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A Comparative Study of Oral Gabapentin and Oral Clonidine as Preemptive Analgesia under Spinal Anesthesia for Abdomino-Pelvic Surgeries

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Abstract

Aim: To assess the effect of oral Gabapentin and oral Clonidine used as Preemptive analgesia to attenuate postoperative pain in patients undergoing elective Abdomino-Pelvic surgeries under Spinal Anesthesia. *Objective:* To assess postoperative analgesic benefit, their postoperative efficacy with respect to duration of analgesia and total postoperative requirement and side effects if any of both the groups. *Material and Method:* 60 patients of either sex of age between 18-65 years, ASA grade I & II, patient admitted to Khaja banda nawaz teaching and general hospital for elective abdominal surgeries under spinal anesthesia were included in the study. The patients were randomly allocated into two groups of 30 each, group G received Gabapentin 300 mg tablet orally 90 min before surgery, group C received clonidine 100 µg tablet orally 90 min before surgery. Duration of postoperative analgesia, Degree of postoperative pain (VAS score) and added rescue analgesia required in 24 hrs were recorded postoperatively. *Result:* Analysis revealed the postoperative analgesic efficacy of oral Gabapentin showed better pain tolerance compared to that of oral Clonidine. The Ramsay sedation score showed a significant sedative effect by Gabapentin than in Clonidine at 90 mins, haemodynamic parameters changes suggested Gabapentin to be haemodynamically stable than clonidine, Morphine consumption in 24 hrs was significantly high in Clonidine group with increased incidence of nausea and vomiting. *Conclusion:* Oral Gabapentin 300 mg given before 90 minutes as preemptive analgesia was more effective in reducing postoperative pain and morphine consumption, also providing better anxiolysis in patients undergoing abdomino-pelvic Surgeries under spinal anesthesia compared to Oral Clonidine 100 µg.

Keywords: Analgesia; Clonidine; Gabapentin.

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Introduction

Anesthesia as a subject by itself originated in an endeavor to offer pain relief to the patient during surgical procedures. But acute pain following surgery has been managed inadequately because of wide variety of myths and fears. The incidence of post operative pain has been found to be between 25%-76%.[1]

Preemptive analgesia is an antinociceptive treatment that prevents establishment of altered processing of afferent input, which amplifies postoperative pain. The concept of preemptive analgesia was formulated by Crile at the beginning

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of the previous century on the basis of clinical observations.

Three different definitions have been used as the basis for the recent clinical trials. Preemptive analgesia has been defined as treatment that:

1. Starts before surgery;
2. Prevents the establishment of central sensitization caused by incisional injury (covers only the period of surgery);
3. Prevents the establishment of central sensitization caused by incisional and inflammatory injuries (covers the period of surgery and the initial postoperative period).[2]

Owing to this 'protective' effect on the nociceptive system, pre-emptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery. Gabapentin, a structural analog of gamma aminobutyric acid, is used as an anticonvulsant drug since 1993. Their main site of action is α_2-δ ligand that has analgesic, anxiolytic and sleep-modulating activities Pre-treatment with gabapentin can block the development of hyperalgesia. Studies have demonstrated that mechanical hyperalgesia surrounding the wound in postoperative patients and experimentally, heat-induced, secondary hyperalgesia share a common mechanism and that central neuronal sensitization contributes to post-operative pain. Gabapentin has a selective effect on the nociceptive process involving central sensitization.[3,4]

Clonidine, a centrally acting α_2 agoinst is a potent antihypertensive drug has shown properties that are potentially beneficial for premedication to reduce sympathetic activity, to minimize fluctuations in the hemodynamic profile during anesthetic induction and to decrease anesthetic requirement for both opioid and volatile anesthetics. Clonidine provides significant benefits for preoperative anxiety and analgesia. Clonidine has non-opiate antinociceptive properties, which might be used as an alternative to postoperative analgesia without opioid-induced side effects.[5,6]

Hence the present study will be done to study & compare effects of Oral Gabapentine & Oral Clonidine on Post-operative analgesia in abdomino-pelvic surgeries when used along with central neuraxial blockade as a Preemptive analgesia.

Materials and Methods

A prospective randomized double blind study was conducted in Khaja Banda Nawaz Teaching and general hospital Kalaburagi for the collection of data. 60 patients of ASA grade I and II between age group 18-65 years scheduled for elective abdomino-pelvic Surgeries, with estimated duration of surgery 90-120 minutes, to be performed under SAB were enrolled in the study after obtaining clearance from the institutional ethical committee. After taking a detailed history, thorough general physical examination, and all pertinent investigation were carried out to exclude any systemic disease. Exclusion criteria included: 1) Patient refusal, 2) history of Uncontrolled Hypertension, Diabetes, and Liver disease & Peripheral vascular disease 3) Pregnant & Lactating patients, 4) Patients on Antihypertensive drugs, Sedatives, Hypnotics, Antidepressants, Corticosteroids, 5) Patients with Chronic pain syndrome & patients who have taken NSAID in last 48 hrs, 6) Patients having absolute contraindication for spinal anesthesia 7) Patients already taking oral Gabapentin, oral Clonidine.

Consent was taken, the procedure was explained to each patient. Absolute fasting of at least 8 hours was advised, without (prior) administering any premedication. ***Visual Analog Score and Ramsay Sedation score***, was explained to the patients. Patient's basal pulse rate and basal blood pressure was recorded. A peripheral intravenous line with 20 gauge cannula was secured in one of the upper limbs. Patients were preloaded with 10 ml/kg of Ringer lactate 30 minutes prior to the scheduled time of surgery and all Haemodynamic parameters were recorded. Patients were randomly divided in two groups by a staff nurse who was not involved in the study.

Group G: recieved Tablet gabapentin 300 mg orally 90 mins preoperatively.

Group C: recieved Tablet Clonidine 100 µg orally 90 mins preoperatively.

Hemodynamic parameters were noted. Upon the arrival in Operation room, Baseline Non-Invasive Blood Pressure (NIBP), Electrocardiogram (ECG), Pulse Rate (PR) and Oxygen Saturation (SpO_2%) was noted & monitored, thereafter Under aseptic precautions Lumbar puncture was performed with 25 gauge Quincke's spinal needle using a midline approach with the patients in the left or right lateral decubitus position at lumbar 3-4 inter space and when a free flow of clear cerebrospinal fluid is obtained, the local anaesthetic agent that is 3.5 ml of 0.5% hyperbaric Bupivacaine administered. Immediately after the injection the needle withdrawn, the patient turned supine, onset of sensory block upto T6 dermatome assessed bilaterally by loss of pinprick sensation with a short

hypodermic needle and we will allow the surgery to begin.

Parameters measured

- Ramsay sedation score, Heart rate, Systolic & Diastolic BP just before giving the drug orally in the ward on the day of surgery till taking the patient to OT.
- Heart rate, Systolic & Diastolic BP just before the start & the end of the spinal subarachnoid block on OT table.
- Onset of sensory blockade, Maximum sensory blockade, Duration of two segment sensory regression.
- Post-operatively, patients pain by VAS at 1, 4, 8, 12, 24 hours after surgery.
- Duration of analgesia.
- Morphine received in this 24 hr was noted.
- Nausea & Vomiting, if any, & other side effects of both drugs were recorded.

Statistical Analysis

Student's Unpaired, t' test, chi-square test, Kolmogorov-Smirnov test.

Significant figures: Two tailed $p<0.05$ taken as significant.

Statistical software: The Statistical software namely SAS 9.2, SPSS 18 for Windows (SPSS Inc., Chicago, Illinois)., Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables.

Results

Table 1: Age, gender and weight wise distribution of patients

Parameters	Clonidine	Gapapentine
Gender		
Male	17	16
Female	13	14
Age in years Mean ± SD	46.40 ± 21.02	46.93 ± 19.69
Weight in Kgs. Mean ± SD kgs.	60.43 ± 8.02	61.4 ± 7.77

Table 2: Comparison of haemodynamic parameters in oral Clonidine and oral Gabapentine group from Preoperative baseline, after morning dose of drug, and Intra-operative duration

Haemo-dynamic parameters	Preoperative Baseline		After Morning Dose of Drug				Intraoperative at 140 min	
			10 mins		90 mins			
	C (n=30) Mean ± SD	G (n=30) Mean ± SD	C (n=30) Mean ± SD	G (n=30) Mean ± SD	C (n=30) Mean ± SD	G (n=30) Mean ± SD	C (n=30) Mean ± SD	G (n=30) Mean ± SD
Systolic blood pressure (SBP)	117.60 ± 22.06	125.07 ± 14.31	122.27 ± 11. 15	126.20 ± 12.73	115.26 ± 11.62	121.60 ± 11.24	108.73 ± 10.65	119.46 ± 9.03
Diastolic blood pressure (DBP)	77.00 ± 12.05	76.86 ± 10.85	76.60 ± 10.03	78.46 ± 8.70	71.53 ± 9.83	75.26 ± 9.18	67.8 ± 9.99	74.33 ± 7.83
Heart rate	77.27 ± 7.49	80.33 ± 9.56	79.13 ± 7.09	81.60 ± 7.76	74.40 ± 6.22	80.73 ± 8.46	74.20 ± 7.32	79.40 ± 5.61

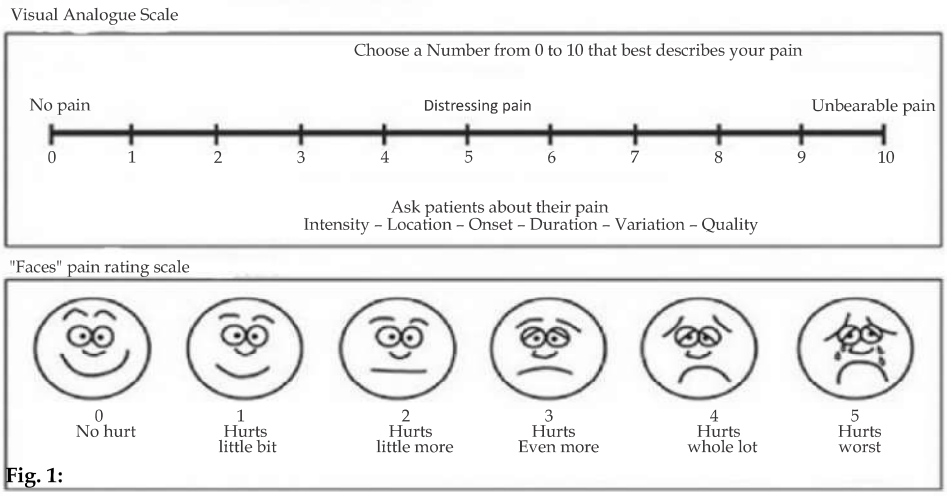

Fig. 1:

Mean age in Clonidine group was 46.40 ± 21.02, and in oral Gabapentin group was 46.93 ± 19.69 (p 0.397). Mean weight in Clonidine group was 60.43 ± 8.02, and in oral Gabapentin group was 61.4 ± 7.77 (p 0.328). There was no significant difference in the age distribution of patients between the groups (p >0.05) (Table 1).

By applying Student's Unpaired 't' test, there is a significant difference between mean values of SBP, DBP and Heart rate after morning dose of drug at 10 minutes, at 90 minutes and Intra-operative at 140 minutes in Clonidine and Gabapentine groups (p < 0.05) (Table 2).

By applying Student's Unpaired, t' test there is a no significant difference between time of sensory, maximum sensory block, duration of 2 segment regression when Clonidine group is compared with Gabapentine group (p > 0.05) (Table 3).

Sedation score in group Clonidine was 1 in 10 patients (33.33%) and 2 in 8 patients (26.66%) which suggests more number of patients were Anxious or restless or both. In Gabapentin group sedation score was 2 in 7 patients (23.33%) and 3 in 13 patients (43.33%) suggesting that more number of patients were awake and responding to commands. Also, 5 patients (16.66%) had a score of 4 and 2(6.66%) patients had score of 5 in the Gabapentin group suggesting they were deeply sedated (Table 4).

Gabapentin group in comparison with Clonidine had significantly lower VAS at 8 h after surgery (p < 0.05). The VAS pain scores at measured times 1st, 4th, 12th & 24th hr were lower in the Gabapentin group than the Clonidine group. The difference was not considered significant (p > 0.05). Patients who were premedicated with Gabapentin showed better pain tolerance compared to those who had been given Clonidine (Table 5).

Duration of analgesia: p value between Clonidine group vs Gabapentin group was 0.001 which was statistically significant suggesting that total duration of analgesia was more in Gabapentin group than in Clonidine.

Duration of Surgery: There was no significant difference for the duration of surgery when both the groups were compared (p > 0.05).

Morphine Consumption: The total postoperative IV morphine in Gabapentin group was significantly less than in the Clonidine group; (p < 0.001).

1 of 30 the Patients in Gabapentin group did not require Morphine IV ; whereas 100% (all 30) patients who received Clonidine required Morphine IV.

Gabapentin group showed lesser incidence of requiring Morphine, but in those who did require, they showed longer duration and intensity of pain compared to Clonidine group. Patients in the Clonidine group showed higher incidences of requiring relief (Table 6).

Table 3: Comparison of Sensory Block parameters in oral Clonidine and oral Gabapentin

Sensory block	Clonidine (n=30) Mean ± SD	Gabapentine (n=30) Mean ± SD	Student's unpaired 't' test value	'p' value and result
Time of sensory onset to T10	172.66 ± 19.81	173.00 ± 24.91	0.057	p>0.05, not significant
Maximum sensory block T6	292.33 ± 22.33	295.00 ± 18.89	0.57	p>0.05, not significant
Duration of 2 segment regression	104.33 ± 11.50	100.67 ± 12.78	0.46	p>0.05, not significant

Table 4: Comparison of Ramsay Sedation Score in oral Clonidine and oral Gabapentin group from preoperative baseline and 90 min. after drug preoperatively

Ramsay Sedation Score	Gabapentine (n=30)		Clonidine (n=30)	
	Baseline No. (%)	90 min after drug No. (%)	Baseline No. (%)	90 min after drug No. (%)
1	30(100%)	3(10%)	30(100%)	10(33.33%)
2	0	7(23.33%)	0	8(26.66%)
3	0	13(43.33%)	0	8(26.66%)
4	0	5(16.66%)	0	4(13.33%)
5	0	2(6.66%)	0	0
6	0	0	0	0

Table 5: Comparison of Postoperative Visual Analog Score (VAS) in oral Clonidine & Gabapentin at 1st, 4th, 8th, 12th and 24th hours

Post Operative visual analog score	Gabapentine (n=30) Mean ± SD	Clonidine (n=30) Mean ± SD	'p' value
1st hour	4.23 ± 1.75	4.33 ± 1.71	0.823
4th hour	3.33 ± 1.66	3.77 ± 1.99	0.356
8th hour	2.43 ± 1.95	3.70 ± 1.93	0.014
12th hour	2.26 ± 1.89	3.00 ± 2.08	0.154
24th hour	1.43 ± 1.38	1.61 ± 1.12	0.581

Table 6: Comparison of duration of analgesia and surgery and I.V morphine consumption in oral Clonidine and oral Gabapentine

	Gabapentine (n=30) Mean ±SD	Clonidine (n=30) Mean ±SD	'p' value and result
Duration of Analgesia (mins)	238.33 ± 50.45	217.00 ± 11.45	p<0.001, significant
Duration of Surgery (mins)	115.33 ± 13.06	117.00 ± 12.07	p>0.05, not significant
Total Morphine consumption in 24 hrs (I.V.)	9.84 ± 5.28 mg	13.92 ± 6.65 mg	p<0.001, significant

Discussion

Preoperative anxiety has been found to be one of the major predictor of post operative pain. The postoperative period was defined as the period between arrival of the patient in recovery room to 7 days after surgery, with day 1 being 24 hours after surgery.

The world needs to have cheaper, safer economical ways of postoperative pain management in contrast to highly technologically dependent majors prevalent in western world. Opioids have been the mainstay of post operative pain management but these have adverse effects of respiratory depression, pruiritis, constipation, and development of tolerance.

Results of our study shows that at 8th postoperative hour, mean VAS scores of Gabapentin group was significantly lesser than Clonidine group (p=0.014). The Postoperative morphine consumption in Gabapentin group was significantly less than Clonidine (p<0.01). Also, patients who were premedicated with Gabapentin showed better pain tolerance compared to those who had been given Clonidine, the results are in accordance with studies conducted by Mohd Hossein Ghafari *et al.*[7], Sussan Soltani Mohammadi *et al.*[8] which states that VAS pain scores were significantly lower in the two groups compared to the placebo group, Total morphine consumption in gabapentin group was significantly less than clonidine and gabapentin administration significantly decreased morphine consumption by 25% in comparison to clonidine.

Our study shows significant association between Ramsay sedation score & when both drugs are compared, Gabapentin showed a better sedative. study conducted by Jay Brijesh *et al.*[9], Vikas Saini *et al.*[10] and Singhal *et al.*[11] states that clonidine is effective in attenuating preoperative anxiety & stress response to endotracheal intubation when compared to gabapentin (p<0.05). Majumdar et al.[12] conducted a similar study and observed that both drugs are equally effective in producing preoperative sedation. In our study the time for 2 segment sensory regression was prolonged in Clonidine group but it was not considered statistically significant when compared to Gabapentin group.

The effect of clonidine on hemodynamic parameters is similar to the study done by H.Talebi *et al.*[14]. They observed decrease in HR and SBP with clonidine 200 mcg compared to placebo group which is highly significant. Fassoulaki A *et al.*[15] observed that gabapentin 1600 mg given at various time intervals decreases blood pressure but HR did not differ at all time intervals which was similar to our study in which Clonidine, showed significant fall in Systolic & Diastolic Blood pressure in comparison to Gabapentin group.

In a trial of 60 cases in which our research was applied,

1. The postoperative analgesic efficacy of oral Gabapentin showed better pain tolerance compared to those who had been given oral Clonidine.
2. The Ramsay sedation suggested good anxiolysis with Gabapentin.

3. As haemodynamic parameters changes in Gabapentin group were statistically insignificant, Gabapentin is considered haemodynamically stable.
4. Morphine consumption in 24 hrs was significantly high in Clonidine group compared to Gabapentin.
5. There were no significant change in time of sensory onset, maximum sensory block and duration of 2 segment regression when Clonidine was compared with drug Gabapentin.
6. In comparison of side effects, there was increased incidence of nausea and vomiting in Clonidine group.

Conclusion

We conclude that, Oral Gabapentin 300 mg given before 90 minutes as preemptive analgesia was more effective in reducing postoperative pain and morphine consumption, also providing better anxiolysis in patients undergoing abdomino-pelvic Surgeries under spinal anesthesia compared to Oral Clonidine 100 µg.

Conflict of Interest: None

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