ORIGINAL ARTICLE

PRE-OPERATIVE SEDATION USING ORAL CLONIDINE AND ORAL GABAPENTINE: A COMPARATIVE STUDY

Prasad Kulkarni[1], Kartik Nagashiva Badaru[2], Srirang Joshi[3], Srinivasa B[4], Hoysala H. N[5]

HOW TO CITE THIS ARTICLE:
Prasad Kulkarni, Kartik Nagashiva Badaru, Srirang Joshi, Srinivasa B, Hoysala H. N. "Pre-Operative Sedation Using Oral Clonidine and Oral Gabapentine: A Comparative Study". Journal of Evidence based Medicine and Healthcare; Volume 1, Issue 13, December 01, 2014; Page: 1675-1685.

INTRODUCTION: Anxiety is a "psychophysiological phenomenon experienced as a foreboding dread or threat to a human organism whether the threat is generated by internal, real or imagined dangers.[1] Anxiety has been described as a subjective feeling of distress and anguish that has affective, motivational, behavioral, and physiologicalcomponents.[2] A key feature of anxiety is its subjective nature.

The anticipation of undergoing surgery or anesthesia can cause psychological stress to patients which are manifested as anxiety.[3] The cause of patients' preoperative anxiety is multifactorial. It can be divided into three distinct dimensions of anxiety, 1) fear of the unknown. 2) Fear of the waiting period before surgery/anesthesia. 3) Fear of unconsciousness and other anxieties like fear of feeling ill, fear of postoperative nausea or vomiting fear of perioperative pain, fear of the discomfort of postoperative awakening fear of intraoperative awareness, fear for one's life fear of not regaining consciousness, a fear of dying or remaining in coma, fear of anesthesia-induced physical or mental harm.

Young patients, female patients, patients with less education and patient's with no previous anaesthetic experience or a previous negative anaesthetic experience will have higher anxiety scores[-4]

Operations associated with high preoperative anxiety include thoracic and otorhinolaryngological surgery.[4]

It has been shown that psychologically prepared patients who are less anxious before surgeries have improved postoperative clinical recovery as assessed by outcomes such as pain and analgesic use, postsurgical complications, and hospital stay.[5]

The measures to allay pre-operative anxiety include Non pharmacologic interventions such as:

1. Anaesthetist's visit is more effective than a sedative pre medicant in relieving preoperative anxiety.[3]
2. Hypnosis may also have a positive effect in reducing pain and anxiety.[3]
3. Provision of information, distraction, attention focusing.[4]
4. Relaxation procedures.[4]

These methods are economical, lack undesirable side effects, and are associated with high patient acceptance and motivation

Pharmacological intervention:[3]

The use of small doses of benzodiazepines for premedication is a well-established practice. As expected, the amnesic and anxiolytic properties of these drugs are also useful in the outpatient setting. Although diazepam was the most commonly used oral benzodiazepine, midazolam has become the drug of choice because of short elimination half-life. Although larger doses of midazolam are required when it is administered orally because of first-pass metabolism, it is a highly effective oral sedative-anxiolytic in both adults and children. Temazepam and alprazolam have also been reported to be effective oral premedicants for outpatient surgery. Although oral triazolam can produce effective sedation and amnesia, it is less effective than diazepam or midazolam in decreasing preoperative anxiety. Lorazepam, because of its long duration of amnesia, is not routinely used in the ambulatory setting.

Premedication with α2 -adrenergic agonist drugs can reduce anaesthetic and analgesic dosage requirements and produce sedation and anxiolysis while also decreasing the heart rate and blood pressure during anaesthesia. Oral Clonidine, the prototypical α2 -agonist, has been successfully used for ambulatory premedication.

Assessment of pre-operative anxiety:

- STAI (State trait anxiety inventory): It is the gold standard in evaluating preoperative anxiety-4

Other scales which can be used are

- The Hospital Anxiety and Depression Scale[6]
- The Multiple Affect Adjective Check List[6]
- The Amsterdam Preoperative Anxiety and Information Scale[7]
- The Yale Preoperative Anxiety Scale for children[8]
- Visual analogue scale-4
- Verbal rating scale

Assessment by Ramsey Sedation Scale:

Ramsay sedation scale is a contrivance which is used to appraise sedation in a patient.

Agitation is most often described as excessive restlessness which is characterized bynon-purposeful mental and physical activity due to internal tension andanxiety[9, 10, 11].

In general, clinicians assess for agitation as they subjectively observe the patient's physical activity, nonverbal behavior, and verbalizations. Consequently, findings of agitation may vary among clinicians due, at least in part, to confusion about the definition of agitation. To minimize this variation, experts have developed scales to assess agitation; most also include measures of sedation. The most commonly used scales are the Ramsay Sedation Scale, the Riker Sedation-Agitation Scale (SAS), and the Richmond Agitation Sedation Scale (RASS),[12] Each of these scales evaluates the degree of agitation at one point in time and describes patient behavior.

In this scale 6 levels are used to represent different levels of sedation.

First level represent the least amount of sedation and sixth the most.[13]

1. Awake and anxious, agitated, or restless
2. Awake, cooperative, accepting ventilation, oriented, tranquil
3. Awake; responds only to commands
4. Asleep; brisk response to light glabellar tap or loud noise
5. Asleep; sluggish response to light glabellar tap or loud noise stimulus but does not respond to painful stimulus
6. Asleep; no response to light glabellar tap or loud noise. This scale is widely used by doctors, nurses, anesthesiologists to find out the effect of treatment and receive of optimal dosage by a patient. The disadvantages of this scale are that it purely depends upon the patient response.

MATERIALS AND METHODOLOGY: Hospital ethical committee clearance was obtained for this study. Written informed consent was taken from all the patients. Patients taken into study were posted for Surgical, Orthopedic, Gynaecological procedures under combined spinalepidural block.

Source of data: Adult patients 18-50 yrs of physical status ASA I and II scheduled to undergo elective surgical procedures under combined spinal epidural block for lower limb and abdominopelvic surgeries

Study Design: A prospective randomized comparative study was planned. 100 patients satisfying all the inclusion criteria were enrolled in the study.

Inclusion criteria:

1. ASA grade I and II.
2. 18-50 years of age.
3. Weighing 40-85 kg
4. Patients who consented.
5. Patients scheduled to undergo elective surgical procedures.

Exclusion criteria:

1. Pregnant, lactating and females.
2. Patients with chronic pain, psychiatric disease, peripheral vascular disease.
3. Patients with severe renal or hepatic disease.

METHODS: Patients were divided into 2 groups. Group G and Group C. All patients were assessed the day before surgery.

1 Tablet of Gabapentin (300 milligrams) was given for Group G patients.

1 Tablet of Clonidine (100 micrograms) was given for Group C patients.

Visual analogue anxiety score (0= no anxiety, 100= worst imaginable anxiety) was explained to them.The tablets were given to the patient by the attending anesthesiologist with sips of water 120 minutes before induction in the preoperative ward. The identity of the

tablet was not revealed to the patient. No other premedication was given other than the study drugs.

Upon arrival in the operating room, baseline reading of all vital parameters was taken. 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 was carried out.

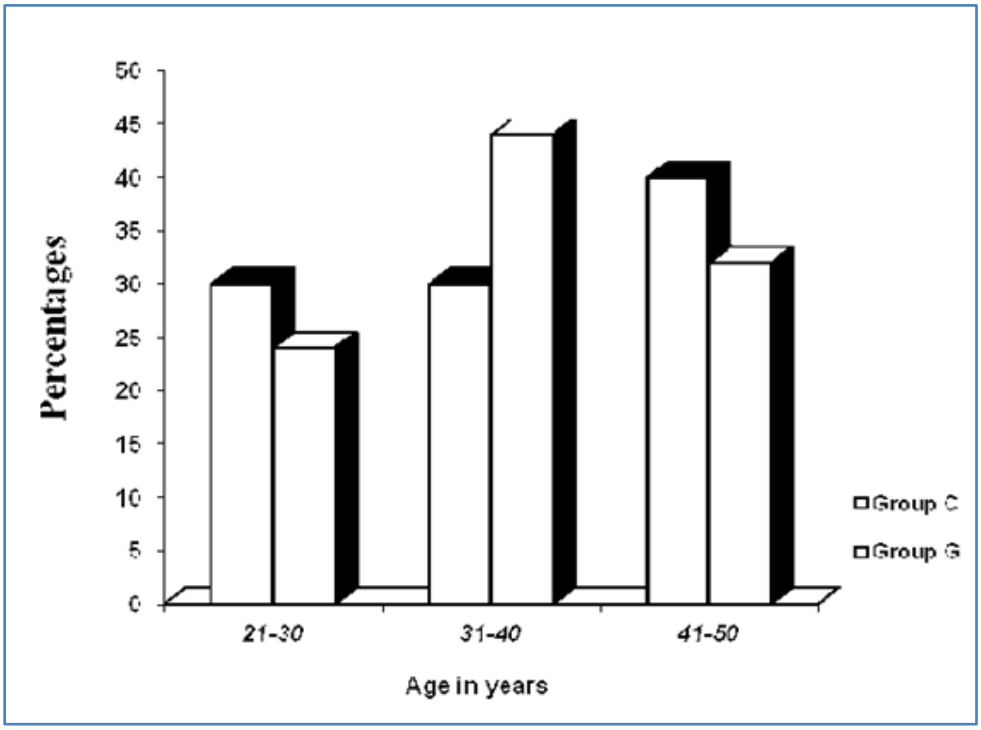
Anaesthesia was achieved by combined spinal-epidural technique with Quincke spinal needle and 18 gauge Tuohy epidural needle and catheter. 3 ml of Bupivacaine 0.5% heavy was used for spinal anaesthesia and 0.125% Bupivacaine was used epidurally for top-ups. Common complications such as nausea, vomiting, constipation, dizziness if present, was recorded and effectively treated Parameters observed were: heart rate and baseline blood pressure, orientation level of the patient before giving the drug orally in the ward on the morning of surgery.

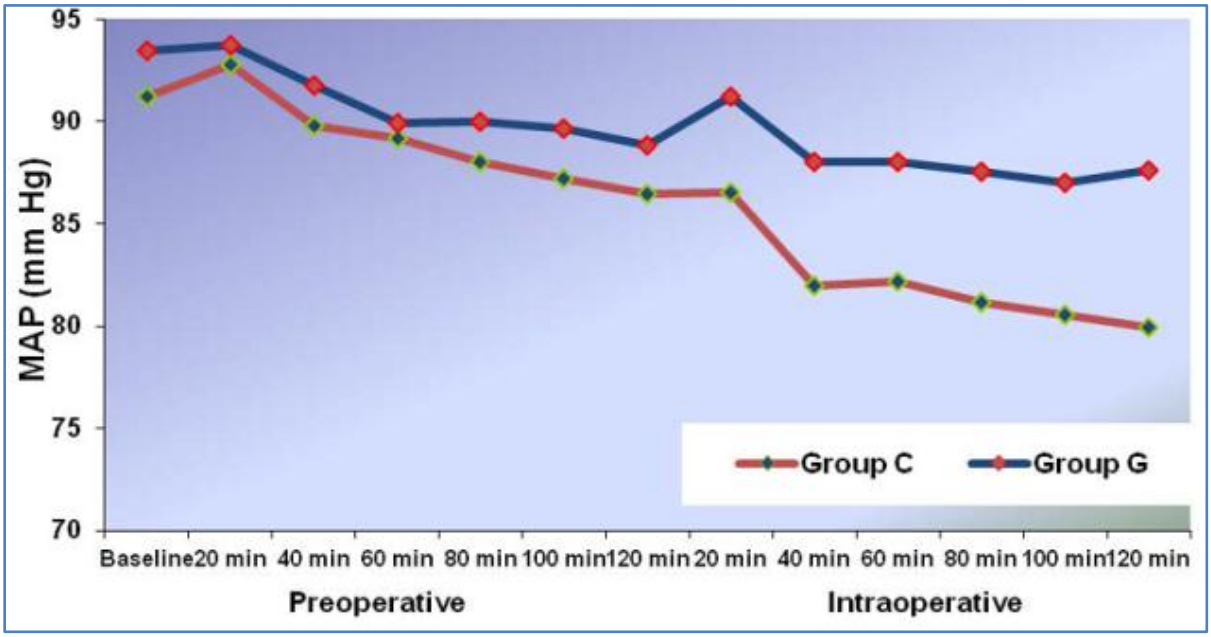
Heart rate, systolic BP and diastolic BP and sedation level just before taking the patient to OT.

- Heart rate, Systolic BP and diastolic BP, sedation just before the start of the epidural procedure on OT table.
- Heart rate, systolic BP and diastolic BP, sedation level immediately after the completion of the epidural procedure. Occurrence of side effects of Gabapentin like dizziness, headache, nausea and vomiting were recorded.
- Heart rate, systolic BP, diastolic BP, sedation level through-out the duration of procedure at 20 minutes interval Occurrence of side effects of Clonidine like bradycardia, profound hypotension were recorded.

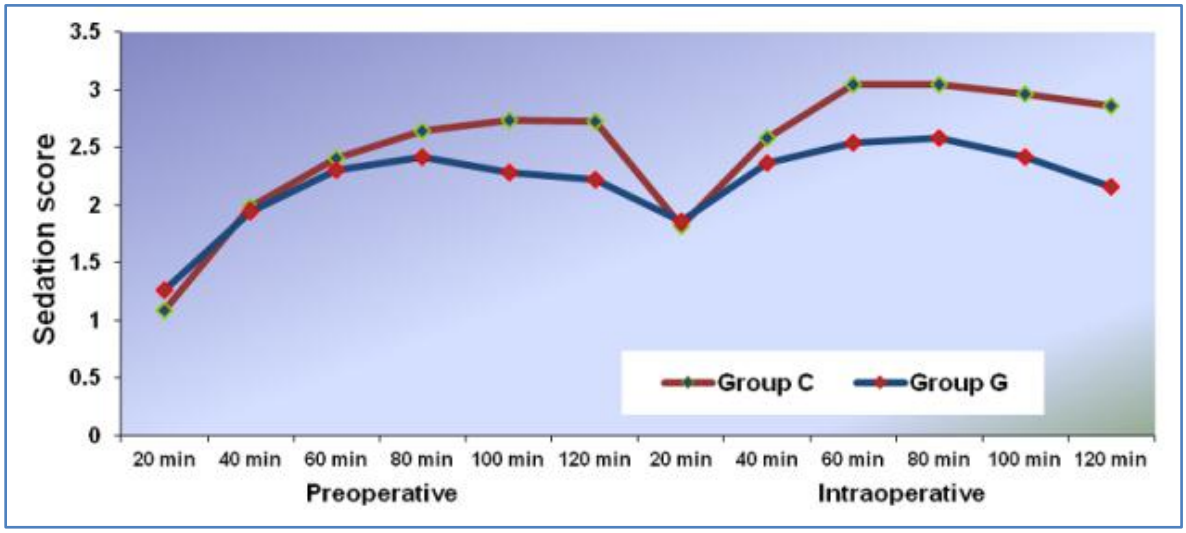
	Group C		Group G	
	no	**%**	**no**	**%**
21-30	15	30.0	12	24.0
31-40	15	30.0	22	44.0
41-50	20	40.0	16	32.0
Total	50	100.0	50	100.0

Table 1: Age distribution of patients studied Age in years

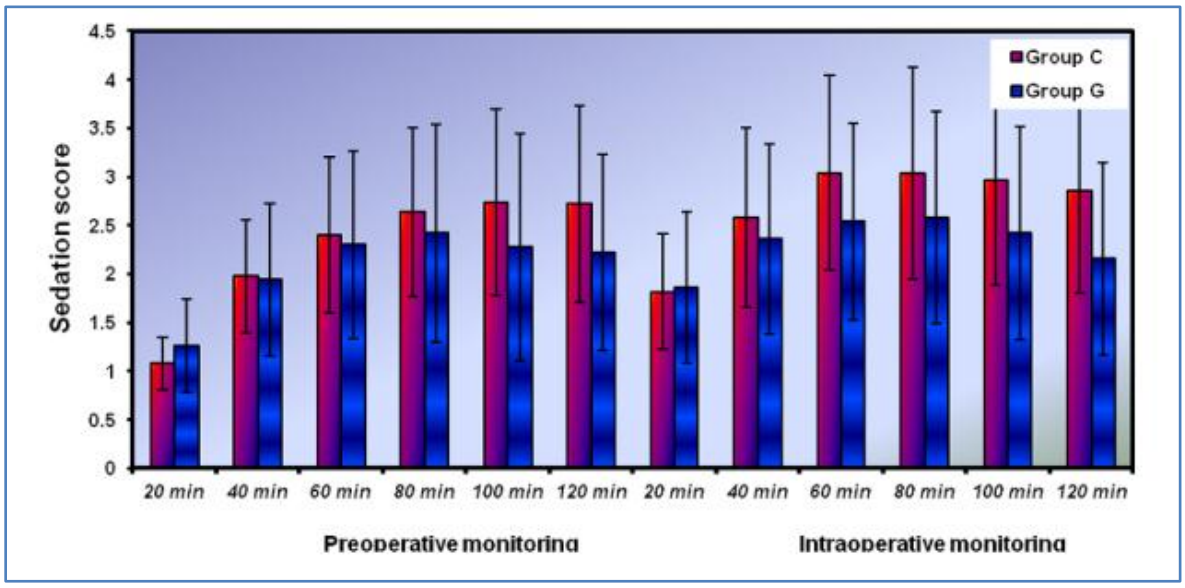




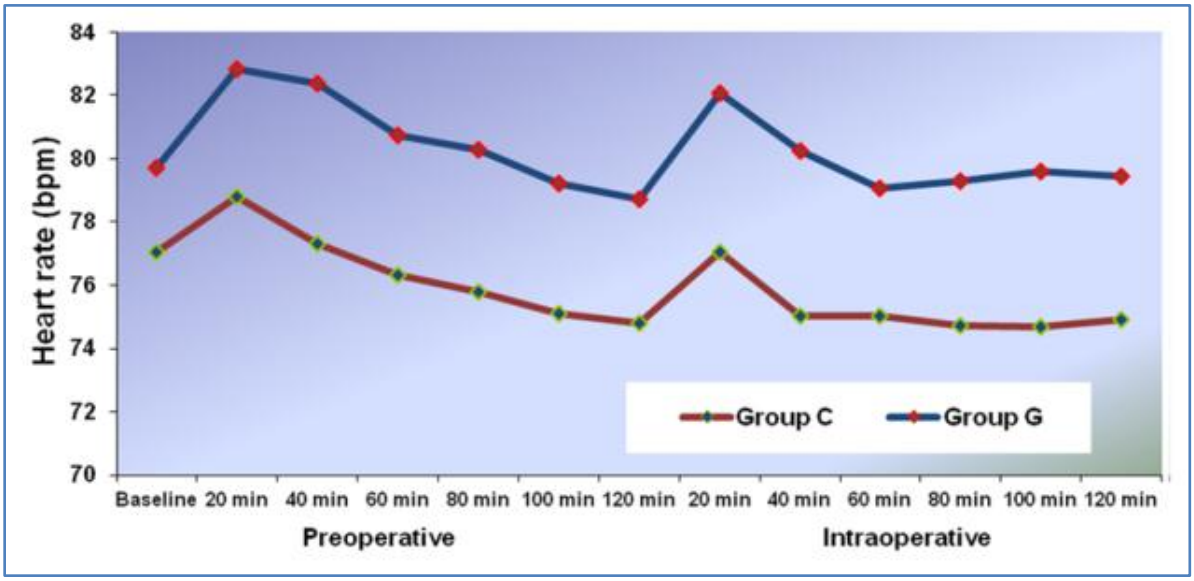
Graph no. 3 Shows mean blood pressures in two groups.



Graph no 4 Showing sedation scores.



Graph no. 5 Shows sedation scores in both the groups.



Graph no. 6 Showing heart rate changes

DISCUSSION: Preoperative anxiety has been found to be a major predictor of post-operative pain apart from type of surgery, age of the patient and related psychological distress. [14]

Anxiety lowers pain threshold, results in exaggeration of pain intensity and activation of hippocampal formation. It not only changes doses of drugs which are needed for induction, maintenance of anaesthesia, recovery from anaesthesia, but also it affects psychological condition of patients. Stress and anxiety activate hypothalamopituitary-adrenal axis and increase glucocorticoid level. Stress releases hormones such as cortisol, cathecolamines and cytokinine. These hormones increase negative nitrogen balance and catabolism and ultimately delay wound repair and weaken immune system postoperatively.

Hence ASA task force in its guidelines for acute pain management has recommended premedication before surgery to be included as a part of multimodal analgesia. Clonidine is a selective central α2 agonist and is a potent antihypertensive drug. The alpha 2-adrenoceptor agonists have several beneficial actions during the perioperative period. They exert a central sympatholytic action, improving haemodynamic stability in response to endotracheal intubation and surgical stress, reducing the anaesthetic and opioid requirements and causing sedation, anxiolysis and analgesia. The alpha2-adrenoceptor agonists have an analgesic action at several sites of the peripheral and central nervous system as well as the prolongation of epidurally or intrathecally administered local anaesthetics and opiodes techniques in pain management. Oral Clonidine at a dose of 1.5-2 micro/kg combines the advantages of benzodiazepines and morphine i.e. anxiolysis, sedation and analgesia with stable haemodynamics and respiration.

Clonidine does not have morphine related side effects such as nausea and vomiting. Equally importantly it does not depress resting ventilation or elevate arterial carbon dioxide. Doses of up to 5 micro g/kg have been administered to young and healthy patients preoperatively in dental and maxillofacial surgery without significant side effects.[15, 16]

Gabapentin is a structural analogue of gamma-amino butyric acid, which was introduced in 1994 as an antiepileptic drug. Gabapentin has demonstrated its utility in the treatment of chronic neuropathic pain. Gabapentin does not bind with plasplasma protein and is not metabolized in humans. Despite its structural similarity to GABA, it does not act via mechanisms related to GABA.[17] Though the exact mechanism of action of Gabapentin is not known, the proposed mechanisms are its ability to increase the concentration and the rate of synthesis of GABA in brain, binding with high affinity to α-binding sites in brain tissues that are associated with an auxiliary sub unit of voltage-sensitive calcium channels (α2δ subunits), reducing the release of monoamine neurotransmitters, inhibiting voltage activated sodium channels, and increasing serotonin concentrations in human blood.[17, 18, 19] Gabapentin has been reported to possess anti-hyperalgesic and antiallodynia properties. . For preoperative anxiolysis Gabapentin pretreatment has been reported to produce significantly lower preoperative VAS anxiety scores and to thus allay preoperative anxiety.

The Ramsay sedation score which was used in this study showed a better sedative effect by Clonidine than Gabapentin in the preoperative and intraoperative period. At 100 minutes following administration of either Clonidine or Gabapentin the difference in sedation levels became prominent (p=0.023). At 240 minutes there was a significant difference in the sedation scores (p=0.002 Vikas Saini et al. and Ahmed B A et al. have used oral Clonidine for premedication in the dose of 5µg/kg and 150µg respectively 90-120min before intubation.[20,21] These authors observed good anxiolysis with the said doses of oral Clonidine. We used 100µg oral Clonidine and found effective pre-operative anxiolysis. Clonidine produced sedation in 33.33 percent of patients in Ahmed'sstudy.[21] In our study also it was observed that Clonidine produces a good preoperative sedation which became significant in comparison to Gabapentin at the100th minute (p=0.023) and peaked at 120th minute (p=0.018) just before the patient was shifted into the operating room.

Hidalgo et al. conducted a study on 61 patients undergoing abdominal hysterectomy of ASA status I–II, were randomly assigned to receive either oralClonidine 100 µg (n = 29) or placebo (n = 32) before surgery and 24 h after surgery.

The use of Clonidine resulted in anxiolysis and analgesia throughout the 72 h after surgery, Clonidine blunted the sympathetic activity with good haemodynamic stability. They concluded that Clonidine should be a good therapeutic alternative to other preoperative sedatives and further studies are necessary to compare its effects with those of different anxiolytics on postoperative outcomes over time. In a study by Leandro G Braz et al. published in 2002 on evaluating Clonidine and Midazolam's sedative effects as a pre-anaesthetic by clinical and electroencephalographic analysis. They concluded that Clonidine and Midazolam have similar sedation levels in patients ASA I when evaluated by sedation scale and Bispectral index. Like in our study, the Ramsay scale was used to measure sedation levels and it showed that sedation level was higher in Clonidine and Midazolam groups at 60 minutes as compared to placebo.[8] Similarily we used the Ramsay Scale to measure the sedation levels and at 60 minutes it showed a value of2.40±0.80 for Clonidine group in comparison to 2.30±0.97 for the Gabapentin group, the p value being 0.540 which was not considered significant.

A study by Zuleyha Kazak et al. to study the effectiveness of single dose of Gabapentin (600 mg) for intraoperative sedative effects was published in 2009. The scores for sedation were recorded in 1st hour intraoperatively. Sedation was achieved with an IV bolus of propofol and continuous infusion of remifentanil. There were significant differences between Gabapentin and placebo groups with regard to total consumptions of remifentanil ($p = 0.033$) and propofol ($p = 0.001$).[15] A Turan's study on effect of oral Gabapentin on postoperative epiduralanalgesia where 1200 mg of Gabapentin was used showed that The most common side-effects during the postoperative period were nausea, vomiting, and dizziness .

The incidence of dizziness was greater in the Gabapentin group than in the control group (35% vs 5%; $p<0.05$).[20] Our study showed more occurrence of dizziness in Clonidine group (6%) compared to Gabapentin group (2%). The p value was 0.617 which was not considered significant. Incidence of nausea was 18% in Gabapentin group was strongly significant being higher compared to 0% in Clonidine group ($p=0.003$). Vomiting occurred in14% of Gabapentin patients in comparison to 2% of Clonidine patients ($p=0.059$) which was suggestively significant. Incidence of headache was 6% in Gabapentin group compared to 4% in Clonidine group.

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

Our goal was to compare the pre-operative sedation produced by oral Gabapentin and oral Clonidine. The Ramsay sedation score which was used in this study showed a better sedative effect by Clonidine than Gabapentin in the preoperative and intraoperative period. Clonidine group showed significant sedation past 100 minutes following administration, with the maximum effect occurring between 3 to 4 hours after administration. Also in additional comparison of side effects, there was increased incidence of nausea and vomiting in Gabapentin group where as those in Clonidine group showed higher incidence of dizziness.

REFERENCES:

1. Emilien G, Durlach C. Anxiety Disorder. Pathophysiology and pharmacological treatment. Birkhauser Verlag; 2002.
2. McReynolds P. Assimilation and anxiety. In: Zuckerman M, Spielberger CD, eds. Emotions and Anxiety: New Concepts, Methods, and Applications. Hillsdale, NJ: Lawrence Erlbaum Associates; 1976: 35-86.
3. Paul F White, Alejandro R F. Ambulatory anaesthesia. Miller's Anaesthesia 6th ed. Elsevier Ltd.2005; Chapter 68: 5759-5863
4. Christopher H. The Visual Analog Scale Allows Effective Measurement of Preoperative Anxiety and Detection of Patients Anaesthetic Concerns. Anesth Analg 2000; 90: 706 –12
5. Zeev N. Preoperative anxiolysis and postoperative recovery in women undergoing abdominal hysterectomy. Anesthesiology 2001; 94: 415–22
6. Hicks JA, Jenkins JG. The measurement of preoperative anxiety. J Royal Soc Med 1988; 81: 517–9.

7. Moerman N, van Dam FS H. The Amsterdam Preoperative Anxiety and Information Scale (APAIS). Anesth Analg 1996; 82: 445–51.
8. Kain Z N, Mayes L C. The Yale Preoperative Anxiety Scale: how does it compare with a "gold standard"?. Anesth Analg 1997; 85: 783– 8.
9. Sessler C N, Grap M J. Multidisciplinary management of sedation and analgesia in critical care. Semin Respir Crit Care Med 2001; 22: 211-226.
10. Jacobi J, Fraser GL . Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med2002; 30: 119-141.
11. Cohen I L, Gallagher T J. The management of the agitated ICU patient. Crit Care Med. 2002; 30: 97-123.
12. Ramsay MA, Savege TM. Controlled sedation with Alphaxalone -alphadolone. Br Med J 1974; 2: 656-659.
13. Stawicki S P. Sedation scales: Very useful, very underused. OPUS 12 Scientist 2007 Vol. 1, No. 2.
14. Hui Yun Vivian, Amir Abrishami. Predictors of postoperative pain and analgesic consumption. Anesthesiology 2009; 111: 657–77.
15. Spencer Liu, Andrew A Chiu. Oral Clonidine prolongs lidocaine spinal anaesthesia in human volunteers. Anesthsiology 1995; 82: 1353-135.
16. Boussofara M, Mtaallah MH, Nefaa MN, Kaddour. Clonidine and anaesthesia. Tunis Med. 2004 Mar; 82(3): 249-57.
17. Mohammadi S S, Seyedi M. The effects of Gabapentin on early postoperative pain, nausea and vomiting in laparoscopic surgery for assisted reproductive technologies. 2008 Jul 15; 11(14): 1878-80.
18. Clivatti J, Sakata R K. Review of the use of Gabapentin in the control of postoperative pain. Rev Bras Anestesiol. 2009 Jan-Feb; 59(1): 92-8, 87-92.
19. Dauri M. Gabapentin and pregabalin for the acute post-operative pain management. A systematic-narrative review of the recent clinical evidences. 2009 Aug; 10(8): 716-33.
20. Vikas Saini, Lakesh K Anand. Oral Clonidine premedication in patients undergoing intraocular surgery under local anaesthesia. J Anaesth Clin Pharmacol 2009; 25(3): 311-315.
21. Ahmed B A, Kakroo S. Effect of oral Clonidine premedication on anxiety and sedation in patients undergoing TURP under spinal Anaesthesia. JK Practitioner. 2001 Jan-Mar; 8(1): 9 – 18.

ORIGINAL ARTICLE

AUTHORS:

1. Prasad Kulkarni
2. Kartik Nagashiva Badaru
3. Srirang Joshi
4. Srinivasa B.
5. Hoysala H. N.

PARTICULARS OF CONTRIBUTORS:

1. Professor, Department of Anaesthesiology, MVJMC and RH, Hoskote, Bangalore.
2. Post Graduate Student, Department of Anaesthesia, MVJMC and RH, Hoskote, Bangalore.
3. Senior Resident, Department of Anaesthesia, MVJMC and RH, Hoskote, Bangalore.
4. Post Graduate Student, Department of Anaesthesia, MVJMC and RH, Hoskote, Bangalore.
5. Post Graduate Student, Department of Anaesthesia, MVJMC and RH, Hoskote, Bangalore.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Prasad K. Kulkarni,
G-5, Geetanjali Icon Apartment,
Nagavar Palya Main Road,
CV Raman Nagar, Bangalore.
E-mail: prasadkulk@yahoo.com

Date of Submission: 07/11/2014.
Date of Peer Review: 08/11/2014.
Date of Acceptance: 10/11/2014.
Date of Publishing: 28/11/2014.