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Evaluation of Optimal Preemptive Dose of Oral Gabapentine for Postoperative Epidural Analgesia

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Abstract

The international association for the study of pain has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Unrelieved postoperative pain can lead to lot of problems. Gabapentine is an anti convulsant which can be used as a preemptive analgesic. *Aim:* to assess the optimal dose of preemptive oral gabapentine *Materials and Methods:* The patients were divided into following groups: *Group 1:* Patient receiving only postoperative Epidural analgesia with 6 ml of 0.125% Bupivacaine plus 1 mcg / Kg Fentanyl. *Group 2:* Patient receiving postoperative Epidural analgesia with 6 ml of 0.125% Bupivacaine plus 1 mcg / Kg Fentanyl with 10 mg / Kg Oral Gabapentin 1 Hour before induction with a sip of water. *Group 3:* Patient receiving postoperative Epidural analgesia with 6 ml of 0.125% Bupivacaine plus 1 mcg / Kg Fentanyl with 15 mg / Kg Oral Gabapentin 1 Hour before induction with a sip of water. *Group 4:* Patient receiving postoperative Epidural analgesia with 6 ml of 0.125% Bupivacaine plus 1 mcg / Kg Fentanyl with 20 mg / Kg Oral Gabapentin 1 Hour before induction with a sip of water. All patients surgery was carried out under standart general anaesthetic technique and for postoperative pain epidural catheter was placed in L1-L2 space before induction. *Results:* on comparing VAS score there was not much difference in each group while shifting. Number of epiduaraltopups was significantly reduced in group 3 and 4. Patient satisfaction was good in group 3 and 4. But complication were less in group 3 compared to group 4. *Conclusion*: So oral Gabapentin 15mg / kg dose would be the optimal preemptive dose for postoperative epidural analgesia.

Keywords: Preemptive Analgesia; Gabapentine; Postoperative Pain; Epidural Analgesia.

Introduction

The international association for the study of pain has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. Only 20% of patients undergoing surgery don't need postoperative analgesia [2. Unrelieved postoperative pain leads to many serious consequences [3]. Postoperative pain after laprotomy is usually managed by epidural administration of local anaesthetic drugs with adjuvants like opioids. Preemptive analgesia is defined as, what is administered before surgical incision, what prevents establishment of central sensitization resulting from incisional and inflammatory injuries (i.e., intraoperative and postoperative period) [4]. There are many methods and drugs which are used for preemptive analgesia like local anaesthetics, ketamine, opioids, NSAIDS, clonidine and etc. Now a day's anticonvulsants like Gabapentin, pregabaline are used for postoperative analgesia as preemptive analgesia. Being a non opiod drugs these has the advantage of preventing the side effects of opioids. We conducted this study to find optimal preemptive dose of Gabapentin, observe the reduction in dose of postoperative epidural analgesia, and observe side effects of Gabapentin.

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Materials and Methods

This is a randomized, placebo-controlled trial was conducted in patients undergoing hysterectomy under generalanaesthesia between August 2015 and August 2016 with ASA Grade 1 and 2. The exclusion criteria were Patient refusal for consent, Coagulapathy and bleeding diasthesis, Anticoagulant therapy, Spinal deformity, raised intracranial pressure, Local infection at the site of epidural insertion.

Using a computer-derived random number sequence, 100 women's were allocated by means of sealed opaque envelopes into four groups.

The patients were divided into following groups:

Group 1

Patient receiving only postoperative Epidural analgesia with 6 ml of 0.125% Bupivacaine plus 1 mcg/Kg Fentanyl.

Group 2

Patient receiving postoperative Epidural analgesia with 6 ml of 0.125% Bupivacaine plus 1 mcg/Kg Fentanyl with 10 mg/Kg Oral Gabapentin 1 Hour before induction with a sip of water.

Group 3

Patient receiving postoperative Epidural analgesia with 6 ml of 0.125% Bupivacaine plus 1 mcg/Kg Fentanyl with 15 mg/Kg Oral Gabapentin 1 Hour before induction with a sip of water.

Group 4

Patient receiving postoperative Epidural analgesia with 6 ml of 0.125% Bupivacaine plus 1 mcg/Kg Fentanyl with 20 mg/Kg Oral Gabapentin 1 Hour before induction with a sip of water.

After careful preoperative assessment the patients were taken inside the operation theatre and standard monitors were applied. With strict asepsis, with help of 18G Touhy Epidural needle, the epidural space was reached with loss of resistance technique through L1–L2 inter space. When epidural space was reached, 45mg lignocaine with 1:20000 Adrenaline was given to confirm the position that it has not reached intrathecal space or intravascular compartment respectively.

After this all these patients were premedicated with Inj. midazolam 1mg, Inj. Glycopyrolate 0.2mg, Inj. Ondensetron 4mg, and Inj. Fentanyl 2mcg/kg IV. Then they were induced with Inj. Propofol 2mg/kg, and Inj.Vecuronium 0.1mg/kgIV and intubated with proper sized cuffed endotracheal tube and were connected to circuit. Anaesthesia was maintained with 60% Nitrous Oxide, 40% Oxygen, and 0.02mg/kg Inj. Vecuronium IV and 0.5% sevoflurane. All these patients were reversed with 0.05mg/kg Inj. Neostigmine with 0.02mg/kg Inj. Glycopyrolate IV. All the patients received bolus dose of 6ml 0.125% bupivacaine plus 1mcg/kg Fentanyl through epidural catheter for postoperative analgesia just before extubationand also in first 24 hours of postoperative period whenever patient demands. The time of pain relief and maximum number of Epidural top up doses in first 24 hours of postoperative period were recorded. Pain is assessed by VAS(0- no pain, 100 – severe pain) at the time of shifting the patient to postoperative room, there after 1 hour and 2 hours, after that for every 4 hours for first 12 hours and then every 6 hours for next 12 hours. These patients were also noted for complications like Nausea, Vomiting, Dizziness, Sedation, and Hallucination and Urinary retention. After 24 Hours, all patients those have undergone study were asked for satisfaction for postoperative pain relief which was graded as,

0 – highly dissatisfied

100 – Completely satisfied

After this all the values were collected and entered in a separate sheet and statistical analyses were made.

Results

A total of 124 patients were assessed for eligibility from August 2015 to August 2016, out of which 100 subjects received study medication after randomization. Demographic details like age, weight, and duration of surgery shows no significant difference (Table 1). On comparing the VAS score between the groups which showed that there is significant reduction in VAS score between group 1 & 3, 1 & 4, 2 & 3, 2 & 4, at the different time intervals. But there is no significant reduction in VAS score between groups at the time of shifting the patients and also between group 1 & 2 and group 3 & 4 at different time interval (Table 2, Figure 1). On seeing the number of times the epidural drug given, there is significant reduction is seen with group 4 than other

groups (Table 3, Figure 2). On comparing patient satisfaction for pain relief which showed that there is clinically and statistically significant difference in between the patient satisfaction between the groups except for between group 3 and 4 which showed statistically insignificant (Table 3, Figure 2). Analyzing the complications showed, there is significant increase in dizziness, sedation and hallucination in group 2, 3 and 4 compared to group 1, in which group 4 patients showed more increase in sedation and dizziness. There is significant decrease in nausea and vomiting in group 2, 3, and 4 compared to group 1, but there is no significant decrease in group 3 and 4 (Table 4, Figure 3).

Discussion

On comparing the demographic data of all four groups, mean age (in years) of Group 1 was 38.80 ±

Table 1: Demographic detail

	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Group 3 (Mean ± SD)	Group 4 (Mean ± SD)	P VALUE
N	25	25	25	25	
Age (years)	38.80 ± 6.60	37.96 ± 6.27	39.04 ± 6.51	38.20 ± 7.02	P > 0.05(NS)
Body weight (kgs)	62.78 ± 4.56	62.16 ± 4.67	63.52 ± 4.17	62.82 ± 3.40	P > 0.05(NS)
Duration of surgery(min)	169.20 ± 16.11	171.40 ± 19.01	168.80 ± 21.66	170.40 ±21.83	P > 0.05(NS)

N – Number of subjects
SD – standard deviation
NS- not significant

Table 2: Comparison of vas between groups at different time interval

S. No.	Time	GROUP 1 (Mean±S.D.)	GROUP 2 (Mean±S.D.)	GROUP 3 (Mean±S.D.)	GROUP 4 (Mean±S.D.)
1	At the Time of Shifting (0 Hours)	15.6±5.83	16.00±5.77	14.8±5.85	13.6±4.89
2	1 HOUR	31.2±10.13	26.00±8.16	15.6±7.11	18.00±6.45
3	2 HOURS	27.6±8.30	33.6±12.20	19.6±7.89	20.00±7.63
4	4 HOURS	34.4±10.44	33.2±10.29	25.2±8.71	23.6±7.57
5	8 HOURS	33.2±12.49	30.8±11.15	22.8±10.21	21.6±8.98
6	12 HOURS	40.4±11.35	34.4±10.44	24.4±7.68	28.4±10.27
7	18 HOURS	31.6±9.86	32.8±10.61	22.4±8.30	19.6±7.34
8	24 HOURS	37.2±13.69	31.6±9.86	20.8±7.02	22.8±8.42

Table 3: Number of epidural and patient satisfaction

N	Group 1 (Mean ± SD) 25	Group 2 (Mean ± SD) 25	Group 3 (Mean ± SD) 25	Group 4 (Mean ± SD) 25	P VALUE
Number of times Epidural drug given	17.52 ± 1.68	11.84 ± 1.65	5.68 ± 1.70	4.52 ± 1.08	P<0.001
Patient Satisfaction	33.2±12.81	61.60±9.43	71.20±11.66	72.40±10.50	P<0.05 between all groups P>0.05 between group 3and4

Table 4: Complications

Complications/ Groups	Nausea	Vomiting	Dizziness	Sedation	Hallucination
Group 1	16(35.55%)	15(38.46%)	3(6.98%)	2(5.71%)	1(7.14%)
Group 2	13(28.88%)	11(28.20%)	11(25.58%)	10(28.57%)	4(28.57%)
Group 3	8(17.77%)	6(15.38%)	12(27.91%)	9(25.71%)	4(28.57%)
Group 4	8(17.77%)	7(17.94%)	17(39.53%)	14(40%)	5(35.71%)
TOTAL	45	39	43	35	14
P VALUE	0.05	0.03	0.001	0.004	0.393
X^2	6.16	8.57	16.44	13.14	2.99

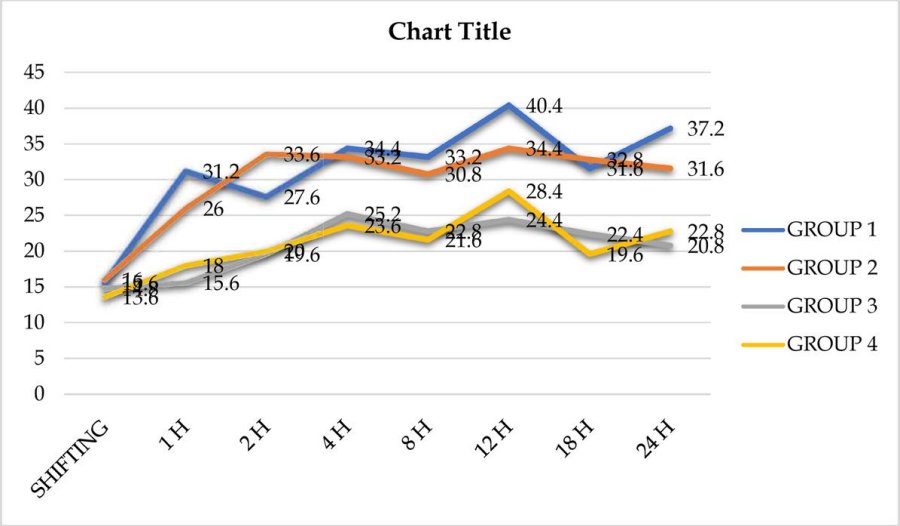

Fig. 1: Comparison of vas between groups at different time interval

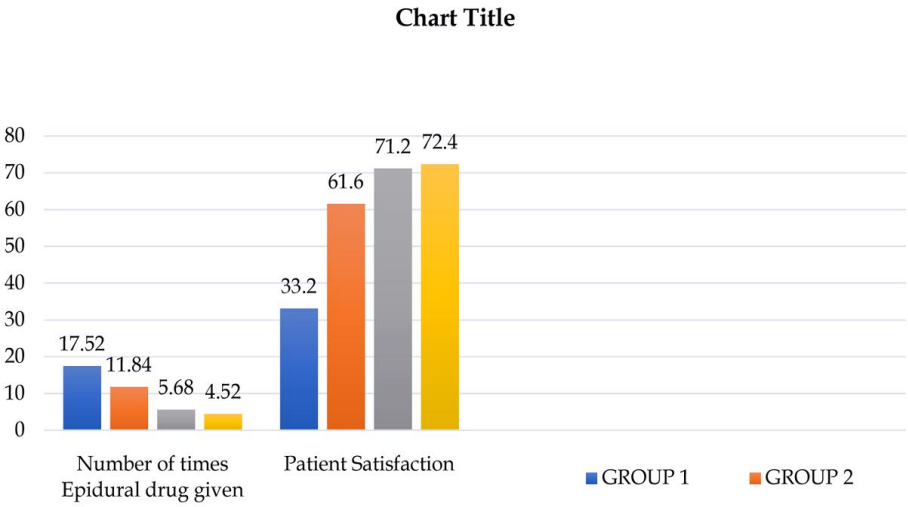

Fig. 2: Number of epidural and patient satisfaction

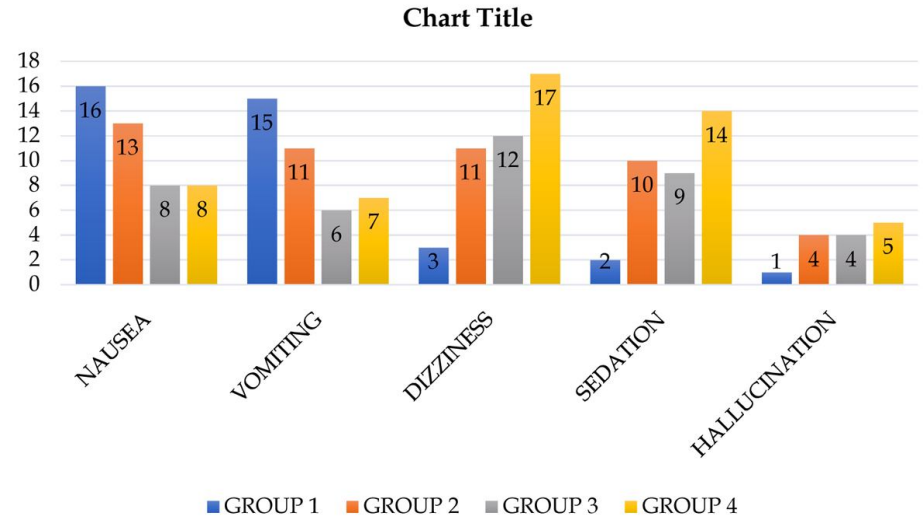

Fig. 3: Complications

6.60, for group 2 was 37.96 ± 6.27, for group 3 was 39.04 ± 6.51and for group 4 was 38.20 ± 7.02. Mean weight (in kgs) of the patients, in group 1 was 62.78 ± 4.56, for group 2 was 62.16 ± 4.67, for group 3 was 63.52 ± 4.17, for group 4 was 62.82 ± 3.40. Mean duration of surgery (in min) of the patients, in group 1 was 169.20 ± 16.11, for group 2 was 171.40 ± 19.01, for group 3 was 168.80 ± 21.66, for group 4 was 170.40 ± 21.83. All these demographic data regarding age, weight, and duration of surgery was similar in all groups and showed no difference (P>0.05).

In our study on comparing the postoperative VAS score, groups receiving Gabapentin 15mg/kg, and Gabapentin 20mg/kg showed significant reduction in VAS score when compared to placebo group at 1, 2, 4, 8, 12, 18, and 24 hours(P<0.05). There is no significant reduction in VAS score between Gabapentin 15mg/kg, and Gabapentin 20mg/kg groups (P>0.05) and between Gabapentin 10mg/kg and placebo group (P>0.05). And also there is no significant difference in VAS between all groups at the time of shifting, which may be due to the fact that epidural Bupivacaine was given just before extubation in all groups.

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et al [5], showed that VAS score was significantly reduced in patients who received Gabapentin 1200mg 2 hours before surgery after abdominal hysterectomy. Montazeri K et al [6] showed that with 300 mg gabapentin VAS scores at all time intervals of 2, 4, 12, and 24 hours, was lower than those in the placebo group ($P<0.05$). They concluded that pre-emptive use of gabapentin 300 mg orally significantly decreases postoperative pain and rescue analgesic requirements in patients who undergo lower extremity orthopedic surgery. Our study showed reduction in VAS score with oral gabapentin 15mg / kg, all other studies showed only effect of single dose.

Comparison of the reduction in number of times the epidural topup given showed that there is significant decrease in gabapentin groups when compared to placebo group.

Mean ± SD (17.52 ± 1.68, 11.84 ± 1.65, 5.68 ± 1.70, 4.52 ± 1.08) of placebo group, gabapentin 10mg / kg, 15mg / kg, 20mg / kg groups respectively.

Our finding was comparable with the study conducted by Turan et al [7] in patients undergoing lower extremity surgery procedures

Patient satisfaction was good in gabapentin group than placebo group, as placebo group showed 33.2± 12.81 on an average, but gabapentin group 10 mg / kg, 15mg / kg, 20mg / kg showed 61.60 ± 9.43, 71.20 ± 11.66, 72.40 ± 10.50 respectively. This showed that on increasing the dose of gabapentin had good patient satisfaction.

There is significant increase in dizziness, sedation and hallucination in gabapentin group than placebo group. Gabapentin 20 mg / kg group (39.53%, 40%, and 35.71% respectively) showed more increase than 10mg / kg (25.58%, 28.57%, and 28.57%) and 15mg / kg (27.91%, 25.71%, and 28.57%) groups which showed almost equal incidence.

Candrakant Pandey et al [8] and Philip WH Peng et[9] al also showed that there is increased dizziness and sedation with gabapentin on increasing the dose. Our study also showed that there is decreased incidence of nausea and vomiting in gabapentin group, compared to placebo group [10,11].

Painful stimuli to the body are detected by the free endings of peripheral nerves (primary afferent neurons) called as nociceptors. Nociceptors are subdivided into, the myelinated A delta fibres which are large in diameter specialized for detecting mechanical and thermal injury and for triggering a rapid sharp pain response, termed 'first pain' and, unmyelinated C nociceptors respond to strong mechanical, thermal and / or chemical stimuli, and they mediate a more delayed burning pain response, termed 'second pain' [12].

Gabapentin, an anticonvulsant drug, was first reported to be effective for the treatment of neuropathic pain [14]. The absorption of gabapentin is dose-dependent thus the oral bioavailability varies inversely with dose. It is not bound to plasma proteins. Concentrations of gabapentin in cerebrospinal fluid are approximately 5–35% of those in plasma, whereas concentrations in brain tissue are approximately 80% of those in plasma [15]. It is eliminated unchanged in the urine and any unabsorbed drug is excreted in the faeces. Gabapentin modulates Ca^{2+} current by selectively binding to $\alpha 2\delta$ subunit of voltage-dependent Ca^{2+} channels ([^{3}H] gabapentin (a radioligand)) so that it decreases the release of excitatory neurotransmitters [16]. Somnolence, dizziness, asthenia, headache, nausea, ataxia, weight gain, and amblyopia are the common side effects which are observed [18].

Conclusion

To conclude, we observed that reduction in VAS score, reduction in postoperative analgesic requirement, and patient satisfaction was almost equal in 15mg / kg and 20mg / kg dose, but control of vomiting was better in 15mg / kg and incidence of dizziness, sedation and hallucination was less in 15mg / kg dose than 20mg / kg dose.

So oral Gabapentin 15mg / kg dose would be the optimal preemptive dose for postoperative epidural analgesia.

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