Pregabalin was found effective in maintaining hemodynamic stability perioperatively by authors such as D.singh, K.Gupta(16)(12)

Epidural analgesia was found to provide stable hemodynamics in laparoscopic surgeries. SBP and DBP were successfully attenuated in Combined Epidural GA group. There was significant rise in HR, BP in control group. Similar results were observed by V.Suryavanshi(8), Funayama(17), Qu DM (18), Von Dossow(19)

POSTOPERATIVE PAIN

In our study we assessed VAS score at 0hr,1hr, 2 hr, 4 hr and 6 hrs postoperatively. Rescue analgesia was provided byi.vDiclofenac 1.5 mg/kg if VAS score was ≥ 4. For the 1^{st} 2 hrs in the postoperative period, none of the patients in pregabalin group required rescue analgesia. In group E 3.33 % patients and in group C 33.33% patients required rescue analgesia .At 4^{th}hr, 10 % patients in pregabalin group, 16 % in epidural group,63% in control group required rescue analgesia.

The mean duration of pain relief in group P and E was 6.48 hr and 4.91 hrs respectively whereas in group C it was 2.68 hrs. These results reflected the better control of postoperative pain in group P and E than control group.M.Luchetti have also observed similar results in their study and have concluded epidural analgesia as effective and safe technique for postoperative pain control.(24)

Cabrera in their study observed significantly lower VAS scores in pregabalin group as compared to placebo and morphine consumption was also less in pregabalin group.(11) Sebastian in their study have noticed longer duration of pain relief and reduced number of rescue analgesics requirement in 24 hr in pregabalin group as compared to control group.(20). Various authors have observed similar results in their studies as U.Bafna(21), Bindu(22), Cabrera (11), Balaban(23)

In this study overall longer mean duration of pain relief with pregabalin group as compared to epidural group was observed.

Similar to our study, Agarwal(9) found that pregabalin significantly decreased pain in patients during movement and at rest after laparoscopic cholecystectomy surgery. These results have been confirmed by Carmichael (25)Ittichaikulthol(26)Noriyuki Matsutani(27)

SEDATION

As per the RSS, all the patients were cooperative, oriented and RSS were found to be statistically non-significant ($p>0.05$).

Similar results were observed in other studies like A Agarwal(9), Balaban(23), Z Asgari(10).

PONV AND OTHER SIDE EFFECTS

In our study it was found that in group C 20%, in group E 3.33 %, in Group P 0 % patients had PONV. The difference was statistically significant. ($p=0.008$)

All groups were observed for other complications as hypersensitivity, bradycardia, airway obstruction, desaturation (SPO2<90%). None of the patients had these complications.

Thus, our study demonstrated that single preemptive oral tablet of 150 mg pregabalin maintains hemodynamic stability and postoperative analgesia for longer duration in comparison to Lumbar epidural analgesia and control group without significant sedation and other adverse effects in laparoscopic surgeries.

V.CONCLUSION

From this study it can be concluded that Pregabalin given orally in dose of 150 mg 1 hr prior to surgery as compared to 10 ml 0f 0.25 % of Bupivacaine by lumbar epidural analgesia before induction in patients scheduled for elective laparoscopic surgeries under general anesthesia had lower VAS scores in postoperative period, longer time of requirement of rescue analgesia in post-operative period, provided better hemodynamic stability of patients perioperatively, lesser incidence of PONV and other side effects.

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