

**PRE-EMPTIVE ORAL PREGABALIN VERSUS CLONIDINE FOR IMMEDIATE POST OPERATIVE PAIN IN SURGERIES UNDER SUB ARACHNOID BLOCK**Sumit Beniwal^{a*} and Satish Chaudhary^b^aAssistant Professor, Department of Anaesthesia, Saraswathi Institute of Medical Sciences, Hapur Rd, Anwarpur, Uttar Pradesh, India.^bAssistant Professor, Department of Orthopaedics, N.C. Medical College, Panipat, Haryana, India.***Corresponding Author: Dr. Sumit Beniwal**
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ABSTRACT

Introduction: One of the most important and pressing issue in the field of anesthesia and surgery is effective control of postoperative pain. It has significant impact on our health care system. Millions of people worldwide who undergo operations each year experience postoperative pain of varying intensity. **Aims and Objectives:** To evaluate postoperative analgesic benefit in patients administered pregabalin or clonidine or placebo as oral premedication for below umbilical surgeries performed under SAB. **Material and Methods:** The study was carried out in 90 patients scheduled for Elective below Umbilical Surgeries, with estimated duration of surgery 90-120 minutes, to be performed under SAB. Patients in treatment group were given Tab. Pregabalin 300mg or Tab. Clonidine 150mcg or placebo one hour before commencement of surgery. Statistical analysis was done and compared among groups. **Results:** The age in our study was 18-65 years. The comparison of total duration of analgesia in three groups was statistically significant. The mean duration in control group was 264.83 ± 13.67 minutes, mean duration of total analgesia in clonidine group was 492.66 ± 78.29 and duration of total analgesia in pregabalin group was 632.83 ± 103.95 minutes. Total dose of analgesic required in 24 hours in all the three groups was significant; p-value is 0.00 which was highly significant if compared with control group, else amongst CL & PG group it was also significant (p-value 0.016). The lowest VAS score was in pregabalin group at 30 minutes postoperatively and maximum seen at 12 hrs postoperatively followed by clonidine group and maximum was seen in control group. **Conclusion:** Clonidine hydrochloride 150 µg and pregabalin 300mg was found to be effective in reducing postoperative pain when given 1 hour preoperatively. Pregabalin proved to have a better analgesic effect than clonidine, reducing the total consumption of rescue analgesic and prolonging first rescue dose. Both the drugs are good alternative to each other and can be used safely as preemptive analgesia under SAB.

KEYWORDS: Pregabalin, SAB, analgesia.**INTRODUCTION**

Below umbilical surgeries are very commonly performed under *subarachnoid block (SAB)*, being simple and economical technique with complete muscle relaxation. It is advantageous due to high efficacy with less drug doses and less chances of aspiration pneumonitis. Due to its limitations in the form of lesser control of block height and limited duration of analgesia, researchers have used variety of drugs intrathecally like vasoconstrictors (epinephrine), opioids (fentanyl, buprenorphine) benzodiazepines (midazolam), ketamine and many others as adjuvant to local anaesthetics to prolong the duration of sensory block and achieve longer perioperative analgesia.^[1] But each of these adjuvant have certain limitations of their own, hence search for better options for acute postoperative analgesia research is still continuing. The concepts like

pre-emptive and multimodal analgesia could be the fruitful results of it. Poorly controlled postoperative analgesia results in harmful acute effects (adverse physiologic response) and chronic effects (delayed recovery) and chronic pain syndrome.^[2] Provision of effective pain relief is a prerequisite accelerated convalescence. Previously the drugs used for acute and chronic pain were categorically different. Opioids, NSAIDs and local anaesthetics were tools for dealing with acute pain and tricyclic antidepressants (TCAs) were used for chronic neuropathic conditions.

Pregabalin is a structural analogue of the inhibitory neurotransmitter γ -aminobutyric acid but it is not functionally related to it.^[3] Like its predecessor gabapentin, it binds to the α -2- δ subunit of voltage-gated calcium channels reducing the release of several excitatory neurotransmitters and blocking the

development of hyperalgesia and central sensitization.^[4,5] Pregabalin has anticonvulsant, antihyperalgesic and anxiolytic properties similar to gabapentin, but it has a more favourable pharmacokinetic profile including dose-independent absorption.^[6,7] It is also several times more potent than gabapentin while producing fewer adverse effects.^[3] Recently it has been introduced as an adjunct in the multimodal management of postoperative analgesia.^[8] *Clonidine* is an α_2 -adrenoreceptor agonist whose analgesic properties have been well documented in adults by many investigators for its various routes of administration like intravenous clonidine in spine surgery^[9]; intrathecally it prolongs spinal anaesthesia.^[10] Oral clonidine premedication produces a significant prolongation of spinal anaesthesia with bupivacaine^[11] or tetracaine^[12] and provides better pain relief in the early postoperative period after minor orthopaedic surgeries.^[13] Recently the role as oral pre-emptive analgesic of both the drugs viz. pregabalin^[14-16] and clonidine^[17-19] for postoperative pain relief has been reviewed.

AIMS AND OBJECTIVES

With the concept of pre-emptive analgesia for control of acute postoperative pain our primary aims were.

1. To evaluate postoperative analgesic benefit in patients administered pregabalin or clonidine or placebo as oral premedication for below umbilical surgeries performed under SAB.
2. To study their postoperative efficacy with respect to duration of analgesia and total postoperative requirement of analgesics.
3. To study side effects if any attributable to pregabalin or clonidine.

REVIEW OF LITERATURE

Pre-emptive analgesia is defined as a treatment that is initiated before surgery in order to prevent the establishment of central sensitization evoked by the incisional and inflammatory injuries occurring during surgery and in the early postoperative period.

Pregabalin

The use of *pregabalin* in acute postoperative pain management has been evaluated in recent studies. These studies sought to determine whether perioperative pregabalin was effective in reducing post operative pain and whether it had opioid-sparing effects. However, differences in the pregabalin dosages and types of surgery had yielded contrasting results.

In 2001 Hill CM et al conducted a study on pregabalin in patients with postoperative dental pain. They compared pregabalin to placebo and 400 mg of ibuprofen. Study medication was administered postoperatively, evaluated for pain relief (PR) and duration of analgesia. Pregabalin at doses of 50mg and 300mg showed that there were statistically significant differences in PR and duration of analgesia with 300-mg pregabalin group. In addition, the

300-mg pregabalin group had a significantly longer duration of analgesia than the ibuprofen group. They concluded that pregabalin had significant analgesic properties.

In 2006 Reuben SS et al conducted a study on the analgesic efficacy of celecoxib, pregabalin and their control as total placebo and concluded that perioperative administration of the combination of celecoxib and pregabalin improved analgesia and caused fewer side effects than either analgesic drug alone after spinal fusion surgery.

In 2008 Agarwal et al conducted a study and evaluated single preoperative dose of pregabalin to attenuate postoperative pain after laparoscopic cholecystectomy to be performed under G.A. Postoperative VAS was altogether less in pregabalin group than in placebo group.

In 2008 O.Mathiesen et al conducted a study on evaluating oral pregabalin and dexamethasone for postoperative pain control in patients undergoing hip arthroplasty under subarachnoid block. Group A (placebo + placebo), Group B (oral pregabalin 300mg + placebo), Group C (oral pregabalin 300mg + dexamethasone 8mg intravenously). VAS pain score at rest and during mobilization were observed. They concluded that 24hr morphine consumption was significantly reduced in Group B and Group C compared to Group A.

In 2009 Ittichaikulthol W et al conducted a study on effects of pregabalin on post operative morphine consumption and pain after abdominal hysterectomy with/without salphingo-oophorectomy. Lorazepam 0.5 mg or pregabalin 300 mg was given 1 hr before surgery. The VAS scores of the pregabalin group were significantly lower than the control group. The total morphine consumption at 24 hours post operatively of pregabalin group (7.11 +/- 5.57) was significantly lower than the control group (21.18 +/- 7.12) ($p < 0.01$). Pregabalin hence significantly reduced morphine consumption at 24 hr post operatively.

In 2010 Sandeep Sahu et al conducted a study for evaluation of pregabalin for attenuation of postoperative pain in below umbilical surgeries under spinal anaesthesia.

In 2010 Kim SY et al concluded that perioperative administration of pregabalin (150 mg twice per day) was effective in reducing early postoperative pain but not chronic pain in patients undergoing robot-assisted endoscopic thyroidectomy.

In 2012 Mahzad Alimian et al conducted a study on effects of single-dose pregabalin on postoperative pain in dacrocystorhinostomy surgery and concluded that a single 300 mg dose of pregabalin an hour before effectively reduces pain intensity.

Clonidine

In 1992 Kouichi Ota *et al* concluded that prolongation of tetracaine sensory analgesia may be produced by premedication with 0.15 mg of oral clonidine.

In 1996, Toru Goyagi *et al* conducted a comparative study of Oral Clonidine Premedication 5 µg/kg with control group and concluded that oral clonidine preanesthetic medication enhances the postoperative analgesia of intrathecal morphine plus tetracaine without increasing the intensity of side effects from morphine.

In 2000 Sung *et al* evaluated the effect of oral clonidine premedication on perioperative hemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy and concluded that oral clonidine premedication helped to provide perioperative hemodynamic stability, spared the use of isoflurane and reduced the requirement of postoperative analgesia so as to smoothen the way to recovery in patients undergoing laparoscopic cholecystectomy.

In 2003 Yu HP *et al* concluded that oral clonidine preserves heart rate control in pneumoperitoneum surgery and recovery periods and oral clonidine premedication also reduces the requirement for postoperative analgesia.

In 2011 Shivinder Singh *et al* concluded that oral clonidine premedication was helpful in providing perioperative hemodynamic stability, spared the use of isoflurane and reduced the requirement of postoperative analgesia and good postoperative recovery in patients undergoing laparoscopic cholecystectomy.

MATERIAL AND METHODS

The present was a prospective, double blind, controlled, randomized, comparative study between pre-emptive oral pregabalin and clonidine administered to patients undergoing surgeries under subarachnoid block. Randomization was done by *random table method*

1st Gp PG : Tablet **Pregabalin** 300 mg orally 1 hour preoperatively.
 2nd Gp CL : Tablet **Clonidine** 150 mcg orally 1 hour preoperatively
 3rd Gp PC : Tablet **Multi vitamin** (Placebo) orally 1 hour preoperatively

Visual Analogue Scale (VAS) was used for assessment of post-operative pain relief at every 30 minutes interval in postoperative period for first two hours, and then hourly till fourth hour postoperatively and then every four hourly till 24 hours. Effectiveness of pain relief was assessed on the basis of.

1. Visual analogue scale (VAS) at rest. As per scale 10 represents worst unimagined pain and 0 as no pain.
2. The time at which patient demanded first rescue analgesic (Injection Diclofenac 75 mg I.V.) was noted.

(computer generated randomization table); random sequence was generated by random allocation software. The study was *carried* out in 90 patients scheduled for Elective below Umbilical Surgeries, with estimated duration of surgery 90-120 minutes, to be performed under SAB. Study was carried out from December 2010 to September 2012.

Inclusion Criteria

1. Patients with ASA I and II grades.
2. Patients with height more than 150-180 cms.
3. Patients between the age group of 18 and 65 years.
4. Patients willing to give informed consent.
5. Surgeries Below umbilicus & lower limbs including peri-anal region performed under SAB.

Exclusion Criteria

1. Conditions that preclude spinal anesthesia.
2. ASA Grade III & above.
3. Patients with any known contraindication for SAB.
4. Cardio respiratory disorder.
5. Neuropathy & neurological disorder.
6. Hepato-Renal disorders.
7. Diabetes mellitus.
8. H/O Alcohol & substance abuse.
9. Ongoing therapies with sustained release opioids.
10. Seizure disorder.
11. Immunocompromised patients.
12. Psychiatric disorders.
13. Chronic pain at puncture site.
14. History of hypersensitivity to study drug & allergy.

A written informed consent was taken. Patients were explained about Visual analogue scale (VAS) and were taught how to express the degree of pain on the scale. Preparation of patients included over-night fasting for 8-10hrs. All patients preloading with Ringer's lactate 10ml/kg was done. Patients in treatment group were given Tab. Pregabalin 300mg or Tab. Clonidine 150mcg or placebo one hour before commencement of surgery by a staff nurse who was not involved in the study. Patients were randomly allocated to 3 groups of 30 each.

3. The total number of times patient demanded rescue analgesic was noted for 24 hours postoperative period.
4. Total dose of postoperative analgesic requirement was calculated from above data.
5. At the same time any side effects like (nausea, vomiting, dizziness, somnolence, visual disturbances, vertigo, urinary retention, headache etc.) were recorded till 24 hours postoperatively.

OBSERVATIONS**Table 1: Age wise distribution of patients.**

Age Group	Control	CL	PG	χ^2 -value
15-20	0(0.00%)	3(10.00%)	4(13.33%)	8.35 p=0.45 NS,p>0.05
21-30	9(30.00%)	7(23.33%)	8(26.67%)	
31-40	10(33.33%)	6(20.00%)	5(16.67%)	
41-50	5(16.67%)	8(26.67%)	4(13.33%)	
51-60	6(20.00%)	6(20.00%)	9(30.00%)	
Total	30(100%)	30(100%)	30(100%)	
Mean	39.83	39.50	38.86	
SD	12.33	13.18	14.87	

Table 2: Gender wise distribution of patients.

Gender	Control	CL	PG	χ^2 -value
Male	21(70%)	26(86.67%)	23(76.67%)	2.44 p=0.29 NS,p>0.05
Female	9(30%)	4(13.33%)	7(23.33%)	
Total	30(100%)	30(100%)	30(100%)	

Table 3: Distribution of patients according to type of surgeries in three groups.

Type of surgeries	Control	CL	PG	χ^2 -value
Inguinal Hernia	9(30%)	10(33.33%)	10(33.33%)	3.71 p=0.99 NS,p>0.05
Fracture Tibia	3(10%)	2(6.67%)	1(3.33%)	
Debridement	2(6.67%)	3(10%)	2(6.67%)	
Amputation	5(16.67%)	4(13.33%)	3(10%)	
Varicocele	4(13.33%)	4(13.33%)	4(13.33%)	
Appendectomy	2(6.67%)	1(3.33%)	1(3.33%)	
Skin Grafting	3(10%)	4(13.33%)	6(20%)	
Para umbilical hernia	2(6.67%)	2(6.67%)	3(10%)	
Total	30(100%)	30(100%)	30(100%)	

Table 4: Comparison of total duration of analgesia in three groups.

	Control		CL		PG		value-p
	Mean	SD	Mean	SD	Mean	SD	
Total duration of analgesia	264.83	13.67	492.66	78.29	632.83	103.95	0.000 S,p<0.05

- CL Versus PG – p-value=0.029, Significant, p<0.05

Table 5: Comparison of VAS in three groups

VAS		N	Mean	Std. Deviation	Std. Error	F-value	p-value
1 hr	Control	30	2.63	0.55	0.10	34.41	0.000 S,p<0.05
	CL	30	2.60	0.49	0.09		
	PG	30	1.66	0.47	0.08		
2 hrs	Control	30	3.10	0.40	0.07	80.04	0.000 S,p<0.05
	CL	30	2.76	0.43	0.07		
	PG	30	1.80	0.40	0.07		
3 hrs	Control	30	3.56	0.77	0.14	65.23	0.000 S,p<0.05
	CL	30	2.50	0.57	0.10		
	PG	30	1.80	0.40	0.07		
4 hrs	Control	30	4.00	0.52	0.09	72.32	0.000 S,p<0.05
	CL	30	3.06	0.90	0.16		
	PG	30	2.06	0.25	0.04		
8 hrs	Control	30	3.86	0.73	0.13	32.72	0.000 S,p<0.05
	CL	30	2.86	0.73	0.13		
	PG	30	2.51	0.50	0.09		

12 hrs	Control	30	3.16	0.87	0.15	7.21	0.001 S,p<0.05
	CL	30	2.73	0.44	0.08		
	PG	30	3.33	0.47	0.08		
16 hrs	Control	30	3.03	0.66	0.12	12.75	0.000 S,p<0.05
	CL	30	2.40	0.49	0.09		
	PG	30	2.40	0.49	0.09		
20 hrs	Control	30	3.00	0.52	0.09	5.06	0.008 S,p<0.05
	CL	30	3.53	0.81	0.14		
	PG	30	2.90	0.56	0.10		
24 hrs	Control	30	3.43	0.77	0.14	32.99	0.000 S,p<0.05
	CL	30	2.16	0.46	0.08		
	PG	30	2.02	0.54	0.09		

Table 6: Distribution of side effects in three groups.

Side effects	Control	CL	PG	χ^2 -value
Bradycardia	0 (0.00%)	2 (6.67%)	0 (0.00%)	22.57 p=0.004 S,p<0.05
Hypotension	0 (0.00%)	2 (6.67%)	0 (0.00%)	
No side effects	25 (83.33%)	20 (66.67%)	22 (73.33%)	
Dizziness	0 (0.00%)	0 (0.00%)	6 (20.00%)	
Others/Nausea, Vomiting/urine retention	5 (16.67%)	6 (20%)	2 (6.67%)	
Total	30 (100%)	30 (100%)	30 (100%)	

Table 7: One way ANOVA

VAS		Sum of Squares	df	Mean Square	F	p-value
2 hrs	Between Groups	96.95	2	48.47	136.78	0.000 S,p<0.05
	Within Groups	30.83	87	0.35		
	Total	127.78	89			
8 hrs	Between Groups	72.42	2	36.21	63.81	0.000 S,p<0.05
	Within Groups	49.36	87	0.56		
	Total	121.78	89			
12 hrs	Between Groups	28.28	2	14.14	51.77	0.000 S,p<0.05
	Within Groups	23.76	87	0.27		
	Total	52.05	89			
16 hrs	Between Groups	25.26	2	12.63	32.01	0.000 S,p<0.05
	Within Groups	34.33	87	0.39		
	Total	59.60	89			
24 hrs	Between Groups	19.48	2	9.74	78.25	0.000 S,p<0.05
	Within Groups	10.83	87	0.12		
	Total	30.32	89			

DISCUSSION

Postoperative pain after surgery is the greatest concern of the patients, as well as surgeons and anaesthesiologists. By keeping the concept of postoperative pain control in mind, we performed a comparative study of two drugs which take care of postoperative pain, if given before starting of the surgery or the painful stimuli (pre-emptive analgesia). Several clinical studies have shown that the preemptive use of oral pregabalin and clonidine in surgeries performed under SAB, prolonged and

improved the quality of postoperative analgesia, reduced total analgesic requirements postoperatively and prolonged the demand of first rescue analgesic.

The demographic characteristics of patients in all the 3 groups i.e PG gp (300 mg), CL gp (150 µg) and PL gp (multi vitamin tablet) were comparable with respect to their age, height, and weight and ASA status. The *age* in our study was 18-65 years and was almost similar to most of the previous studies conducted. The *gender wise* distribution in our study in all three groups was

comparable ($p > 0.05$). The difference was not statistically significant. The *weight wise* comparison in our study in all three groups was comparable ($p > 0.05$). The difference was not statistically significant. The ASA status in our study in all three groups was comparable. The difference was not statistically significant. The distribution of patients according to types of surgeries in all three groups was also comparable.

In our study the comparison of *total duration of analgesia* in three groups was statistically significant. The mean duration in control group was 264.83 ± 13.67 minutes, mean duration of total analgesia in clonidine group was 492.66 ± 78.29 and duration of total analgesia in pregabalin group was 632.83 ± 103.95 minutes. The comparison of total post operative analgesia amongst clonidine & pregabalin was also significant. CL Versus PG group p-value was 0.029 which was significant less than 0.05 and shows that pregabalin had provided prolonged postoperative analgesia as compared to clonidine and control group.

In our study we found that the *total dose of analgesic* required in 24 hours in all the three groups was significant, p-value is 0.00 which was highly significant if compared with control group, else amongst CL & PG group it was also significant p-value 0.016 which was less than 0.05. The mean requirement of doses in all three groups were : Control group 4.03 ± 0.66 , Clonidine group 2.20 ± 0.61 and Pregabalin group 1.73 ± 0.44 .

In our study we have observed the lowest VAS score in pregabalin group at 30 minutes postoperatively and maximum seen at 12 hrs postoperatively followed by clonidine group and maximum was seen in control group. *Toru Goyagi et al* used clonidine for post operative analgesia and found that VAS was significantly low with clonidine group. *Aftab Beigh et al* concluded in their study that VAS score was lower in clonidine group as compared to control group. *Joseph Park MD et al* conducted study in 44 adults undergoing orthopaedic knee surgery under standard general anesthesia and found that oral clonidine reduced postoperative PCA morphine requirements. Patients were given oral placebo or oral clonidine ($5 \mu\text{g}/\text{kg}$) 1.5 hour before surgery, and at 12 hr, and 24 hr after surgery. They observed PCA morphine use, visual analogue scale (VAS) for pain and sedation for 36 hr postoperatively. They observed cumulative PCA morphine used was 37% lower after clonidine 57.3 ± 26.8 mg (mean \pm SD) compared with placebo 91 ± 31.6 mg ($P = 0.031$).

Vishal arora et al observed postoperative *side effects* of using pregabalin 300 mg one hour prior to SAB and they found that dizziness and somnolence was the most common side effect with pregabalin. In our study we also found that using pregabalin causes dizziness but somnolence was not noticed in our study.

SUMMARY AND CONCLUSION

To summarize we can say that both clonidine and pregabalin provide pain relief and sedation in acute postoperative period in the doses studied. Clonidine hydrochloride 150 μg and pregabalin 300mg was found to be effective in reducing postoperative pain when given 1 hour preoperatively. Pregabalin proved to have a better analgesic effect than clonidine, reducing the total consumption of rescue analgesic and prolonging first rescue dose. Both the drugs are good alternative to each other and can be used safely as preemptive analgesia under SAB.

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