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Comparative evaluation of Gabapentin and Clonidine for Premedication on postoperative analgesia in patient undergoing modified radical mastectomy under general anesthesia

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ABSTRACT

Background: Early post-operative pain is the most common complain after elective surgery. Gabapentine and Clonidine have antinociceptive property. This prospective, randomized study evaluated the effect of oral clonidine and oral gabapentin premedication on postoperative pain intensity, analgesic consumption and side effects in patient undergoing modified radical mastectomy. **Methods:** Ninety patients of ASA grade I or II, aged between 35 to 55 years undergoing MRM were randomly allocated to receive either Tablet gabapentin 600 mg (group G, n=30) or Tablet clonidine 200mcg (group C, n=30) or Tab placebo (group P, n=30) orally one hour before operation. They were anesthetized using the same technique. Postoperative visual analog scale (VAS) for pain, time of first analgesic and total amount of analgesic requirement was observed in the recovery room at 0, 2,6 and 12 hours following the surgery. **Results:** The patients' characteristics were alike in three groups. The VAS pain scores at measured times were significantly lower in the gabapentin (3.0± 0.4, 3.4±0.5, 3.6± 0.5, 2.9±0.6) group as compared to clonidine (3.8± 0.7 , 4.4± 0.58, 4.8± 1.6, 3.7± 1.7) and placebo group (5.28±0.34, 6.6±0.32 ,5.2±0.8, 4.9±0.5). Time to first rescue analgesia was significantly longer in group G (10 .32± 0.62 hr) as compared to group C (7.24± 0.82 hr) and group P (1.34 ± 0.72 hr). The post-operative diclofenac sodium consumption in gabapentin group (22.12 ± 4.33) was significantly less than clonidine (75.2±7.41 mg, P<0.05) and placebo groups (150 ± 0.42mg) P<0.001. Nine patients in group G, fifteen patients in group C and all patients in group P required rescue analgesia postoperatively. Number of patients required > one dose of rescue analgesic were highest in placebo (30) group as compared to group G (1) and group C (8). **Conclusion:** Oral premedication with gabapentin significantly decreases the post-operative pain and diclofenac sodium consumption without any significant side effects.

Keywords: Gabapentine, Clonidine, Postoperative Pain.

Introduction

Prevention and treatment of postoperative pain continue to be a major challenge in post-operative care and plays an important role in the early mobilization and well-being of the surgical patient.[1] Postoperative pain is typically regarded as a type of nociceptive pain involving peripheral mechano-receptor stimulation. It is clear that inflammatory, neurogenic, and visceral mechanisms also contribute to acute pain symptoms. It has been suggested that central neuronal sensitization contributes to postoperative hypersensitivity to pain. As such, post-operative pain may be considered as a transient, reversible type of "neuropathic" pain and, consequently there is a rationale for the exploitation of anti-hyperalgesic drugs for post-operative analgesia.[2] Gabapentin, a structural analogue of GABA, is a novel anticonvulsant drug and has analgesic effects on neuropathic pain, diabetic neuropathy, post herpetic neuralgia and reflex sympathetic dystrophy. Gabapentin is an anticonvulsant that has anti nociceptive and anti hyperalgesic properties. In pain

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models it has shown anti-hyperalgesic properties, possibly by reducing central sensitization, a prerequisite for postoperative hyperalgesia.[3] It binds to the α2 subunits of voltage dependent calcium ion channels and blocks the development of hyperalgesia and central sensitization (Goa & sorkin, 1993) [4] Recently it has also been used for postoperative pain relief (Cutrer & Maskowirz, 2004). [5] This drug is relatively well tolerated and belongs to a class that has anxiolytic properties.Each of these properties suggests that Gabapentin may be useful postoperatively (Meniguax et al, 2005).[6]Several workers have found that 300-1200mg oral Gabapentin given 2 hrs before stimulus significantly reduces the incidence of pain and post-operative opioid consumption without significant side effects (Pandeyc k et al 2006). [7] Following single oral dose of 300 mg gabapentin the mean maximum plasma concentration attained in 2-3 hr. Bio-availability of a single 300 mg oral dose of gabapentin is 60% and decreases with increasing the dose. Elimination of gabapentin is through renal clearance and is about 5-7 hr following a single oral dose of 200 to 400 mg. [4]Clonidine is a α_2 adrenergic agonist that produces dose dependent analgesia at spinal and supraspinal sites. Oral clonidine is almost completely absorbed and peak plasma concentration is reached after 1-3 h of administration and half life is 9 to 12 hours. It is highly lipid soluble, crosses the blood brain barrier easily. Clonidine inhibits neurotransmission in both A-delta and C fibers and potentiates inhibitory effect of the local anesthetic on the C-fiber activity. [8,9,10]The aim of our study was to compare the duration and quality of post-operative analgesia after premedication with oral gabapentin and clonidine. The time of first rescue analgesia, amount and number of rescue analgesia required during the first 12 hour in patient undergoing modified radical mastectomy was observed. We also assessed the side effects of study drugs such as respiratory depression, nausea, vomiting and dryness of mouth.

Materials and Methods

After institutional ethical committee approval and written informed consent, 90 patients of ASA grade I or II, aged between 35–55 yrs scheduled for Modified radical mastectomy under general anesthesia were enrolled into the randomized, placebo controlled study. Patients with previous treatment with either gabapentin or clonidine, mental impairment, chronic pain, pregnancy, or a history of congestive heart failure, valvular heart disease, renal or hepatic disease, or who had used psychotropic drugs in the present or in the past, or had language or communication difficulties were excluded. Also, patients with a body mass index higher than 25 kg m^{-2}, those with sleep disorders, a history of known allergy to any drug used or a history of a peptic ulcer or bleeding diathesis were excluded.

The patients were randomly divided into three groups to receive either 600 mg gabapentin group G, 300mcg clonidine group C or placebo tablets group p (orally one hour before surgery). No other preoperative medication was given. All patients were instructed preoperatively on the use of a visual analogue scale (VAS, range 0-10 cm using a ruler) in which 0=no pain and 10=worst pain imaginable.

In the operating room continuous electrocardiography, mean arterial blood pressure (MAP), heart rate (HR), peripheral oxygen saturation (SpO_2) and end tidal carbon dioxide were monitored. Anesthesia was induced with injection thiopentone sodium 5-6 mg kg^{-1} and fentanyl 2 μg kg^{-1}. Succinylcholine 1-2 mg/kg IV was used to facilitate orotracheal intubation. Neuromuscular block was maintained with intermittent injection vecuronium bromide when indicated. Mechanical ventilation was adjusted to maintain end-expiratory CO_2 between 34-36 mm Hg. General anaesthesia was maintained with isoflurane and a fresh gas flow of 2 L min^{-1}. The concentration of agent was adjusted to maintain adequate depth of anesthesia as in routine practice.After completion of surgery, neuromuscular blockade was reversed with neostigmine 0.04 mg kg^{-1}, and glycopyrrolate 0.008 mg kg^{-1} and patients were extubated when adequate spontaneous ventilation was established. After tracheal extubation, patients were transferred to the postanesthesia care unit (PACU).Assessment of postoperative pain was made by observer, who was not the part of the anesthesia team, on the basis of the visual analogue score (VAS), where VAS; 0 cm = no pain to 10 cm = the worst possible pain. Patients received injection diclofenac sodium 1-2 mg kg^{-1} IM on demand (VAS $\geq$ 3). The time from the end of the surgery until the first bolus of diclofenac sodium administered on demand, number and the total rescue analgesic requirements in the first 12 hours were recorded. The occurrence of any side effects, such as nausea, vomiting, respiratory depression, dizziness, nystagmus, tremor, diplopia, peripheral edema, diarrhea, headache, and pruritis was recorded. Postoperative nausea and vomiting were treated with 4 mg IV ondansetron.

Statistical analysis

The data were analyzed with SPSS version 15.0 (SPSS Inc, Chicago, IL, USA). On the assumption that a 20% difference in diclofenac sodium consumption between

the groups would be of clinical interest, Continuous variables were described as mean±SD of means as appropriate. Comparison between the three groups was done using ANOVA test. ANOVA for repeated measures was used to evaluate the effect of each drug. Categorical data were compared using Chi-square test. The data were considered significant if p values were equal to or less than 0.05.

Results

The demographic data of all three groups is shown in Table 1. The groups were matched in terms of age, weight, duration of surgery (*P*> 0.05).No significant difference was observed in the heart rate and respiratory rate recorded preoperatively, among the groups (*P*>0.05). Similarly, no significant difference was observed in the mean systolic and diastolic blood pressures preoperatively, postoperatively among all the three groups.As in table 2 VAS pain scores at measured times were significantly lower in the gabapentin (3.0 ± 0.4, 3.4±0.5, 3.6± 0.5, 2.9±0.6) group as compared to clonidine (3.8±0.7, 4.4±0.58, 4.8±1.6, 3.7±1.7) and placebo group (5.28±0.34, 6.6±0.32 ,5.2±0.8, 4.9±0.5). Time of first rescue analgesic given was longer in group G as compared to group C and group P(P < 0.05).The mean doses of diclofenac given in the postoperative period was significantly less in gabapentine group as compared to clonidine and placebo group (P < 0.05) as in Table 3. Numbers of patient requiued rescue analgesic were significantly reduced in the gabapentin group as compared to clonidine and placebo group.

Discussion

Good postoperative analgesia is an important component of adequate perioperative care. This is associated with improved outcome, improved patient satisfaction, reduction in perioperative stress, and coupled with a reduction in analgesic consumption and fewer adverse effects. [11]The chosen dose (600 mg) is within the limits of a recommended single dose in the treatment of neuropathic pain (300 to 1200 mg three times daily).[12] Pandey et al. randomized patients undergoing lumbar discectomy to receive a one-time dose of either placebo or gabapentin 300, 600, 900 or 1200 mg pre-operatively. The optimal dose was 600 mg; at higher doses (900 and 1200 mg), patients exhibited more side effects with no additional reduction in pain. [7] The test drugs were administered one hour before surgery as the peak plasma level of gabapentin is achieved 3 hours after ingestion of a single 300 mg capsule. [2]In gabapentine group patients had a significant decrease in postoperative VAS score for pain and mean VAS score did not exceed more than 4. Patients who received 200mcg clonidine had decreased postoperative pain intensity .Mean VAS score was less than 5 at all time interval. VAS score was significantly lower in gabapentine group than clonidine (P < 0.01) and placebo group (P < 0.001). Similar to our study Sussan soltani et al in 2009 compared oral gabapentine and clonidine and found VAS ≥ 3 in 13 patients in clonidine group and 2 patient in gabapentine group and 29 patients in placebo group.They found mean value of morphine consumption significantly lower in gabapentine group as compared to clonidine group.[13]Similar to above study we also found that number of injection of diclofenic sodium and total amount of diclofenic was significantly decreased in gabapentine group as compared to clonidine and placebo group (P < 0.001). Dirks J and Fredensborg BB in 2002 did a randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy. They concluded that a single dose of 1200 mg Gabapentin given orally resulted in substantial reduction in postoperative morphine consumption and movement related pain after radical mastectomy. [14]Turan A and Kaya G hypothesized that oral gabapentin may have an effect on postoperative epidural analgesia and conducted trials. They concluded that oral gabapentin at 1200 mg dose/day as an adjunct to epidural analgesia decreased pain and analgesic consumption. Overall patient satisfaction was better in gabapentin group. [15]Mohd Ghafari & Majid Akrami in 2009 did a study on Preoperative Gabapentin or Clonidine decreases postoperative pain and morphine consumption after abdominal hysterectomy. After the study, they concluded that pre-operative oral gabapentin or clonidine lowers pain score and total morphine consumption for analgesia after abdominal hysterectomy[16]Shivinder singh *et al* studied 150mcg oral clonidine in laparoscopic chlecystectomy and found prolonged time interval for first request of analgesia in postoperative period. Similar to our study they found clonidine group required no meperidine or diclofenac or only one dose in postoperative period during first 24 hour but placebo group required 2 or more than 2 doses of both the drug.[17]In the systematic review by Mathiesen *et al*., analysis of side effects showed a significantly lower incidence of nausea in favour of gabapentin for patients undergoing abdominal hysterectomy. They did not find any reports of clinically limiting side-effects i.e., sedation and dizziness with gabapentin. This is consistent with the results of the our study.[18]

Table 1: Demographic Data

	Group G Gabapentine	Group C Clonidine	Group P Placebo
Number of Patients	30	30	30
Age (years) (mean ± sd)	46.3 ± 5.1	48.1 ± 4.3	47.5 ± 5.2
Weight (kg) (mean ± sd)	58.8± 8.2	56.2± 6	57.6± 6.4
Height (cm) (mean ± sd)	152.4 ± 8.7	146.8 ± 6.3	151.2 ± 7.4
Duration of Surgery (min) (mean ± sd)	126 ± 26	135± 40	111 ± 32

Value shows mean ± SD

Table 2: VAS scale at different time interval (Values are presented as mean ± sd)

	Group G Gabapentin	Group C Clonidine	Group P Placebo
0 hour	3.0 ± 0.4 G & C *G & P **	3.8± 0.7 C & G *C & P *	5.28± 0.34
2 hour	3.4 ± 0.5 G & C *G & P **	4.4 ± 0.58 C & G *C & P *	6.6 ± 0.32
6 hour	3.6 ± 0.5 G & C *G & P *	4.8 ±1.6 C & G *C & P *	5.2 ± 0.8
12 hour	2.9 ±0.6 G & C *G & P *	3.7 ± 1.1 C & G *C & P *	4.9 ± 0.5

* P < 0.01 ** P < 0.001

Table 3: Rescue analgesic requirement

	Group G Gabapentin	Group C Clonidine	Group P Placebo
Time of 1st Rescue analgesic in hrs (mean ± sd)	10.32 ± 0.62 G & C *G & P **	7.24± 0.82 C & G *C & P *	1.34 ± 0.72
Total amount of diclofenac in mg (mean ± sd)	22.12 ± 4.3 G & C *G & P **	75.2 ± 7.41 C & G *C & P *	150 ± 0.42
No of pt required rescue analgesic (%)	9 (30 %) G & C *G & P **	15 (50 %) C & G *C & P *	30 (100%)
No of pt required > 1 dose of rescue analgesic (%)	1 (3.3%) G & C *G & P **	8 (26.66 %) C & G *C & P *	30 (100%)

* P < 0.01 ** P < 0.001

Conclusion

Oral premedication with gabapentin and clonidine significantly decreases the post-operative pain and diclofenac sodium consumption without any significant side effects. Gabapentin decreases pain intensity more

than Clonidine in patients undergoing modified radical mastectomy.

References

1. Rose MA, Kam PC. Gabapentin: pharmacology and its use in pain management. Anaesthesia 2002;57:451-62.
2. Chase JE, Gidal BE. Melatonin: therapeutic use in sleep disorders. Ann Pharmacother 1997; 31(10):1218-26.
3. Lee KJ, JH Kirn, SW Cho. Gabapentin reduces rectal mechanosensitivity and increases rectal compliance in patients with diarrhoea-predominant irritable bowel syndrome. Alimentary iharmdcol. Therapeutics 2005, 22: 981-988. DOT: 10.111,I/J.1365-2036.2005.02685.x.
4. Goa KL, EM Sorkin. Gabapentin. A review of its pharmacological properties and clinical potential in epilepsy.Drugs1993,46(3):409-427.
5. Cutrer P.M. and M.A. Moskowitz 2004. Headache and Other Head Pain. In Goldman, L. and D. Ausieilo (Eds.). Cecil Textbook of Medicine 22th. Philadelphia: Saunders, pp: 2226-2230. ISBN: 0-7 21 6-9652-X
6. Menigaux C, F Adam, B Guignard, D Sessler, M Chauvin. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery.AnesthAnalg2005,100:1394-1399.
7. Pandey CK, S Priye, SF Ambesh, S Singh, U Singh, PK Singh. Prophylactic Gabapentin for prevention postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: A randomized double-blinded placebo-controlled study. J Postgrad Med 2006, 52 (2): 97-101.
8. Arikkath J, Campbell KP. Auxiliary subunits: Essential components of the voltage-gated calcium channel complex. CurrOpinNeurobiol 2003;13:298-307.
9. Bian F, Li Z, Offord J, Davis MD, McCormick J, Taylor CP, *et al*. Calcium channel alpha2-delta type 1 subunit is the major binding protein for pregabalin in neocortex, hippocampus, amygdala, and spinal cord: An *ex vivo* auto radiographic study in alpha2-delta type 1 genetically modified mice. Brain Res 2006; 1075:68-80.
10. Belliotti TR, Capiris T, Ekhato IV, Kinsora JJ, Field MJ, Heffner TG, *et al*. Structure-activity relationships of pregabalin and analogues that target the alpha (2)-delta protein. J Med Chem 2005;48:2294-307.
11. Wu C.L. Correlation of post-operative pain to quality of recovery in the immediate post-operative period. Regional Anaesth Pain Med. 2005;30:516–22.
12. Rowbotham M, Harden N, Stacey B, et al. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA 1998; 280:1837–42.
13. Sussan Soltani, Mohamadi and Mirsadegh Seyedi. Comparing oral gabapentin versus clonidine as premedication on early postoperative pain,nausea and vomiting following general anesthesia. Saudi journal of anaesthesia Vol 3,No.1 April 2009 :25-28
14. Dirks J, Fredensborg BB. A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy. Anesthesiology 2002 Sep;97(3):560-564.
15. Tarun A DJ. Gabapentin: a new drug for postoperative pain? Br J Anaesth 2006;96(2):152-155
16. Gafari MH Akrami M, Sadegh A.Preoperative Gabapentin or Clonidine Decreases Postoperative Pain and Morphine Consumption after Abdominal Hysterectomy. Res Biol Sci 2009;4(4):458-463
17. Shvinder singh and Kapil Arrora Effect of oral clonidine premedication on perioperative haemodynamic response and postoperative analgesic requirement for patients undergoing laproscopic chlecystectomy. Indian Journal of Anaesthesia:2011 Jan-Feb 55 (1) : 26-30
18. Mathiesen O, Møiniche S, Dahl JB: Gabapentin and postoperative pain: a qualitative and quantitative systematic review, with focus on procedure. B MC Anestheiol;2007:7:6

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