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Research Article

A PROSPECTIVE RANDOMIZED SINGLE-BLIND STUDY COMPARING ALPRAZOLAM VERSUS CLONIDINE AND PREGABALIN AS PREANAESTHETIC MEDICATION IN PATIENTS UNDERGOING ELECTIVE LOWER LIMB SURGERIES

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ABSTRACT

Objective: The objective of the study was to study comparison of alprazolam versus clonidine and pregabalin as pre-anesthetic medication in patients undergoing elective lower limb surgeries.

Methods: The present study was undertaken to compare the effects of alprazolam 0.5 mg, clonidine 100 μg, and pregabalin 75 mg as premedicant drugs for the reduction of pre-operative anxiety. 90 patients of ASA Grades I and II, between 18 and 60 years, of either sex, undergoing elective lower limb surgery were divided into three groups of 30 patients each. Baseline anxiety level and level after 2 h of the drug were assessed. Side effects due to drugs were noted before going to OT (Post drug, i.e., 2 h after drug administration), after the completion of the surgery, and at 24 h.

Results: There is a significant post-drug reduction in s-STAI score, t-STAI score, and CGI score when compared to baseline values in all the Group's A, C, and P. Side effects were mild and there were no serious adverse effects observed in all three groups. In Group A, 10% of patients complained of fatigue while in Group C, 13.3% of patients complained of dryness of mouth, and 10% of patients complained of headache 2 h post drug administration but in Group P, no side effect was noted.

Conclusion: Premedication with 0.5 mg alprazolam, 100 μg clonidine, and 75 mg pregabalin for control of pre-operative anxiety was comparable though pregabalin offered a significant advantage in terms of less side effects.

Keywords: Alprazolam, Clonidine, Pregabalin, Anxiety, s-STAI score, t-STAI score, CGI score, Elective lower limb surgery.

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INTRODUCTION

Surgeries are often viewed by patients as major life-altering interventions. Preoperatively, the apprehension attached with surgery leads to the development of many unwanted physiological and psychological responses in the patients. Psychologically, patients may have anxiety and insomnia while physiologically, there may be sympathetic activation leading to an increase in blood pressure and heart rate [1]. The major objectives of pre-anesthetic medication are to decrease the stress response with preservation of hemodynamic parameters, facilitate anesthesia induction and produce amnesia. These are also given to avoid the adverse events associated with general anesthesia, facilitate surgery and reduce the risk of post-operative complications. Various pharmacologic agents (barbiturates, benzodiazepines [BZDs], major tranquilizers, opioid [narcotic] analgesics, anticholinergics, etc.) are administered to facilitate the process of pre-operative preparation [2]. Alprazolam is one of the most commonly prescribed benzodiazepines for the treatment of generalized anxiety disorder [3]. Premedication with clonidine (α2-adrenergic agonist) can produce sedation and anxiolysis along with decreasing the heart rate and blood pressure during anesthesia [4]. Pregabalin is used as a sedative and anxiolytic as pre-anesthic medication. It is an α_2–δ ligand that has analgesic, anticonvulsant, anxiolytic, and sleep-modulating activities [5]. Even though all drugs are used as pre-anesthetic medication but efficacy and tolerability are of paramount concern. For the smooth running of the surgery, an ideal pre-anesthetic medication is the need of the hour. In this study, we tried to compare these drugs for their effects on the pre-operative anxiety of patients.

METHODS

This prospective, single-blinded, randomized, and comparative clinical study was undertaken after institutional ethics committee approval. This research is registered in CTRI (CTRI/2021/04/032494). 90 patients of either sex, having American Society of Anaesthesiologists (ASA) Grade I/II, aged between 18 and 60 years, undergoing elective lower limb surgeries under local anesthesia were screened and selected as per inclusion and exclusion criteria for this study. Patients with a history of chronic pain and psychiatric disease; history of severe hepatic and renal disorders; pregnant and lactating females and patients who refused to participate in the study were excluded from the study. A patient's information sheet was provided to every eligible subject for the study and thereafter informed written consent was taken from the participants of this study.

The eligible subjects after screening were randomly divided into three study groups, that is, Group A, Group C, and Group P with the help of computer-generated numbers. Each study group had 30 patients and was received three different treatments. Group A, Group C, and Group P: Received oral alprazolam tablet (0.5 mg), oral clonidine tablet (100 μg), and oral pregabalin capsule (75 mg), respectively, 2 h before going to operation theater (post drug, i.e., 2 h after drug administration). The drugs were given to the patient with a sip of water. The identity of the tablet was not revealed to the patient. No other drug as premedication was given to the subject other than the study drugs.

Clinical assessment was carried out on all patients in terms of anxiety and safety issues. In all the groups, on the day of surgery, anxiety was

assessed by the state-trait anxiety inventory (STAI) scale and 7 point of clinical global impression (CGI) scale at baseline and 2 h prior to entry to the operation theater (post drug, i.e., 2 h after drug administration). Any side effects due to drugs were noted before going to OT after the completion of surgery and at 24 h.

Then intravenous access was secured by an 18G venous catheter inserted into a peripheral vein and ringer lactate solution was started. Monitoring of non-invasive blood pressure (NIBP), heart rate, electrocardiogram and arterial oxygen saturation were carried out. Anesthesia was achieved by combined spinal technique with Quincke spinal needle and 18-gauge Tuohy epidural needle and catheter. 3 mL of Bupivacaine 0.5% heavy was used for spinal anesthesia.

The STAI is a 40-item self-reported questionnaire designed to measure both state and trait anxiety. The original STAI consists of two separate scales to measure state and trait anxiety. The S-Anxiety scale (STAI Form Y-1) consists of 20 items (item 1 to item 20) that measure the respondent's feelings at that moment [6]. The S-Anxiety scale is also abbreviated as s-STAI [7]. The T-Anxiety scale (STAI Form Y-2) also consists of 20 items (item 21 to item 40), and this scale measures how the respondent "generally" feels [6]. The T-Anxiety scale is also abbreviated as t-STAI [7]. Scores for both the State Anxiety Scale and Trait Anxiety Scale ranged from a minimum of 20 to a maximum of 80. A score of more than 44 on STAI was taken as significant anxiety and the patient was categorized as having high anxiety (STAI score >44) while an STAI score ≤44 categorized as low anxiety (STAI score ≤44) [6].

The level of anxiety was assessed on a 7-point clinical global impression (CGI) scale 0=Relaxation, 1=Apprehension, 2=Mild anxiety, 3=Moderate anxiety, 4=Manifest anxiety, 5=Severe anxiety, and 6=Very severe anxiety [8].

OBSERVATIONS

On comparing demographic data, the mean age was 32.07±11.101, 37.77±12.03, and 35.20±11.081 in Groups A, C, and P, respectively, which was comparable. The number of females were 3 (10%), 6 (20%), and 6 (20%) in Group A, Group C, and Group P, respectively. The number of males was 27 (90%), 24 (80%), and 24 (80%) in Group A, Group C, and Group P, respectively.

The s-STAI in Groups A, C, and P, the baseline mean±SD was 37.33±3.11, 37.07±2.88 and 36.90±2.857, respectively. The post-drug mean±SD was 21.30±1.57, 21.33±1.53 and 21.43±1.633, respectively. On intragroup analysis, while applying paired T-test results were statistically significant when post-drug values were compared to baseline. On intergroup comparison, while applying ANOVA, the mean s-STAI scores were not statistically significant. (Fig. 1)

The t-STAI in Groups A, C, and P, the baseline mean±SD was 40.30±2.493, 40.00±2.393 and 39.83±2.365, and post drug mean±SD was 23.00±1.414 and 23.07±1.388, 23.13±1.456, respectively. On intragroup analysis, while applying paired t-test results were statistically significant when post-drug values were compared to baseline. On inter group comparison, while applying ANOVA, the mean t-STAI scores were not statistically significant (Fig. 2).

The CGI in Groups A, C, and P, the baseline mean±SD was 3.33±0.884, 3.43±0.728, and 3.47±0.730, and post drug mean±SD was 1.53±0.507, 1.73±0.583, and 1.80±0.551, respectively. On Intragroup analysis, while applying paired T-test results were statistically significant when post-drug values were compared to baseline. On intergroup comparison, while applying ANOVA, the mean CGI scores were not statistically significant (Fig. 3).

During the entire study period, all patients were closely monitored for systemic side effects. Side-effects were mild and there were no serious adverse effects observed in all three groups. In Group A, 10% and

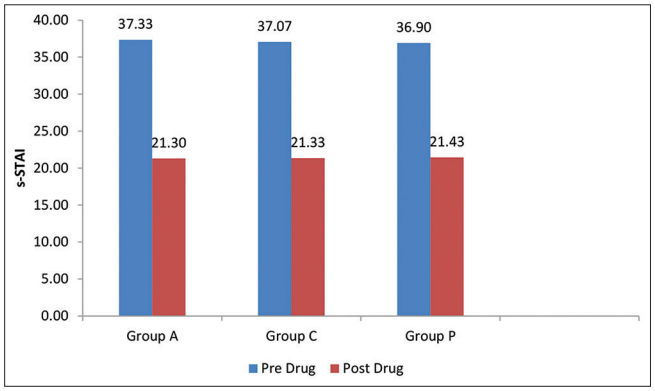

Fig. 1: Intragroup and Intergroup Comparison of State part of State Trait Anxiety Inventory(s-STAI) scale

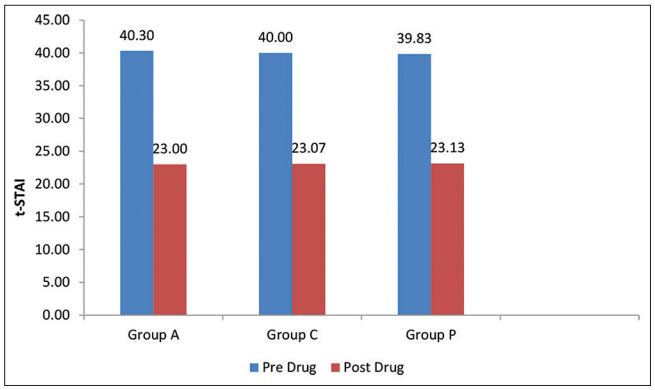

Fig. 2: Intragroup and Intergroup Comparison of Trait part of State Trait Anxiety Inventory (t-STAI) scale

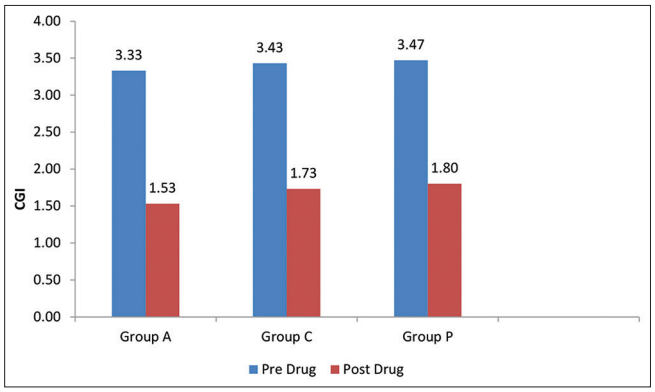

Fig. 3: Intragroup and intergroup comparison of clinical global impression for anxiety scale

13.3% of patients complained of fatigue post drug and after surgery, respectively. In Group C, 13.3% and 20% of patients complained of dryness of mouth post drug and after surgery, respectively, while 10% and 6.6% of patients complained of headache post drug and after surgery respectively. In Group P, no side effect was noted. There was no requirement of treatment for adverse drug reactions.

DISCUSSION

Clonidine is marketed as antihypertensive and pregabalin is used in neuropathic pain. Only very few studies have shown clonidine and pregabalin anxiolytic effects. In our study, it is observed that A, C, and P groups have shown a significant decrease in the anxiety status of the patient as seen by the s-STAI scale, t-STAI scale and CGI scale.

The result showed that groups A, C, and P produced a significant decrease in the anxiety status of the patient as seen by the s-STAI scale post-drug. Ozkan *et al.* revealed that using alprazolam before flexible cystoscopy reduces both anxiety and pain [9]. Nasr *et al.* compared melatonin and pregabalin and concluded that the anxiety scores decreased significantly >50% after premedication in both groups compared to baseline values ($p<0.01$) with no statistically significant difference between the two groups [10]. Chaurasia *et al.* revealed that the anti-anxiety effect of clonidine was found to be better than that of the diazepam-atropine combination [11]. The result of our study was in co-relation to the study result of Ozkan *et al.*, Nasr *et al.,* and Chaurasia *et al.*

The result showed that Groups A, C, and P produced a significant decrease in the anxiety status of the patient as seen by the t-STAI scale post-drug. Bugbee *et al.* revealed that the use of oral anxiolytic medication before breast CNB can significantly reduce anxiety women experience during the procedure [7]. Khanna *et al.* showed that melatonin was more sedative than pregabalin and alprazolam in patients undergoing laparoscopic surgery but all the three Groups M, P, and A had comparable perioperative anxiety, post-operative analgesia [12]. Hossain *et al.* found that clonidine is a better agent as an anxiolytic and sedative than gabapentin [13]. The result of our study was in co-relation to the study result of Bugbee *et al.*, Khanna *et al.,* and Hossain *et al.*

In this study, we have observed that A, C, and P groups produced a significant decrease in the anxiety status of the patient as seen by the CGI scale post-drug. De Witte *et al. showed that o*ral alprazolam 0.5 mg and midazolam 7.5 mg comparably reduce anxiety in ambulatory surgery patients [14]. Gupta *et al. c*oncluded that the pregabalin and clonidine are effective oral premedicant drugs with safe and multimodal drug profile as they cause sedation, anxiolysis, and analgesia [15]. The result of our study was in co-relation with the study result of Witte *et al*. and Gupta *et al*. The result showed that Groups A, C, and P produced a significant decrease in the anxiety status of the patient as seen by the CGI scale post-drug.

Side-effects were mild and there were no serious adverse effects observed in all 3 groups. Daoud *et al.* conducted a review of alprazolam use, misuse, and withdrawal. The results of this study revealed that patients complained of fatigue [16]. Hossain *et al.* conducted a comparative study of oral clonidine versus gabapentin as premedication for anxiolysis, sedation, and attenuation of pressor response to laryngoscopy and tracheal intubation. The result of this study revealed that 46% of patients complained of dry mouth [13]. Nasr et al. revealed that the patients receiving pregabalin did not complain of any other adverse effects, and it was proved that pregabalin is well tolerated and associated with dose-dependent adverse effects that are mild-to-moderate and are usually transient [10]. The result observed in our study was similar to the result of the study done by Daoud *et al.*, Hossain *et al.,* and Nasr *et al.*

CONCLUSION

Premedication with 0.5 mg alprazolam, 100 μg clonidine, and 75 mg pregabalin for control of preoperative anxiety was comparable though pregabalin offered a significant advantage in terms of fewer side effects. Therefore, pregabalin seems to be an alternative to alprazolam as pre-anesthetic medication for patients undergoing elective lower limb surgeries.

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AUTHORS' CONTRIBUTIONS

Dr. Mohd Fazal Ahmed Makki, Dr. Seema Rani, Dr. Sanjeev Kumar, and Dr. Pranav Bansal conceptualized, designed the study, collected data, analyze, and prepared the manuscript. Manuscript editing and the citation were done by Dr. Rahul Saini, and Dr. Abhinav Goyal. Final proof reading was done by all.

CONFLICTS OF INTEREST

The authors have no conflict of interest.

AUTHORS' FUNDING

Nil.

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