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Randomized Control Trial of Two Doses of Pregabalin as a Premedication for General Anaesthesia in Major Abdominal Surgeries and it's Fentanyl Sparing Effect in a Tertiary Care Hospital

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ABSTRACT

Preoperative sedation and cardiovascular stability along with the reduction of pain perception during induction, laryngoscopy and intubation in general anesthesia and throughout the surgical procedure and postoperative period is the most essential part of anesthesia practice for better patient outcome. Present study was aimed to compare two doses of pregabalin as a premedication for general anaesthesia in major abdominal surgeries and it's fentanyl sparing effect in a tertiary care hospital. Present study was Prospective Hospital-based Interventional study, conducted in patients of age 18-65 years, either gender, scheduled for elective major abdominal surgeries under general anesthesia. Patients were divided into 3 groups as Group C (placebo) Group PG 150 (Tab Pregabalin 150 mg) and Group PG 300 (Tab Pregabalin 300 mg) 1 hr before the surgery. In present study, difference in mean systolic blood pressure at post intubation (PI) post intubation (PI) 15/30/60 min, in PACU and average score was statistically significant. The difference in mean diastolic blood pressure at pre intubation, post intubation (PI) post intubation (PI) 15/30/60 min, in PACU and average score was statistically significant. The difference in mean diastolic blood pressure at post intubation (PI) 15/30/60 min, in PACU and average score was statistically significant. The difference of mean MRSS 1 hour before the operation, arrival in OT, in PACU at baseline 3-6 hrs and 18-24hrs was statistically significant. The difference of mean VAS SCORE in PACU at baseline 3-6 hrs and 18-24 hrs was statistically significant. Association of Intraop fentanyl top-up, rescue Analgesia (paracetamol 1 gm IV) and rescue analgesia second analgesic statistically significant ($p<0.0001$) in group C as compared to group -PG 150 and group -PG 300. More intraoperative fentanyl, rescue analgesia (Paracetamol 1 gm) and second rescue analgesic was required in the control group compared to PG 150 and PG 300.

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Key Words
Pregabalin, premedication, general anaesthesia, fentanyl sparing effect

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INTRODUCTION

Preoperative sedation and cardiovascular stability along with the reduction of pain perception during induction, laryngoscopy and intubation in general anesthesia and throughout the surgical procedure and postoperative period is the most essential part of anesthesia practice for better patient outcome. Anxiety remains a major problem for many patients during the preoperative period. Apt premedication, smooth induction and rapid intubation can prevent the associated risk and complication of the hemodynamic pressor responses[1,2].

Numerous pharmacological procedures were assessed as premedication to diminish the untoward hemodynamic response to laryngoscopy, for instance developing sedation, pretreatment with vasodilators, adrenoreceptor blockers, calcium channel blocker and narcotics/opioids yet with variable outcomes. The current predominant approach of multimodal analgesia is mostly based on a combination of opioids, non-steroidal anti-inflammatory drugs (NSAIDs) paracetamol and preoperative administration of local anesthetics. Each of these approaches comes with its own set of complications[1].

The use of opioids may be limited by adverse side effects such as nausea, vomiting, excessive sedation, respiratory depression, pruritus and urinary retention[1,2]. Recently, pregabalin has been studied as a single or a multimodal analgesic drug for postoperative pain management in different surgeries[3,4]. A decrease in pain scores, superior postoperative analgesia and opioid-sparing effects have been observed during the perioperative period using pregabalin[4,5]. However, sedation-related problems and postoperative confusion may be attributable to the side effects of pregabalin[6]. Present study was aimed to compare two doses of pregabalin as a premedication for general anaesthesia in major abdominal surgeries and it's fentanyl sparing effect in a tertiary care hospital.

MATERIAL AND METHODS

Present study was Prospective Hospital-based Interventional, Double-Blind Randomised Control study, conducted in department of anaesthesiology, at Command Hospital Eastern Command Kolkata, India. Study duration was of 2 years (January-November 2019-2020). Study approval was obtained from institutional ethical committee.

Inclusion criteria:

- Patients of age 18-65 years, either gender, scheduled for elective major abdominal surgeries under general anesthesia, willing to participate in present study

Exclusion criteria:

- Anticipated difficult intubation, Obstructive Sleep Apnea, Obesity, History of Cardiac, Pulmonary, or Renal disease
- Chronic pain syndromes on regular analgesics
- Sensitivity to any drug being used in the study
- Taking antipsychotics, oral hypoglycaemic
- If laryngoscopy needed a second attempt

Study was explained to patients in local language and written consent was taken for participation and study. Simple Randomization was done by computer-generated random numbers in sealed envelopes to divide the patients in each group. After a thorough pre-anesthetic evaluation, simple randomization has been done to allocate the study population into 3 groups (Group C, Group PG 150 and Group PG 300) of 50 patients each by a computer-generated Table. Group allocations were performed by an anesthesiologist who was blinded to the study protocol. Each group had the following interventions.

- Group C received Tab A HS (placebo, previous night) + 1 hr before Surgery
- Group PG 150 received Tab Pregabalin 75 mg HS (previous night) + 150 mg 1 hr before the surgery.
- Group PG 300 received Tab Pregabalin 75 mg HS (previous night) + 300mg 1 hr before the surgery.
- On arrival in the operation theatre (Pre-operative room) patients were evaluated for

Ramsay Hunt Sedation Score 1 hr before the operation and before administering Tab A (Placebo) to patients of Group C or Tab Pregabalin 150 mg to patients of Group PG 150 or Tab Pregabalin 300 mg to patients of Group PG 300. At 1 hr after drug administration patients were shifted to the operating table and all monitors were attached to record baseline heart rate, systolic and diastolic pressure, mean arterial pressure, SpO_2 and entered in case record form. A crystalloid intravenous infusion was started and Inj Ondansetron 4 mg along with Inj Fentanyl with a dose of 0.5 µg per kg body weight was administered to all patients under the study. All patients in the three groups were induced with Inj Propofol (2-2.5 mg kg^{-1} BW) till loss of verbal commands.

After careful check ventilation, Inj Atracurium (0.5 mg kg^{-1} BW) was given to facilitate tracheal intubation. Laryngoscopy and intubation were performed 90 sec after Inj Atracurium by an experienced anaesthesiologist. The patient was excluded from the study if a second attempt (withdrawal and reinsertion of the endotracheal tube) was required for intubation.

Table 1: Demographic And clinical characteristics of patients

	Group- PG 150	Group- PG 300	Group-C	p-value
Number	29	33	28	
AGE(YRS)	46.37±9.23	47.12±9.75	47.85±10.02	0.8472
Genders				0.5305
Female	21	24	17	
Male	8	9	11	
Weight (kg)	63.31±9.41	62.21±8.66	62.35±8.66	0.8750
ASA grade				0.3169
I	10	13	15	
II	19	20	13	
Duration of surgery (min)	199±94.21	212.72±50.80	210.21±64.16	0.8750

Table 2: Comparative analysis of heart rate at various time points

	Group- PG 150	Group- PG 300	Group-C	p-value
Number	29	33	28	
Arrival in OT	80.97±10.26	78.97±9.31	80.32±10.47	0.7234
Preinduction	80.38±9.13	75.85±7.94	79.86±11.21	0.1206
Pre intubation	75.00±9.28	70.12±10.62	73.57±13.05	0.2053
Post intubation (PI)	79.20±12.71	73.39±11.47	97.19±12.67	<0.0001
15 min PI	74.12±9.73	68.42±7.06	95.89±14.43	<0.0001
30 min PI	94.52 ± 15.58	73.49±9.64	97.99±12.77	<0.0001
60 min PI	92.86±12.52	73.81±8.37	67.42±7.50	<0.0001
PACU	94.52±15.58	73.33±7.88	67.91±6.35	<0.0001
Average score	89.03±11.72	76.29±8.65	67.37±4.95	<0.0001

Table 3: Comparative analysis of systolic blood pressure pg 150, pg 300 and control groups at different time intervals

	Group- PG 150	Group- PG 300	Group-C	p-value
Number	29	33	28	
Arrival in OT	136.34±4.92	137.45±8.51	138.71±6.13	0.4233
Preinduction	135.38±5.55	133.94±7.78	138.04±5.97	0.0559
Pre intubation	129.34±6.27	121.18±13.97	131.96±6.60	<0.0001
Post intubation(PI)	133.60±7.84	132.00±12.71	168.34±9.71	<0.0001
15 min PI	127.49±11.48	152.91±7.72	162.50±14.43	<0.0001
30 min PI	162.54±11.34	129.32±11.17	122.33±10.70	<0.0001
60 min PI	121.21±11.09	159.21±10.71	131.96±6.60	<0.0001
PACU	121.18±14.19	162.01±15.53	129.12±10.52	<0.0001
Average score	123.61±10.59	152.91±7.72	127.74±9.78	<0.0001

Patients were handed over for surgical intervention after haemodynamic response to intubation has settled to within 20% of baseline values. Maintenance of anaesthesia was done by 50% N2O + 50% O2 gas mixture with Sevoflurane at 0.7-0.9 MAC at a fresh gas flow rate of 6 L min. Inj. Atracurium was repeated as per requirement in aliquots of 5 mg. An additional dose of Inj Fentanyl was administered at 0.5 µg kg BW if there were signs of inadequate analgesia viz increase in heart rate and blood pressure (more than 20% of baseline) lacrimation and sweating in presence of normal end-tidal carbon dioxide. Any acute or severe changes of haemodynamics, MAP <60 or >110, were treated by decreasing or increasing the concentration of Sevoflurane respectively.

Intra-operative haemodynamics record Heart rate, systolic and diastolic blood pressure, mean arterial pressure (MAP) pulse oximetry (SpO_2) levels were continuously monitored and recorded at Arrival in OT, Pre induction, Pre intubation, Post intubation (PI) 15, 30-60 min PI. Any additional dose of Inj Fentanyl that was given for inadequate analgesia, at any point post-intubation was recorded. If the patient received Fentanyl immediately post-intubation (PI) data entered as PI between post-intubation (PI) to 15 min PI data entered as 15 min PI between 16-30 min PI data entered as 30 min PI and so on till 60 min PI. VAS score was used to assess postoperative pain of patients in all three groups. Patients in all three groups were administered Rescue Analgesia whenever pain has been reported with a VAS score of 2 or more. For standardization purpose, VAS score values were entered at PACU, at 3 hr for any pain after discharge from PACU to 3 hr, at 6 hr for any pain between 3-6 hr, at 18 hr for any pain between 6-18 hr, at 24 hr for any pain between 18-24 hr. Inj Paracetamol 1 gm IV used as first rescue analgesic. If pain recurred before next dose of Inj Paracetamol can be given, a second analgesic (Inj Diclofenac 75 mg) IV is used.

For statistical analysis, data were entered into a Microsoft Excel spreadsheet and then analyzed by SPSS (version 27.0 SPSS Inc., Chicago, IL, USA) and Graph Pad Prism version. One-way analysis of variance (one-way ANOVA) was a technique used to compare means of three or more samples for numerical data (using the F distribution). A chi-squared test (χ^2 test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is chi-squared distribution when the null hypothesis is true. $p<0.05$ was considered as statistically significant.

RESULTS

In present study, Association of mean age (in years) gender, weight (kgs) ASA grade and duration of

Table 4: Variability in mean diastolic blood pressure pg 150, pg 300 and control groups during perioperative period

	Group- PG 150	Group- PG 300	Group-C	p-value
Number	29	33	28	
Arrival in OT	75.72±6.52	77.61±10.19	77.50±9.75	0.6671
Preinduction	72.83±5.65	74.70±8.90	75.43±8.55	0.4372
Pre intubation	69.31±4.26	66.91±7.07	70.82±8.52	0.0834
Post intubation(PI)	81.86±10.55	72.52±6.82	68.37±7.25	0.0005
15 min PI	82.79±8.69	69.00±6.77	73.52±10.70	<0.0001
30 min PI	82.07±5.16	68.94±7.49	67.12±6.01	<0.0001
60 min PI	83.61±7.53	70.73±6.81	67.52±8.02	<0.0001
PACU 80.75±10.61	69.71±5.64	68.37±7.25	<0.0001	
Average score	79.35±7.29	71.09±3.93	67.79±5.57	<0.0001

Table 5: Distribution of mean SPO2 among groups (One-way ANOVA)

	Group- PG 150	Group- PG 300	Group-C	p-value
Number	29	33	28	
Arrival in OT	100	99.96 ± 0.1741	99.89 ± 0.41	0.2673
Preinduction	99.89 ± 0.4093	99.78 ± 0.6963	100	0.2349
Pre intubation	99.76 ± 0.9124	99.76 ± 0.9692	99.75 ± 0.7993	0.9992
Post intubation(PI)	79.20 ± 12.71	73.39 ± 11.47	97.19 ± 12.67	0.2564
15 min PI	99.82 ± 0..5391	99.97 ± 0.1741	99.89 ± 0.5669	0.4673
30 min PI	99.82 ± 0..5391	99.97 ± 0.1741	99.89 ± 0.5669	0.4865
60 min PI	99.76 ± 0.9124	99.94 ± 0.3482	99.89 ± 0.4163	0.0005
PACU 99.41 ± 0.8245	99.91 ± 0.3844	99.14 ± 0.9705	0.4865	
Average score	99.81 ± 0.1756	99.83 ± 0.2044	99.75 ± 0.2836	0.2577

surgery (in min) vs group was not statistically significant (p>0.05). The difference in mean heart rate at arrival in OT, pre induction and pre intubation was not statistically significant (p>0.05). The difference in mean heart rate at post intubation (PI) post intubation (PI) 15/30/60 min, in PACU and average score was statistically significant (p>0.05). The difference in mean diastolic blood pressure at arrival in OT and pre induction was not statistically significant (p>0.05). The difference in mean diastolic blood pressure at pre intubation, post intubation (PI) post intubation (PI) 15/30/60 min, in PACU and average score was statistically significant (p>0.05).

The difference in mean diastolic blood pressure at arrival in OT, pre induction, pre intubation and post intubation (PI) was not statistically significant (p>0.05). The difference in mean diastolic blood pressure at post intubation (PI) 15/30/60 min, in PACU and average score was statistically significant (p>0.05). The difference in mean SPO_2 at arrival in OT, pre induction, pre intubation, post intubation (PI) 15/30/60 min, in PACU and average score was not statistically significant (p>0.05). The difference of mean MRSS 1 hour before the operation, arrival in OT, in PACU at baseline 3-6 hrs 18-24 hrs was statistically significant (p<0.0001). The difference of mean VAS SCORE in PACU at baseline 3-6 hrs 18-24 hrs was statistically significant (p<0.0001). Association of Intraop fentanyl top-up, rescue Analgesia (paracetamol 1 gm IV) and rescue analgesia second analgesic statistically significant (p<0.0001) in group C as compared to group -PG 150 and group -PG 300.

DISCUSSION

Intra and post-operative pain is an acute form of pain that begins with surgical trauma and usually terminates with tissue healing. Even with the recent advances in the knowledge, skill and sophisticated technology that characterize most modalities of treatment, patients continue to experience pain during intra and post-operative periods. Post-surgical pain a major complication of general surgery, has an incidence of 41-86%[7]. Adequate management of acute postoperative pain might increase patient satisfaction and reduce the risk of progression of chronic pain and associated comorbidities[8].

Pregabalin is a structural analog of gamma-aminobutyric acid (GABA). It acts by presynaptic binding to the α-2-λ subunit of voltage-gated calcium channels that are widely distributed in the spinal cord and brain. By this mechanism, pregabalin modulates the release of several excitatory neurotransmitters, such as glutamate, norepinephrine, substance P and calcitonin gene-related peptide. It leads to inhibitory modulation of “overexcited” neurons returning them to a “normal” state. Centrally, pregabalin could reduce the hyperexcitability of dorsal horn neurons that is induced by tissue damage[9,10].

The difference of mean heart rate Post intubation (PI) 15-30 min PI and 60 min PI, in post anaesthesia care unit (PACU) as well as the average score of all observations across the set time intervals, between the three Groups, was statistically significant (p<0.0001) mean of the placebo (Group C) being higher, intermediate in Group PG 150 and lowest Group PG 300. The inter-group comparison shows a statistically significant (p<0.001) difference in Heart Rate across all time intervals after intubation when Group C is compared with the intervention groups which shows better attenuation of stress response with Pregabalin premedication. These observations align with studies made by Gupta *et al.*[11] Khetarpal *et al.*[12] Rastogi *et al.*[13] Bhagat *et al.*[14] Chandra *et al.*[15] and Salma *et al.*[16]. Inter-group comparison of mean Systolic Blood Pressure (SBP) shows statistically significant difference from Post intubation (PI) to PACU including average scores (p<0.001) when Group C is compared with intervention groups PG 150 and PG 300 with positive mean differences. However inter-group comparison between PG 150 and PG 300 shows no

Table 6: Distribution of mean Modified Ramsay Sedation Score (MRSS) among groups

	Group- PG 150	Group- PG 300	Group-C	p-value
Number	29	33	28	
1 hr before surgery	2.00±0.00	2.00±0.00	1.43±0.50	<0.0001
Arrival in OT	1.93±0.26	2.09±0.29	1.14±0.36	<0.0001
PACU 1.97±0.19	2.06±0.24	1.21±0.42	<0.0001	
3 hrs 1.97±0.19	2.03±0.30	1.29±0.46	<0.0001	
6 hrs 1.97±0.33	2.00±0.00	1.18±0.39	<0.0001	
18 hrs	1.93±0.37	2.00±0.25	1.29±0.46	<0.0001
24 hrs	1.90 ± 0.31	2.00±0.00	1.43±0.50	<0.0001

Table 7: Distribution of mean VAS score at intervals among groups

	Group- PG 150	Group- PG 300	Group-C	p-value
Number	29	33	28	
PACU 2.03±0.19	2.00±0.00	3.82±1.36	<0.0001	
3 hrs 2.00±0.00	0.30 ± 0.68	3.71±1.44	<0.0001	
6 hrs 4.57±2.18	2.07±0.37	2.03±0.19	<0.0001	
18 hrs	2.82±0.90	2.03±0.19	0.39±0.56	<0.0001
24 hrs	3.00±1.41	2.14±0.44	0.42±0.79	<0.0001

Table 8: Association between intraop fentanyl top-up and analgesic requirement among groups

	Group- PG 150	Group- PG 300	Group-C	p-value
Intraop fentanyl top-up				<0.0001
0	26	32	0	
1	3	1	3	
2	0	0	3	
3	0	0	22	
Rescue analgesia - paracetamol 1 gm iv				<0.0001
0	25	31	0	56
1	4	2	6	12
2	0	0	16	16
3	0	0	6	6
Rescue analgesia- second analgesic				<0.0001
0	29	33	8	70
1	0	0	20	20

statistical significance implying that both intervention arms are good for stabilizing SBP (Table 3). The findings were in agreement with studies made by Gupta *et al.*[11] Khetarpal *et al.*[12] Rastogi *et al.*[13] Bhagat *et al.*[14] Chandra *et al.*[15] and Salma *et al.*[16].

The inter-group comparison of mean Diastolic Blood Pressure (DBP) shows a statistically significant difference (ranges from p<0.001-0.003) when group C is compared with PG 150 and PG 300 with higher mean in placebo group C, intermediate mean in group PG 150, lowest in group PG 300 implying that premedication with PREGABALIN 150-300 mg prevent stress response to intubation and thereafter control DBP through the intraoperative period. The findings were in consonance with studies made by Gupta *et al.*[11] Khetarpal *et al.*[12] Rastogi *et al.*[13] Bhagat *et al.*[14] Chandra *et al.*[15] and Salma *et al.*[16].

A lower MRSS means less sedation, so it can be inferred that in our study both intervention groups had and comparable sedation as compared to the placebo group where patients were, more often than not, anxious and agitated with nil sedation. These observations were similar to studies made by White *et al.*[17] Gupta *et al.*[11] Bhagat *et al.*[14] Salma *et al.*[16] Rajappa *et al.*[18] and Meena *et al.*[19].

The inter-group comparison showed that VAS scores across all set time intervals have statistically significant difference (p<0.001) from PACU to 24 hr post-discharge from PACU when group C is compared with Group PG 150 and Group PG 300 with mean difference highest in Group C, intermediate in group PG 150, lowest in Group PG 300. The observations aligned with studies done by Ittichaikulthol *et al.*[20] Agarwal *et al.*[21] Freedman[22], Gupta *et al.*[11] Bhagat *et al.*[14] Salma *et al.*[16] Rajappa *et al.*[18] Clarke *et al.*[23] Alimian *et al.*[24] and Wang *et al.*[25]. Intra-op fentanyl was used with a stress response to post-intubation (PI) and thereafter whenever there were signs of inadequate analgesia as per protocol at 0.5 µg kg body weight. Our study showed that the association of the number of intra-op fentanyl top-ups was statistically significant (p<0.0001) when the comparisons were drawn between the Placebo (Group C) and the intervention group (Group PG 150 and Group PG 300). The mean consumption of Inj fentanyl across all intervals 96.22% in Group C, 2.83% in group PG 150 and 0.94% in group PG 300. The findings were in concordance with conclusions drawn by studies by Ittichaikulthol *et al.*[20] Freedman[22], Gupta *et al.*[11] Salma *et al.*[16] Clarke *et al.*[23] and Wang *et al.*[25].

Rescue Analgesia was given once the patient complained of pain (VAS score 2 or more) after the patient was shifted to PACU after the operation and the in the first 24 hr period follow up. In PACU Inj Paracetamol consumption was highest in the Placebo Group C (mean 91.76%) minimal in group PG 150 (mean 5.88%) and negligible in PG 300 (2.35%). The observations align with studies made by Khetarpal *et al.*[12] Bhagat *et al.*[14] Rajappa *et al.*[18] Routray *et al.*[26] and Bafna *et al.*[27].

As compared to placebo group, both intervention groups has better attenuation of stress response and haemodynamic stability with significant fentanyl sparing. However, though both the intervention groups

have comparable sedation levels, pregabalin 300 mg has better postoperative pain relief and minimal consumption of rescue analgesics. The notable shortcomings of this study were small sample size, single centre study. Large multicentric studies are required to validate our findings.

CONCLUSION

Pregabalin can be used as an effective premedication for patients undergoing General Anaesthesia. Premedication with Pregabalin has a fentanyl sparing effect, more in PG 300 group although PG 150 group was a close second. More intraoperative fentanyl, rescue analgesia (Paracetamol 1 gm) and second rescue analgesic was required in the control group compared to PG 150 and PG 300.

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