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Comparison of Efficacy of Pre-Operative Oral Pregabalin versus Oral Gabapentin on Postoperative Analgesia in Patients undergoing Lower Abdominal Surgeries under Spinal Anaesthesia : A Prospective, Randomized, Controlled Study

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Abstract: ***Objective: Our aim was to compare post-operative analgesic potency of oral pregabalin 150mg and gabapentin 600mg administered pre-operatively in patients subjected to lower abdominal surgeries under sub-arachnoid block (SAB). Methods: 90 patients posted for lower abdominal surgery under SAB were randomly allocated to three groups - P, G and C with thirty patients in each group. Cap.Pregabalin 150 mg was administered to Group P (Pregabalin group), Cap. Gabapentin 600mg to Group G (Gabapentin group) and Cap.vitamin B complex to Group C (control group) 1 hour before surgery. Our primary objective was to record time to first rescue analgesic (IV Diclofenac 75mg) requirement and total analgesic consumption 24 hours post-operatively. Results: Post-operatively, Time to first rescue analgesic requirement was Group P > Group G > Group C [9h 19 min ± 3h 50min, 6h 12min ± 3h 52min, 4h ± 1h 39min, respectively (P = 0.001)] and mean rescue analgesic requirement was also Group P > Group G > Group C. Group P showed highest time to two-segment regression of sensory blockade, stable post-operative hemodynamic status and minimal adverse effects. Conclusion: Pregabalin has a better pre-emptive analgesic profile in comparison with Gabapentin***

Keywords: Pregabalin, Gabapentin, lower abdominal surgeries, post-operative analgesia, pre-emptive analgesia

1. Introduction

"Pain" is a very unpleasant emotional and sensory experience which is related to actual or potential tissue damage [1]. Bulk of lower abdominal surgeries are conducted under SAB which however, has a relatively short duration of action. Post-operative pain which ranges from moderate to severe can reduce patient mobility in the initial post-operative period, delay hospital discharge and also lead to chronic pain.

The customary modality to profferpain relief post-operativelyis opioid analgesics. Regardless of its' efficacy, opioids have numerous side effects including possibility of addiction thus preventing appropriate prescription which further leads to poor pain management.

Pre-emptive analgesia, instituted prior to the surgeryavoids initiation of central sensitization elicited by traumatranspiring during surgery and initial post-operative phase. [2] On account of this safety feature, pre-emptive analgesia shows the promise to be more effective than any other analgesic treatment started after the surgery.Pregabalin and Gabapentin are GABA analogues with anti-nociceptive, anti-hyperalgesic and anti-allodynic properties. In our study we used these two drugs to provide pre-emptive analgesia.

2. Literature Survey

Pregabalin and gabapentin have a proven role in the treatment of neuropathic pain and as adjuvants in the treatment of chronic pain. However there are few studies which discuss their role in pre-emptive analgesia and treatment of post-operative pain. Thus,the main intention of our research was to compare post-operative analgesic potency of 150mg Pregabalin and 600mg Gabapentin administered orally as pre-medication in patients subjected to lower abdominal surgeries under SAB in terms of extent of post-operative analgesia, curtailment in total post-operative requisition of analgesics and to also note the occurrence of any side effects and/or complications attributed to these drugs.

3. Methodology

This work was piloted in our institute after acceptance from the Institutional Research Ethics Committee, between December 2019 and December 2020. It was a prospective,

comparative, randomized, controlled, single blinded clinical study.

At the outset, a paired t test was done to decide the sample size following which consent was taken and the patients were admitted into the research. 90 Patients in age group 20-50 years,of both sexes, belonging to American Society of Anaesthesiologists (ASA) physical status I or II, lined up for elective lower-abdominal surgeries were selected for the study and patients with contraindications to spinal anesthesia, history of allergy to pregabalin or gabapentin and pregnant females were eliminated from the study. Patients were then arbitrarily allocated by chit method into three groups with 30 patients in each group –Pregabalin group (Group P), Gabapentin group (Group G) and Control group (Group C).

On day of surgery, patients were handed a sealed envelope containing the capsule which they were instructed to take 1 hour before surgery with a sip of water. This way patients were blinded about the treatment they were receiving. Patients in groups P, G and C were given Cap. Pregabalin 150 mg, Cap.Gabapentin 600mg and Cap.vitamin B complex respectively. In the pre-operative room, patient's information and baseline vitals were documented and intravenous (IV) access was secured.

In the operating theatre (OT), preloading done with 7-10ml/kg ringer's lactate solution over 20 minutes and connected to a multipara monitor and vitals were recorded. Patient was placed in seated posture and under absolute aseptic conditions, spinal anaesthesia was administered using 23/25G Quinke spinal needle at L3-L4 or L4-L5 inter-spinous space and 3ml of (0.5%) hyperbaric bupivacaine was administered after checking for free flow of CSF. The patient was then asked to lie down in supine position and hemodynamic parameters were recorded.

Pin-prick test and Modified Bromage scale were used to assess the maximum level of sensory and motor blockade respectively. This was repeated every 15 minutes until the time to two-segment regression of sensory blockade level was reached and the value was recorded. Intra-operatively, patients who manifested a drop in mean arterial pressure (MAP)<65 mmHg were given IV. Mephenteramine 3 mg and those who showed a drop in heart rate(HR)<50 beats/min were given IV atropine 0.6 mg and the event was recorded.

In the post-operative period, degree of sedation was evaluated using Ramsay Sedation Score (RSS) and pain by Visual Analog Scale (VAS) at immediate post-op, two hours, four hours, six hours, twelve hours, eighteen hours and twenty four hours post-operatively. The time to first rescue analgesic demand was described as time from completion of surgery up till the first demand for rescue analgesic and the duration of effective analgesia was designated as the time from the induction of spinal anaesthesia up till first demand for rescue analgesic. The cumulative dose of analgesic required in a 24 hour period was also recorded. Occurrence of any side effects such as allergic reactions, dizziness, nausea, retching, visual disturbances, urinary retention and etcetera were treated according to routine hospital protocol and the event was recorded. Inj. Diclofenac 75mg aqueous preparation was administered IV as a rescue analgesic when VAS score was more than or equal to four.

4. Results

At the outset, data was logged into Microsoft excel from the custom-made format, for analysis. Graph Pad and Epi Info software was utilized for computing the P values. Collation of means betwixt the three Groups was achieved using chi-square test, ANOVA test and post-hoc Tukey test. Descriptive statistics was propounded as numbers and percentages. Value was considered statistically significant if 'p' value was less than 0.05. The concluding data was set forth in the form of tables and graphs.

All patients in the 3 groups were found to be comparable in their demographic profile (age, sex, ASA grade, type of surgery and time-duration of surgery) (P value > 0.05) [Table 1- Demographic profile of patients]

Variables	Group P	Group G	Group C	F value	P value	Post-hoc Tukey (p value)		
						P-G	P-C	G-C
Age	38.10 ± 10.29	38.67 ± 11.21	35.07 ± 11.63	0.919	0.403, NS	0.979, NS	0.540, NS	0.421, NS
Sex :	**Group P**	**Group G**	**Group C**					
Male	27 (90.0%)	26 (86.7%)	26 (86.7%)		0.902, NS			
Female	3 (10.0%)	4 (13.3%)	4 (13.3%)					
total	30 (100.0%)	30 (100.0%)	30 (100.0%)					
ASA Grade :	**Group P**	**Group G**	**Group C**					
Grade 1	19 (63.3%)	17 (56.7%)	22 (73.3%)		0.398, NS			
Grade 2	11 (36.7%)	13 (43.3%)	8 (26.7%)					
Type of Surgery	**Group P**	**Group G**	**Group C**					
Colostomy closure	5 (16.7%)	4 (13.3%)	6 (20.0%)		0.949, NS			
Fistulectomy	1 (3.3%)	2 (6.7%)	1 (3.3%)					
Hemorrhoidectomy	3 (10.0%)	3 (10.0%)	3 (10.0%)					
Hernioplasty	17 (56.7%)	19 (63.3%)	18 (60.0%)					
Hydrocelectomy	1 (3.3%)	0 (0.0%)	0 (0.0%)					
Orchidectomy	0 (0.0%)	1 (3.3%)	1 (3.3%)					
Pilonidal sinus excision	1 (3.3%)	0 (0.0%)	0 (0.0%)					
Stripping	1 (3.3%)	1 (3.3%)	1 (3.3%)					
Varicocelectomy	1 (3.3%)	0 (0.0%)	0 (0.0%)					

Duration of surgery:	95.07 ± 24.21	99.77 ± 24.35	92.30 ± 24.14	0.728	0.486, NS	0.734, NS	0.898, NS	0.460, NS

*NS – not significant

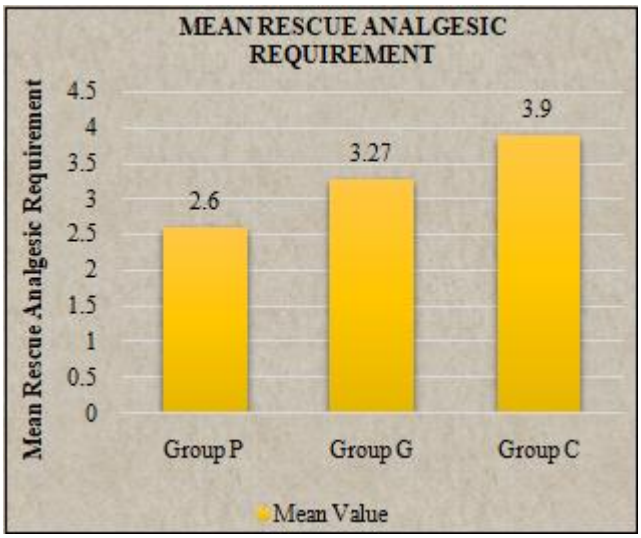
The mean **time to two-segment regression of sensory blockade** was highest in Group P 98 min 16 sec ± 5 min 19 sec, followed by Group G 92 min 12 sec ± 4 min 51 sec and least in Group C 83 min 12 sec ± 6 min 2 sec, (p=0.001) [Table.2 – Comparison of time to two-segment regression of sensory blockade].

Group	No.	Time to 2 segment regression of sensory block (min) [Mean±SD]	F value	P value	Post-hoc Tukey (p value)		
					P-G	P-C	G-C
Group P	30	98.27 ± 5.32	58.511	0.001*	0.001*	0.001*	0.001*
Group G	30	92.20 ± 4.85					
Group C	30	83.20 ± 6.04					

The **mean time to first rescue analgesic requirement** in Group P was 9h 19 min ± 3h 50min, in Group G it was 6h 12min ± 3h 52min and in Group C it was 4h ± 1h 39min (p=0.001) [Table.3 - Comparison of mean time to first rescue analgesic requirement].

Group	No.	Time to first request for rescue analgesic (hours) [Mean±SD]	F value	P value	Post-hoc Tukey (p value)		
					P-G	P-C	G-C
Group P	30	9.33 ± 3.84	19.915	0.001*	0.001*	0.001*	0.030*
Group G	30	6.20 ± 3.87					
Group C	30	4.00 ± 1.66					

The **mean number of doses of rescue analgesia** required in the 3 groups was least in group P (1 - 3), followed by Group G (2 - 4) and highest in Group C (3 - 5), (P=0.001). [Fig.1 - Bar diagram showing comparison of mean rescue analgesic requirement]



The mean **VAS score** was comparable between the three groups till two hours post-operatively. At four hours and six hours postoperatively, the mean **VAS score** was highest in Group C, slightly lesser in Group G and lowest in Group P which was statistically significant. From 12 hours postoperatively, the mean **VAS score** was found to be comparable among the three groups (P>0.05). [Table 4 - Comparison of mean VAS between the three groups at different time intervals]

Time Interval	Group	No.	Pain Score [Mean±SD]	F value	P value	Post-hoc Tukey (p value)		
						P-G	P-C	G-C
Immediate Postoperative	Group P	30	0.00 ± 0.00	0.677	0.511, NS	0.907, NS	0.486, NS	0.747, NS
	Group G	30	0.04 ± 0.20					
	Group C	30	0.10 ± 0.55					
2 hours postoperatively	Group P	30	1.18 ± 1.28	1.111	0.334, NS	0.554, NS	0.323, NS	0.913, NS
	Group G	30	1.71 ± 2.12					
	Group C	30	1.92 ± 2.36					
4 hours postoperatively	Group P	30	2.57 ± 0.94	13.676	0.001*	0.071, NS	0.001*	0.010*
	Group G	30	3.10 ± 1.04					
	Group C	30	3.81 ± 0.74					
6 hours postoperatively	Group P	30	3.81 ± 0.90	10.713	0.001*	0.006*	0.001*	0.361, NS
	Group G	30	4.82 ± 1.28					
	Group C	30	5.26 ± 1.48					
12 hours postoperatively	Group P	30	4.56 ± 0.84	1.567	0.214, NS	0.873, NS	0.203, NS	0.443, NS
	Group G	30	4.69 ± 1.16					
	Group C	30	5.03 ± 1.17					
18 hours postoperatively	Group P	30	4.18 ± 0.91	1.886	0.158, NS	0.882, NS	0.154, NS	0.350, NS
	Group G	30	4.29 ± 1.03					
	Group C	30	4.61 ± 0.69					
24 hours postoperatively	Group P	30	4.09 ± 0.69	1.365	0.261, NS	0.350, NS	0.311, NS	0.997, NS
	Group G	30	4.39 ± 0.85					
	Group C	30	4.40 ± 0.92					

The **Mean Ramsay Sedation Score** between the three groups at different time intervals was found to be comparable [Table 4 -Comparison of mean sedation score between the three groups at different time intervals]

Time Interval	Group	No.	Sedation Score [Mean±SD]	F value	P value	Post-hoc Tukey (p value)		
						P-G	P-C	G-C
Immediate Postoperative	Group P	30	2.13 ± 0.97	0.667	0.516, NS	0.511, NS	0.684, NS	0.958, NS
	Group G	30	2.40 ± 0.89					
	Group C	30	2.33 ± 0.92					
2 hours postoperatively	Group P	30	2.03 ± 0.93	0.299	0.742, NS	0.746, NS	0.829, NS	0.988, NS
	Group G	30	2.20 ± 0.85					
	Group C	30	2.17 ± 0.87					
4 hours postoperatively	Group P	30	1.77 ± 0.73	0.303	0.740, NS	0.736, NS	0.841, NS	0.981, NS
	Group G	30	1.90 ± 0.66					
	Group C	30	1.87 ± 0.68					
6 hours postoperatively	Group P	30	1.50 ± 0.57	1.132	0.327, NS	0.343, NS	0.474, NS	0.970, NS
	Group G	30	1.70 ± 0.54					
	Group C	30	1.67 ± 0.55					
12 hours postoperatively	Group P	30	1.33 ± 0.48	0.938	0.395, NS	0.402, NS	0.557, NS	0.964, NS
	Group G	30	1.50 ± 0.51					
	Group C	30	1.47 ± 0.51					
18 hours postoperatively	Group P	30	1.13 ± 0.35	0.496	0.610, NS	0.792, NS	0.592, NS	0.943, NS
	Group G	30	1.20 ± 0.41					
	Group C	30	1.23 ± 0.43					
24 hours postoperatively	Group P	30	1.03 ± 0.18	0.524	0.594, NS	0.564, NS	0.866, NS	0.866, NS
	Group G	30	1.10 ± 0.31					
	Group C	30	1.07 ± 0.25					

The **total time span of analgesia** (time-span from institution of spinal anaesthesia to first request for rescue analgesia) in Group P was 10h 55min ± 3h 52min, Group G was 7h 52min ± 3h 54min and Group C was 5h 33min ± 1h 42min, (p=0.001).**Side effects** like somnolence, dizziness, vomiting, ataxia, vertigo, visual disturbances, headache, etc were not encountered.

5. Discussion

Post-operative management of pain and its complications is still a major challenge. Pre-incisional or pre-emptive analgesia has demonstrated effective post-operative pain control by reducing the altered central sensory processing and preventing development of chronic pain by inhibiting long term potentiation of pain.

Gabapentin and Pregabalin are gamma amino butyric acid (GABA) analogues which function by attaching to voltage gated calcium channels'- pre-synaptic alpha-2-delta (α2δ) subunit which are found abundantly in the spinal cord and the brain, thus supressing calcium in rush followed byliberation of excitatory neurotransmitters[3] in the pain pathways. This in turn stimulates descending inhibition, thereby decreasing dorsal horn hyper excitability initiated by tissue damage. Pregabalin and Gabapentin have proven utility in the treatment of neurogenic pain and could be valuable in acute post-op pain as well. [4]

In our study we found that the mean **time to two-segment regression of sensory blockade** was highest in Group P 98 min 16 sec ± 5 min 19 sec, followed by Group G 92 min 12 sec ± 4 min 51 sec and least in Group C 83 min 12 sec ± 6 min 2 sec and the **mean time to first rescue analgesic requirement**in Group P was 9h 19 min ± 3h 50min, in Group G it was 6h 12min ± 3h 52min and in Group C it was 4h ± 1h 39min which was statistically significant (p=0.001). These results corroborated with that of **Omara AF et al.** [5]

The **mean NRS score** was comparable between the three groups till two hours post-operatively. At four hours and six hours postoperatively, the mean NRS score was significantly highest in Group C, a slightly lesser in Group G and lowest in Group P. From 12 hours postoperatively, the mean NRS score was found to be comparable among the three groups (P>0.05). The mean **Ramsay Sedation Score** between the three groups at different time intervals were also found to be comparable. There was no significant sedation with the use of either Pregabalin or Gabapentin. These findings were comparable to that of **Routray SS et al.** [6]

We compared the **mean number of rescue analgesic requirement** in the 3 groups and found that it was least in group P (1 - 3), followed by Group G (2 - 4) and highest in Group C (3 - 5) and the **total time span of analgesia** (time-span from institution of spinal anaesthesia to first request for rescue analgesia) in Group P was 10h 55min ± 3h 52min, Group G was 7h 52min ± 3h 54min and Group C was 5h 33min ± 1h 42min, which was statistically significant (p=0.001).

6. Conclusion

From our study, the following conclusions can be derived - Both Cap.Pregabalin 150mg and Cap.Gabapentin 600mg can be used for pre-emptive analgesia as they significantly prolong the extent of post-operative analgesia. They portrayed stable intra and post-operative hemodynamics and a good safety profile. The **mean time to two-segment regression of sensory blockade** was significantly higher in Pregabalin group in comparison to Gabapentin group and Control group and in Gabapentin group it was significantly higher in comparison to Control Group. **Ramsay Sedation Score** was analogous between the three groups and no significant sedation was found with the use of Cap.Pregabalin 150mg and Cap.Gabapentin 600mg. **Mean number of doses of rescue analgesia** was least in Pregabalin group followed by Gabapentin group and highest

in Control group. Pre-emptive Pregabalin displays better **post-operative pain control** and reduces rescue analgesic consumption in post-operative period when compared with pre-emptive Gabapentin and has an added benefit of ameliorating perioperative anxiety.

Hence, it could be postulated that Pregabalin may also be used successfully in the multimodal analgesic approach to prevent acute post-operative pain, much like Gabapentin, which already has an established role.

7. Future Scope

Whilst this study has striven to achieve all the aims and objectives to the best possible extent, there are a few **limitations** such as: We conducted the study in a single center, pregnant females were not included in our study and pre-operative anxiety was not assessed and recorded. To overcome these limitations, a multi-centric study with a substantial sample size would be called for to obtain more conclusive results.

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