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Original Research Article

A Comparative Study of the Effect of Oral Pregabalin Versus Oral Clonidine as Premedication on Early Postoperative Pain, Sedation in Laparoscopic Hysterectomy Under General Anesthesia

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Abstract:

Background: Premedication is the cornerstone of good anesthesia practice. Pregabalin a lipophilic (GABA) analog, a novel anti-convulsant drug and has analgesic effect. Premedication with Clonidine alpha-2 agonist abolishes the stress response to the painful surgical stimulus by inhibiting pre- and possibly the post-synaptic α-2 adrenergic receptors in the spinal cord and medulla. Thus, we aim to compare the duration of postoperative analgesia, sedation, and recovery scores with premedication with oral Pregabalin versus Clonidine during the 1st 24 hours post-surgery among the patients posted for laparoscopic hysterectomy.

Materials and methods: This study was performed on 90 patients of ASA 1, of age 35 to 65 years female posted for laparoscopic hysterectomy, assigned to either of 3 groups of 30 participants randomly. All patients have taken oral Alprazolam (0.5 mg) at night before the operation. Preoperatively, patients had taken oral Pregabalin 75 mg tablet (group A, n=30), Clonidine 150 mg tablet (group B, n=30), and oral placebo tablets in group C(n=30) 60 minutes before surgery. Patients were induced with the injection of Fentanyl, Propofol, and Vecuronium Bromide, and anesthesia was maintained with N_2O and O2 gas mixture with Isoflurane.

Result: It was observed that all most all patients in group A experienced mild pain up to 4 hours postoperatively with VAS score not going more than 3 on average, while 5 patients in Group B experienced moderate pain after 2 hours of surgery, and the 4-hour VAS score was 4 or more on an average. There was not much difference in modified RSS score in group A and group B just after surgery, but 1hr post-operative score was higher among group A in comparison to group B (1.83 in group A *vs* 2.30 in group B). Modified Aldrete score was also observed to be less in the premedicated group compared to the control (9.73 in group A *vs* 9.70 in group B *vs* 10.00 in group C).

Conclusion: It was concluded that clonidine and pregabalin both provide similar pain relief and sedation in the immediate postoperative period in our study. Pregabalin 75 mg pre-emptively provides better analgesia than clonidine 150 mcg. These two drugs are good pre-emptive analgesics for surgeries under general anesthesia and can be used alternatively.

Keywords: Post-operative analgesia, sedation.

Introduction

The meaning of the word "Poena" is punishment. Pain is the result of ongoing and impending tissue injury. Conventional analgesia in the postoperative period consists of opioids, non-steroidal anti-inflammatory drugs (NSAIDs), or regional procedures which are associated with their respective side effects [1].

Excessive use of NSAIDs has been reported with, renal toxicity, gastrointestinal bleeding, and thromboembolic complications as their adverse events, where regional analgesia demands additional intervention and it also has possible risks of hypotension and bradycardia. [1-3] Hence, an ideal drug search continues which has anxiolytic properties without any adverse effects of conventional analgesics [1].

Testing new analgesics drug as well as employing a multi-modal strategy of analgesia to enable patient improvement and reduce the requirement for opioids is the key in acute pain research. [1,2,4] Pregabalin a is a novel analgesic, lipophilic gamma-amino-butyric-acid (GABA) analog, it acts by binding to the α-2 subunits of voltage-gated calcium ion channels thus reducing the central sensitization. This explains its anti-nociceptive and anti-hyperalgesic properties.[3]

Clonidine an α-2 agonist is now being exceedingly used pre-emptively mostly because it decreases the anesthetic and analgesic requirements and provides sedation and anxiolysis.[4] Clonidine premedication reduces the stress response to the surgical stimulus by blocking the pre and possibly the post-synaptic α-2 adrenergic receptors in the medulla and the spinal cord.[1]

The study aimed to compare the duration of postoperative analgesia, sedation, and recovery scores in pre-medication with oral pregabalin versus clonidine versus placebo tablet in the first 24 hours postoperatively in patients undergoing total laparoscopic hysterectomy.

The primary objective is to assess the degree of analgesia at 0, 2, 4, 6, 12, and 24 hours postoperatively in the Pregabalin group and the Clonidine premedicated group in comparison with a placebo group. The secondary objective is to assess the degree of sedation and recovery scores with the individual study drugs and the occurrence of side effects like excessive sedation, dizziness, nausea and vomiting, visual disturbances, and hypotension associated with individual drugs.

Materials and Methods

Study design: The current study was a randomized control study was conducted after Institutional Ethical Committee approval as well as written and informed consent from the enrolled participants, in the Department of Anaesthesiology, IMS and SUM Hospital, Bhubaneswar. The sample size of our study was calculated based on the previous comparative study by Nadia M Bahgat et al [5], taking into consideration the power of the study of 80%, the confidence interval of 95%, the z value of 1.96, the sample size was 28 in each group.

Assuming a 10% dropout rate,30 patients in each group were taken as our final sample size (Fig 1) by Open Epi software.

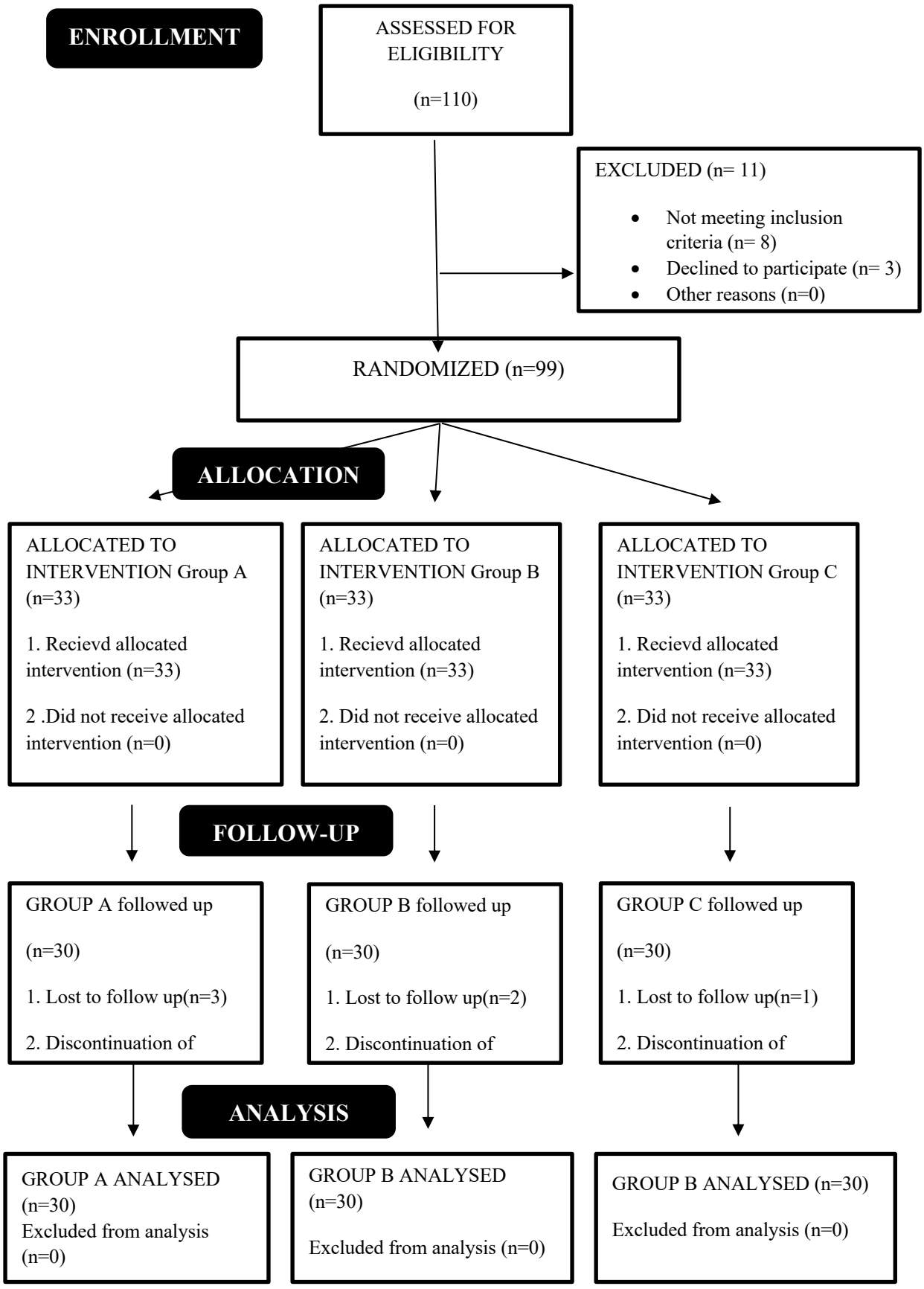

Fig 1: Consort flowchart

The study participants were female (35 to 65 years) of ASA grade-I & II physical status posted for elective laparoscopic hysterectomy. Those patients who refused to participate, belonging to ASA grade III/IV status, any known allergies to clonidine or pregabalin, with any chronic pain syndrome under treatment with any GABAergic drugs, and in whom laparoscopy was converted to laparotomy are excluded from the study. The degree of Pain was measured by Visual Analogue Scale (VAS) on a10 point scale after shifting them to the recovery room (0 hours) and then at1,2,4,6,12 and 24 hours after operation. Degree of sedation measured by Ramsay Sedation Scale (RSS) at 0,6,12 and24 hours after the operation. Recovery was measured using a Modified Aldrete score in the recovery room before discharge to the ward.

Study settings:

This randomized study was performed on patients posted for a laparoscopic hysterectomy at IMS and SUM hospital, Bhubaneswar, India, where the participants were randomly allocated into three equal groups, after excluding the participants who either refused to participate or failed to meet the inclusion criteria.

Patient enrolment:

The patients were allocated into group A (n=30) patients will be receiving an oral pregabalin 75 mg tablet, group B (n=30) patients will be receiving an oral Clonidine150 mcg tablet, group C (n=30) patients will be receiving an oral placebo glucose tablet. After obtaining informed consent, the selected patients underwent a thorough pre-anesthetic check-up and were kept fasting overnight.

All patients were given oral Alprazolam(0.5mg) the night before the operation. In the pre-operative area, the selected patients received the prescribed drug for the particular group they have been allotted to with just a sip of water 60 minutes before surgery.

Thereafter, the patients were shifted to the operation theatre where good intravenous access was secured and iv fluid (Ringer lactate/0.9% normal saline) was given. After attaching all the standard monitors, all patients were pre-medicated with intravenous inj. Glycopyrrolate 0.2mg, inj. Midazolam 0.02mg/kg of body weight and pre-oxygenated for 3 minutes.

Then Fentanyl 2mcg/kg body weight was given and the patient was induced with a bolus injection of 1% Propofol (2-3 mg/kg body weight). After the loss of verbal responses, neuromuscular blockade was attained with inj. Vecuronium 0.1mg/kg body weight and the patients were manually ventilated for over 3 minutes with 100% Oxygen. At the end of 3 minutes, direct laryngoscopy was performed with an appropriate size Macintosh laryngoscope, followed by endotracheal intubation with a cuffed ETT of appropriate size. Anesthesia was maintained with Oxygen, Nitrous oxide, and Isoflurane.

On successful completion of surgery and smooth and uneventful extubation, the patients were transferred to the recovery area where the pain and sedation status were assessed immediately (0 hr) using the VAS score and Ramsay Sedation Scale respectively. Afterward pain and sedation were again assessed at 1,2,4,6,12 and 24 hours. Rescue analgesia with iv Tramadol 100 mg was provided to all the patients 6 hours after the operation, following which VAS score at 12 and 24 hours were taken. Before shifting the patients to the ward, the recovery score was assessed using Modified Aldrete Score.

Statistical analysis:

Statistical analysis was done by using SPSS version 25.0 (Chicago, IL, USA). The demographic data were expressed as means and standard deviation. Duration of surgery was expressed as mean and standard deviation. Hemodynamic variables like Systolic Blood Pressure,

Diastolic Blood Pressure, Mean Arterial Pressure, and Heart Rate were expressed as mean and standard deviation. Pain, sedation, and recovery scores were stated as means and standard deviation and significance was evaluated using the ANOVA test.

The incidence and severity of various complications were assessed by the Chi-square test. All patients will be receiving premedication 60 minutes before the start of surgery. Group A (n=30): patients will be receiving an oral Pregabalin 75 mg tablet, group B (n=30): patients will be receiving oral Clonidine 150 mcg tablet, group C (n=30): patients will be receiving an oral placebo tablet.

Results

A. Demographic profile

The T-test and chi-square test were used to analyze the demographic parameters and ASA's physical status respectively. Data were offered as Mean ± SD or absolute numbers. P value >0.05, which is not statistically significant. [Table 1]

Table 1: Demographic profile of the study groups

	Group A	Group B	Group C	p-value
Age in completed years	48.27±7.26	51.00±5.68	48.50±7.74	0.246
Height (in cm)	154.77±2.91	154.27±3.19	155.17±3.14	0.529
Weight (in kg)	63.70±6.43	62.30±6.02	64.13±6.08	0.489
ASA				
1	13 (43.3%)	15 (50.0%)	15 (50.0%)	0.897
11	17 56.7%	15 50.0%	15 50.0%	

B. Hemodynamic Parameters

All the groups were comparable in hemodynamic parameters like systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), preoperative pulse rate (PR), mean blood pressure (MAP), and peripheral oxygen saturation (SpO2). [Table 2]

Table 2: Distribution of baseline hemodynamic variables of study group

	Group A	Group B	Group C	p-value
Baseline HR	89.97±4.35	84.80±7.92	82.43±7.38	0.008
Baseline MAP	89.37±6.77	86.03±7.36	83.33±6.65	0.111
Baseline SpO_2	99.53±0.51	99.53±0.57	99.53±0.57	1

C. Degree of Pain

Visual Analogue Score (VAS) for dynamic pain assessment exhibited a noteworthy reduction in the pre-medicated group in comparison to the control group at all time intervals [Table 3]. On further analysis, it was observed that all most all patients in Group A experienced mild pain up to 4 hours post-operatively with VAS score not going more than 3 on average, while 5 patients in Group B experienced moderate pain after 2 hours of surgery and the 4hours VAS score was 4 or more on an average [Table 3, Fig 2]. The data was calculated using the ANOVA test and presented as Mean ± SD. The P value is <0.001 as seen in the above table proving the data to be statistically significant.

Table 3: Distribution of VAS score at hourly interval

	Group A	Group B	Group C	p-value
At 0 hr	0.03±0.18	0.03±0.18	0 43±0 50	<0.001
At 1hr	2.13±0.43	2.20±0.41	3.60±0.50	<0.001
At 2hrs	2.90±0.31	3.10±0.48	4.63±0.61	<0.001
At 4hrs	3.77±0.57	4.03±0.49	5.50±0.73	<0.001
At 6hrs	4.83±0.59	5.20±0.55	6.37±0.96	<0.001
At 12hrs	4.20±0.41	4.60±0.72	5.60±0.62	<0.001
At 24hrs	4.03±0.32	4.30±0.53	5.67±0.84	<0.001

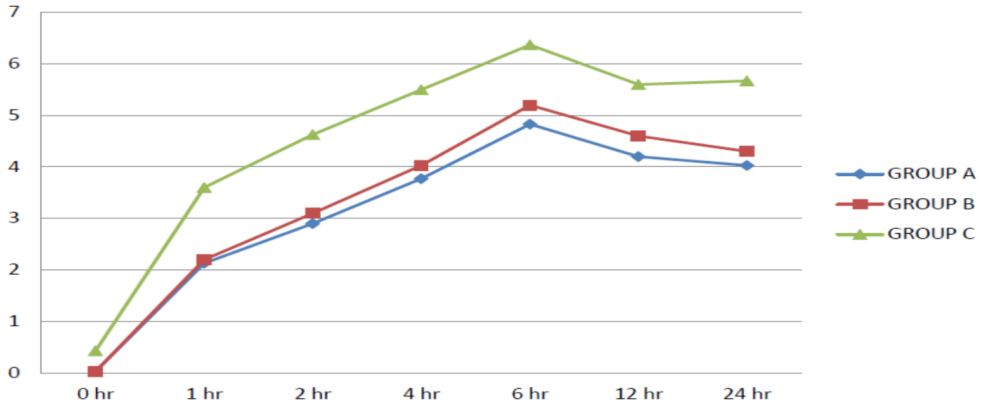

Figure 2: Line diagram of VAS score at various time intervals among the study groups

D. Degree of sedation: There was not much difference in the Modified Ramsay Sedation Score in group A and group B immediately after surgery, but the 1-hour post-operative score was higher among group A patients compared to group B patients (1.83 in group A versus 2.30 in group B). [Table 4, fig 3] The data was calculated using the ANOVA test and presented as Mean ± SD. The p-value is <0.001 as seen in the above table proving the data to be statistically significant.

Table 4: Distribution of sedation scores of the study groups

	Group A	Group B	Group C	p-value
At 0 hr	4.00±0.74	4.40 ± 0.77	2.07±0.83	< 0.001
At 1 hr	1.83±0.83	2.30±1.06	1.03±0.18	< 0.001
At 12hrs	1.00±0.00	1.00±0.00	1.00±0.00	-
At 24 hrs	1.00±0.00	1.00±0.00	1.00±0.00	-

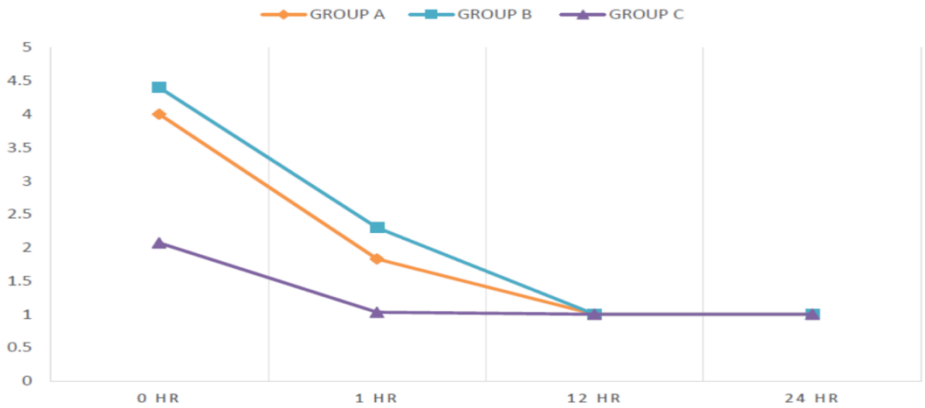

Figure 3: Line diagram of the sedation scores at various intervals among the study groups

E. Degree of Recovery: Modified Aldrete score was also found to be less in premedicated groups compared to the control (9.73 in group A *vs* 9.70 in group B *vs* 10.00 in group C) [Fig 4]. The data was calculated using the ANOVA test and presented as Mean ± SD. The p-value is 0.004 as seen in the above table proving the data to be statistically significant.

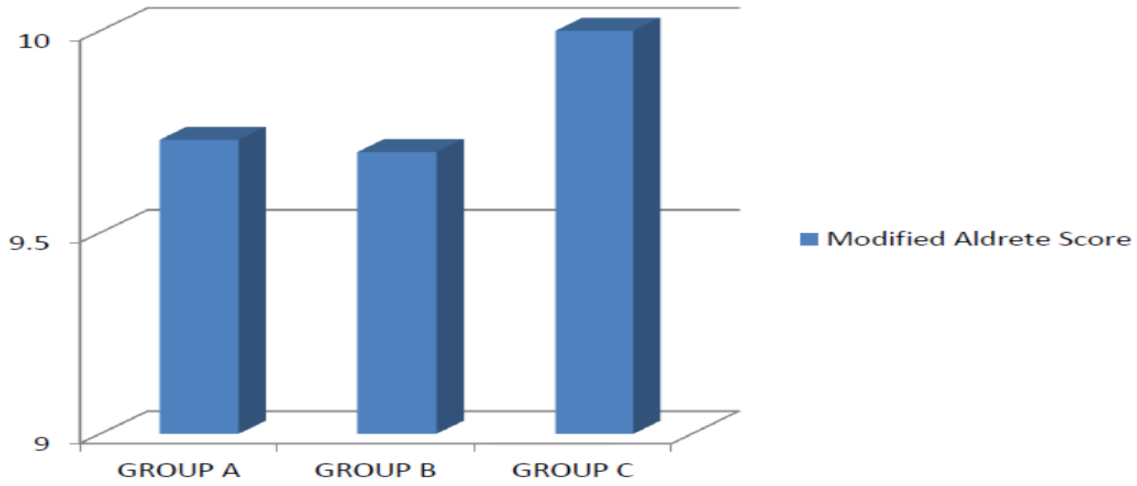

Fig 4: Histogram showing the recovery scores among the study groups

F. Complications

Group A participants exhibited a higher incidence (10%) of post-operative dizziness than in group B (6.7%), whereas nil in the control group [Table 6]. The incidence of hypotension in the Clonidine group (23.3%) was significantly higher than that of the Pregabalin group (0.0%) and control group (3.3%). The incidence of nausea and vomiting in the pregabalin group (16.7%) was similar to the clonidine group (16.7%) and control group (10.0%), but it was not statistically significant (p-value;0.805) [Fig 5]

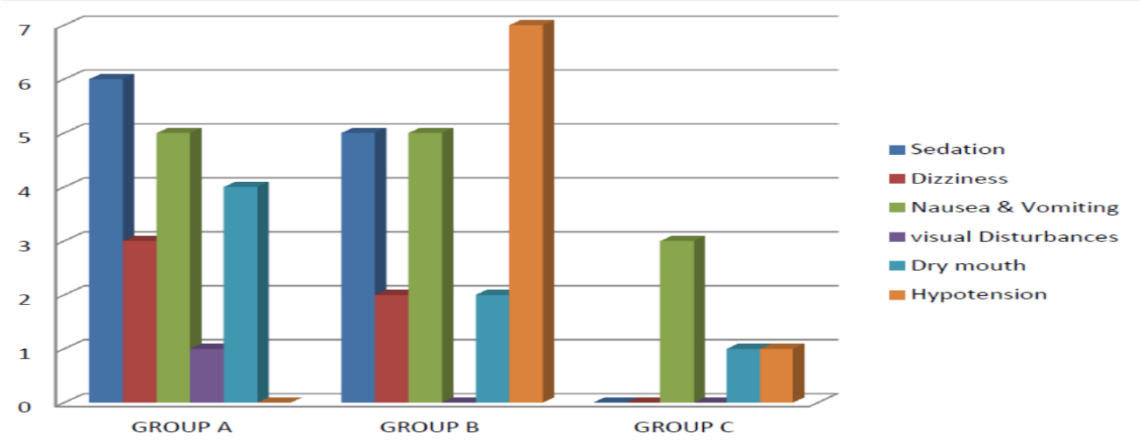

Figure 5: Histogram showing occurrence of complications among the study groups

Discussion

Post-operative discomfort and pain after surgery are the greatest fear of apprehension for patients, surgeons, and anesthesiologists. Considering, the concept of postoperative pain alleviation, we carried out a comparative study of 2 drugs, if given before starting the surgery, or any painful stimuli that can take care of postoperative pain (pre-emptive analgesia).

In the current study, the efficacy in post-operative analgesia was assessed upon pre-

emptively giving oral pregabalin 75 mg and clonidine 150 mcg, which showed a reduction in post-operative pain significantly in both the premedicated groups in comparison to the placebo group, where in contrast to Clonidine, Pregabalin had a slightly better pain relief profile till 24 hours post-surgery. Sedation, however, was found to be more in patients who were on clonidine than in the other premedicated group. The main purpose of mixing separate analgesic agents is to obtain either synergistic or additive effects, which allows a smaller dosage of the drugs being used with a better safety margin. Moreover, the hysterectomy performed laparoscopically has the advantage of being minimally invasive but unlike any other laparoscopic procedure, TLH is a long-duration surgery and is thus subjected to more tissue manipulation. Furthermore, the steep Trendelenburg position during surgery may increase pain in many folds in the shoulder in addition to the pneumoperitoneum. The pain post-TLH is thus, often difficult to manage, which eventually leads to increased use of opioids and late discharge from the hospital.[6]

Therefore, pre-emptive use of certain individually customized drugs is considered to alleviate shoulder pain after surgery. [6]

In contrast to conventional analgesics, GABA-pentanoids such as Gabapentin and Pregabalin decrease the hyperexcitability of dorsal horn neurons caused by tissue damage thus launched as an adjunct in the multi-modal management of postoperative pain. Alongside α2-agonist, Clonidine has anti-nociceptive actions at the spinal and supraspinal sites and acts synergistically with opioids. Unlike opioids, Clonidine has a lower potential for respiratory depression. The low cost and availability of clonidine are also a point in its favor. [7, 8] A study conducted by Bhagat et al who had taken 3 groups: one for clonidine 200 mcg, one for pregabalin 300 mg and the third receiving oral placebo tablet for patients being posted for laparoscopic cholecystectomy found that perioperative sedation was higher with pregabalin than clonidine without much prolongation of recovery time and a reduction in post-operative pain and analgesic requirement. [5] A similar study conducted by Tanthry et al established that, compared to clonidine, preoperative use of oral pregabalin significantly reduces diclofenac requirement post-operatively. It had a definitive role in reducing postoperative pain and analgesic requirements. [9]

Furthermore, Gupta et al. used a 10 cm VAS for sedation (fully awake to extremely drowsy) and anxiety (fully calm to worst possible anxiety) to assess the clinical efficacy of oral premedication with pregabalin (150 mg) and Clonidine (200 mcg). A definite increase in sedation (>6 cm) and a reasonable decrease in anxiety (2.4–3.6 cm) were noted in both premedicated groups as compared with the control groups. [10] In the present study, Visual Analogue Scale was used for pain assessment, in which pre-medication undoubtedly reduced pain post-operatively. However, a pre-emptive oral pregabalin showed better pain relief in comparison to clonidine 150 mcg. Likewise in 2009 Ghafari et al, noted that postoperative VAS score and total morphine consumption in both the gabapentin and clonidine group had less than that of the placebo group. The pain score was better in the Gabapentin group than in the clonidine group. [11] In 2000 Sung et al established that premedication with oral clonidine offer perioperative stable hemodynamics, which helped in omitting isoflurane, and lessened the postoperative analgesic requirement in fast-tracking the way to recovery in patients of laparoscopic cholecystectomy.[12]

The current trial suggested that post-surgical anxiolysis and sedation offered by pregabalin were light and just adequate in

contrast to deeper sedation seen with clonidine. The recovery time was not much delayed in either of the groups. Pregabalin usually has dose-dependent adverse effects, with dizziness and somnolence being the most frequently reported ones. Clonidine also has similar side effects which are very common like hypotension, dizziness, and somnolence. [13] However, Saraswat and Arora et al detected that somnolence and dizziness were the most common side effect of pregabalin. [14] In 2020 a study was structured where two different doses of pregabalin (150 mg and 300mg) given preoperatively are compared for efficacy in patients of laparoscopic cholecystectomy. They recorded a higher incidence of adverse effects like sedation and visual disturbances in the pregabalin 300 mg group than in the 150 mg group. [15] To reduce such instances, we used a lower dose of the drugs in our comparative study.

For the present prospective study, clinically significant side effects with the use of either Clonidine or Pregabalin were not observed, which might be due to the use of a very low dose of either of the drugs used. However, significant episodes of hypotension were observed in the clonidine group amounting to 23.3% of the study population. However, one single study showing the presence of an adverse effect with the use of a particular drug cannot be reflected in a bigger population. Hence a multi-centric clinical trial, involving a larger population with racial and ethnic variations is required for establishing appropriate results.

Limitations of the study:

1. Visual Analog Score might have subjective variations. Hence a proper quantitative evaluation of pain has not been made in our study.

2. The sample size considered for the study is small in comparison to the general number of patients being posted regularly for the said sur Thus, further studies with a bigger study sample size are required to strengthen the findings.

Summary

The demographic parameters like Age, height, and weight were examined by using a t-test and the ASA's physical status was analyzed using the chi-square test. All the 3 groups were similar and comparable in terms of demographic as well as ASA physical status.

There were no significant differences in the three groups in relation to the duration of surgery. (p=0.945).

Postoperatively assessment of the VAS score revealed a noteworthy decrease in pain in the premedicated group as compared to the control group at all time intervals. Pain sensation was less severe for group A in comparison to group B.

Modified RSS score, which was taken for assessment of sedation also showed a statistically significant difference in the premedicated group in comparison to control immediately and 1hr post-surgery (p-value <0.001and <0.001 respectively). There was not much difference in modified RSS score in group A and group B soon after surgery, but 1hr post-operative score was higher among group A patients in comparison to group B patients (1.83 in group A *vs* 2.30 in group B).

Conclusion

Our study showed that premedication of analgesic drug is a newer and better modality of pain control than conventional methods. Both pregabalin and clonidine offer analgesia and sedation in the acute postoperative period in the doses studied.

Pregabalin 75 mg pre-emptively has shown to have a better analgesic agent than clonidine 150 mcg. Both analgesic agents are a good substitute for each other and can be used securely as pre-emptive analgesia for surgeries under general anesthesia.

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