A COMPARATIVE EVALUATION OF GABAPENTIN AND CLONIDINE PREMEDICATION ON POST OPERATIVE ANALGESIA REQUIREMENT FOLLOWING ABDOMINAL SURGERIES UNDER GENERAL ANAESTHESIA

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ABSTRACT: AIM: Aim of our study was to compare the relative effectiveness of gabapentin and clonidine premedication on patients undergoing elective abdominal surgeries under G.A. OBJECTIVE: gabapentin and clonidine have anti-nociceptive properties. This study assess their efficacy in prolonging the analgesic effect intra-operative and postoperative analgesic requirement. MATERIAL AND METHOD: 225 patients of either sex of age between 20-60 years, ASA grade I & II, patient admitted to Hamidia hospital for elective abdominal surgeries under general anaesthesia were included in the study. The patients were randomly allocated into three groups 75 each group I: Control group (patients received placebo tablet at 90 min before the surgery), group II Gabapentin 300 mg tablet orally 90 min before surgery , group III: clonidine 150µg tablet orally given 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 that there was no difference in the HR, SBP among the three group during the study. Duration of postoperative analgesia, observed from time of reversal to first demand of analgesia in the recovery room was more in group II compared to group I and group III (p-value < 0.001, highly significant). Pain perception was highly blunted in groups II compared to group I & group III. Total rescue analgesic requirement during the postoperative 24 hrs period was much lower in group II inj Diclofenac compared to group I and group III. (p-value < 0.001, highly significant). CONCLUSION: Given 90 min before induction of GA oral gabapentin(300 mg) or clonidine(150 µg) preoperatively was effective in lowering postoperative VAS pain score and consumption of analgesics, it was also shows that gabapentin significantly decreases postoperative pain intensity and analgesic consumption after abdominal surgeries.

KEYWORDS: Gabapentine, clonidine, post-operative analgesia

INTRODUCTION: Pain is derived from the word poena meaning punishment. Pain is an unpleasant sensation that originates from ongoing and impending tissue damage. Acute pain accompanies almost all surgical procedures. Adequate pain relief provides a quick return to normal physiological function and prevents the development of chronic pain. Traditional analgesia in the post-operative period is based opioids, non-steroidal anti-inflammatory drugs (NSAIDS) and regional techniques.

Administration of high dose of opioids during the post-operative period can result in higher incidence of complication such as respiratory depression, sedation, vomiting, constipation, pruritus, immune dysfunction and urinary retention. NSAIDS may lead to gastrointestinal bleeding, renal toxicity and thromboembolic complication. Hence the search for the ideal drug continues. A drug,
which has anxiolytic property without the adverse effects of traditional analgesic mentioned, may be the attractive choice for post-operative analgesia.

Opioid analgesia, with their well-known side effects, continues to represents a cornerstone in postoperative pain control and testing new analgesic as well as combinations of analgesics in order to reduce the need for opioids, is a key area in acute pain research (Rose and kam 2002).[1]

The analgesic benefits of controlling postoperative pain are generally maximized when a multimodal strategy to facilitate the patients convalescence is implemented (Kehlet H: 1999).[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. Recently it has also been used for postoperative pain relief (Cutrer & Maskowirz, 2004)[3]

Gabapentin has a selective effect on the nociceptive process involving central sensitization (Lee et al, 2005).[4] 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).[5]

Gabapentin is an anticonvulsant that has antinociceptive and anti hyperalgesic properties. In pain models it has shown anti-hyperalgesic properties, possibly by reducing central sensitization, a prerequisite for postoperative hyperalgesia.

It binds to the α2δ subunits of voltage dependent calcium ion channels and blocks the development of hyperalgesia and central sensitization (Goa & sorkin, 1993).[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 (Pandeyck et al 2006).[7]

Recent studies suggest that Gabapentin may be useful in the perioperative setting, as an adjuvant to parenteral opioid analgesics in post-operative period (Drinks J et al, 2002).[8]

In intraabdominal surgeries, preoperative Gabapentin prolongs analgesic effects of opioids and reduces the doses of perioperative analgesics (Saraswat V et al 2008).[9]

The α2-agonist Clonidine has shown properties that are potentially beneficial for premedication to reduce sympathetic activity, the incidence of shivering and oxygen consumption during recovery from anesthesia, to decrease anesthetic and analgesic requirement and to minimize postoperative pain, nausea and vomiting (Ghignone Et al 1987).[10]

Clonidine provides significant benefits for preoperative anxiety and analgesia. (Hidalgo et al, 2005).[11] Premedication with Clonidine blunts the stress response to surgical stimuli and the narcotic and anesthetic doses are also reduced (Harron DW et al 1989).[12] Clonidine administration, in general Clonidine appears to decrease anesthetic and analgesic requirements (decrease MAC), provide sedation and anxiolysis (Quintin et al 2002).[13]

The aim of our study was to compare the duration of post-operative analgesia with premedication with oral gabapentine and clonidine and the number of doses of diclofenac sodium injection required during the first 24 hrs. after the surgery among the study groups. We also assessed the side effects of study drugs such as respiratory depression, nausea, vomiting and dryness of mouth.

MATERIAL AND METHODS: After obtaining informed consent and approval of the institutional ethics committee, this prospective randomized study was conducted on 225 ASA grade I & II, patient
admitted to Hamidia hospital for elective abdominal surgeries under general anesthesia. After taking a detailed history, thorough general physical examination, all pertinent investigation were carried out to exclude any systemic disease. Exclusion criteria for this study were patient refusal to participate in the study, patient less than 20 year or more than 60 year of age, patient weighing less than 40 kg, patient with BMI >35, patient on β blocker, patients with chronic pain, drug or alcoholic abusers and pregnancy.

The patients were randomly divided into three groups:
- Group I (n= 75): Control group (patients received placebo tablet at 90 min before the surgery).
- Group II (n= 75): Gabapentin 300 mg tablet orally 90 min before surgery.
- Group III (n=75):clonidine150µg tablet orally given 90 min before surgery.

In the operation theater, all the baseline parameters, such as heart rate (HR), electrocardiography (ECG), non-invasive blood pressure (NIBP), pulse oxymetry (SPO2) were recorded and i/v access was established. All the patients were pre medicated with Fentanyl 2 mcg/kg, induced with Thiopentone sleep dose and Vecuronium 0.1mg/ kg to facilitate orotracheal intubation.

Anesthesia was maintained with Halothane (0.2-0.6%) and 60% Nitrous oxide in 40% oxygen and intermittent i/v Vecuronium (0.03-0.05mg/kg).Residual neuromuscular blockade was then reversed with i/v Neostigmine 2.5mg and Glycopyrollate 0.5mg. Trachea was extubated after establishing the adequate return of protective airway reflexes & rhythmic breathing pattern with adequate tidal volume.

(Patient in whom intraoperative analgesia was supplemented with any drug, were excluded).Following parameters were recorded preoperatively and intra operatively after the administration of drug HR, SBP and any added analgesic required at prior to premedication, 30 min, 60 min, 90 min after pre medication, just prior to induction, at the time of induction, 30min, 60 min, 90 min, 120 min after the induction, and just prior to shifting. Duration of postoperative analgesia, Degree of postoperative pain (VAS score)and added rescue analgesia required in 24 hrs. were recorded postoperatively. The statistical significant difference among the groups was assessed by the use of one way ANOVA test, Z-test & Chi-square test. Differences were considered significant at P<0.05.

RESULT AND ANALYSIS: HR and SBP show no significant difference among the three groups during the study. (table1&2 respectively) (Respectively p-value <0.05).

We observed duration of postoperative analgesia, from time of reversal to first demand of analgesia in the recovery room was more in group II (124.62±16.41) mins compared to group I (61.92±8.38) mins and group III (87.23±12.46) mins. (p-value <0.001, highly significant).(ONE WAY ANOVA TEST)(Table-3) statistical comparison of duration of post-operative analgesia of gabapentin against clonidine and control group using z-test.

The z- test between the corresponding variables yielded P values of <0.001 for all three pairs, i.e. gabapentin and control; clonidine and control & gabapentin and clonidine respectively. Hence we can conclude from this finding that both gabapentin and clonidine had better post-
operative analgesic effect compared with control. Furthermore, it is concluded that gabapentin is more effective than clonidine. (Table-4).

We observed that the degree of postoperative pain (assessed by VAS) in group I & III patients are significantly more compared to group II patients. Pain perception was highly blunted in groups II compared to group I & group III.

The table-5 shows 29.3 % of group I patient compared to 6.7 % of group II and 13.2 % of group III patient at 0-6 hrs., 56 % of group I patient compared to 18.6 % of group II and 38.6 % of group III patient at 7-12 hrs., 76 % of group I patient compared to 41.34% of group II and 62.67 % of group III patient at 13-18 hrs., 90.66 % of group I patient compared to 69.33% of group II and 82.67 % of group III patient at 19-24 hrs., had moderate to severe pain. (analgesia score relevance (>3) taken as significant)

This shows that severity of postoperative pain in group I & III patients is more compared to group II patients.

We observed the total rescue analgesic requirement during the postoperative 24hrs period was much lower in group II 72.0±18.23 mg inj Diclofenac compared to group I 84.0 ±12.56 mg and group III 98.0±15.34 mg inj Diclofenac. (p-value < 0.001, highly significant) (ONE WAY ANOVA TEST) (Table-6).

The statistical comparison of duration of post-operative analgesia of gabapentin against clonidine and control group using Z- test. The Z- test between the corresponding variables yielded P values of <0.0001 for all three pairs, i.e. gabapentin and control; clonidine and control & gabapentin and clonidine respectively.

Hence we can conclude from this finding that both gabapentin and clonidine had better postoperative analgesic effect compared with control. Furthermore, it is concluded that gabapentin is more effective than clonidine. (Table-7).

DISCUSSION: There was no significant difference in the heart rate & systolic blood pressure among the three groups during the study.

Our results are in accordance with S. Sharma et al (2012)[14], they studied oral 800 mg Gabapentin, 300 µg Clonidine, combination of oral 400 mg Gabapentin, 150 µg Clonidine and placebo, to attenuate the pressure response to direct laryngoscopy and intubation, and observed that, there was no statistically significant difference in HR. SBP, DBP and MAP.

Our results are also in accordance with A. Fassoulaki et al (2006).[15]

Duration of postoperative analgesia, observed from time of reversal to first demand of analgesia in the recovery room was more in group II (124.62±16.41) mins compared to group I (61.92±8.38) mins and group III (87.23±12.46) mins.

Our results are also in accordance with Mohammad Hussein Ghafan et al, (2009)[16] who conducted a randomized, placebo-controlled, double-blind study, in which patients received oral placebo or Gabapentin 300 mg or Clonidine 100 µg at night (10: 00 pm) before surgery and 1 h pre-operatively and found that total morphine consumption and patient’s pain intensity (according to VAS) were lower in Gabapentin and Clonidine group in comparison to control group (p<0.05). Meanwhile, Gabapentin administration significantly decreased morphine consumption after hysterectomy in comparison to clonidine.
Our results are also in accordance with Sussan Soltani Mohammadi et al (2008)\cite{17} & Jeon et al (2009)\cite{18}.

The degree of postoperative pain in group I & III patients are significantly more compared to group II patients. Pain perception was highly blunted in groups II compared to group I & group III.

Hence the total rescue analgesic requirement during the postoperative 24hrs period was much lower in group II 72.0±18.23 mg inj Diclofenac compared to group I 84.0 ±12.56 mg and group III 98.0±15.34 mg inj Diclofenac.

Our results are in accordance with Sussan Soltani Mohammadi et al(2008)\cite{17} who conducted a randomized placebo controlled study, in which patients received either 0.2 mg oral Clonidine (n = 40), 300 mg Gabapentin (n = 40) or placebo (n = 40) 1 h before surgery and found that both Gabapentin and Clonidine reduced the postoperative pain and total morphine consumption compared with placebo group, but Gabapentin group was more effective than Clonidine group.

Present results for Gabapentin was similar to results presented in a systemic review about qualitative and quantitative effects of Gabapentin on postoperative pain presented by Mathiesen et al. (2007)\cite{19}.

Our results are also in accordance with Tarun et al (2004)\cite{20}.

From the above discussion we found that both Gabapentin and Clonidine reduces postoperative pain and total rescue analgesic consumption. But Gabapentin group was more effective than Clonidine and control group.

Present results for Gabapentin was similar to results presented in a systemic review about qualitative and quantitative effects of Gabapentin on postoperative pain presented by Mathiesen et al (2007)\cite{19}.

**CONCLUSION:** Given 90 min before induction of GA oral gabapentin(300 mg) or clonidine(150 μg) preoperatively was effective in lowering postoperative VAS pain score and consumption of analgesics, it was also shows that gabapentin significantly decreases postoperative pain intensity and analgesic consumption after abdominal surgeries.

| Time interval          | Group I (P-value with baseline value) | Group II (P-value with baseline value) | Group III (P-value with baseline value) |
|------------------------|---------------------------------------|----------------------------------------|-----------------------------------------|
| Basal/before premedication | 73.2±6.54 (Control) | 73.76±10.42 (Gabapentin) | 81.54±12.36 (Clonidine) |
| 30 min after premedication | 70.78±4.32 (0.0083) | 71.25±9.34 (0.1225) | 70.05±10.28 (<0.0001) |
| 60 min after premedication | 69.28±6.76 (0.0004) | 70.46±15.82 (0.1335) | 69.86±8.26 (<0.0001) |
| 90 min after premedication | 71.46±7.48 (0.1315) | 69.05±8.86 (0.0033) | 68.86±17.23 (<0.0001) |
| Just prior to induction | 70.84±8.48 (0.058) | 73.05±6.62 (0.6192) | 69.4±8.38 (<0.0001) |
| Just after the induction & Intubation | 74.09±6.32 (0.3981) | 72.26±14.22 (0.462) | 74.0±13.22 (0.0004) |
### TABLE 1: Showing changes in heart rate at various time intervals in the three groups (beats/min)

| Time interval                        | Group I (Control) (P-value with baseline value) | Group II (Gabapentin) (P-value with baseline value) | Group III (Clonidine) (P-value with baseline value) |
|--------------------------------------|-------------------------------------------------|----------------------------------------------------|--------------------------------------------------|
| Basal/before premedication           | 117.84±9.38                                     | 129.74±15.28                                       | 128.53±6.38                                      |
| 30 min after premedication           | 116.34±6.72 (0.2621)                             | 116.90±8.38 (0.0001)                               | 121.76±12.42 (0.0001)                            |
| 60 min after premedication           | 116.48±8.32 (0.3491)                             | 111.69±18.20 (0.0001)                              | 122.18±14.26 (0.0006)                            |
| 90 min after premedication           | 116.4±12.65 (0.4297)                             | 119.88±13.16 (0.0001)                              | 123.06±11.28 (0.0004)                            |
| Just prior to induction               | 118.94±13.52 (0.5635)                            | 114.65±6.83 (0.0001)                               | 122.24±18.76 (0.0067)                            |
| Just after the induction & intubation| 119.06±11.14 (0.4693)                            | 129.12±12.78 (0.7879)                              | 125.81±16.32 (0.18098)                           |
| 30 min after the induction            | 119.05±11.32 (0.4771)                            | 119.2±8.76 (0.0001)                                | 123.28±8.48 (0.0001)                             |
| 60 min after the induction            | 116.72±12.58 (0.5375)                            | 115.46±16.12 (0.0001)                              | 120.93±14.28 (0.0001)                            |
| 90 min after the induction            | 119.95±12.82 (0.2519)                            | 120.26±7.42 (0.0001)                               | 122.20±10.26 (0.0001)                            |
| 120 min after the induction           |                                                 | 122.26±4.32 (0.0001)                               |                                                  |
| Just prior to shifting                | 123.96±11.72 (0.6371)                            | 1198.54±11.42 (0.0001)                             | 121.65±16.82 (0.0012)                            |

### TABLE 2: Showing changes in systolic blood pressure at various time intervals in the three groups (mmHg):

| Time interval                        | Group I (Control) (P-value with baseline value) | Group II (Gabapentin) (P-value with baseline value) | Group III (Clonidine) (P-value with baseline value) |
|--------------------------------------|-------------------------------------------------|----------------------------------------------------|--------------------------------------------------|
| Basal/before premedication           | 117.84±9.38                                     | 129.74±15.28                                       | 128.53±6.38                                      |
| 30 min after premedication           | 116.34±6.72 (0.2621)                             | 116.90±8.38 (0.0001)                               | 121.76±12.42 (0.0001)                            |
| 60 min after premedication           | 116.48±8.32 (0.3491)                             | 111.69±18.20 (0.0001)                              | 122.18±14.26 (0.0006)                            |
| 90 min after premedication           | 116.4±12.65 (0.4297)                             | 119.88±13.16 (0.0001)                              | 123.06±11.28 (0.0004)                            |
| Just prior to induction               | 118.94±13.52 (0.5635)                            | 114.65±6.83 (0.0001)                               | 122.24±18.76 (0.0067)                            |
| Just after the induction & intubation| 119.06±11.14 (0.4693)                            | 129.12±12.78 (0.7879)                              | 125.81±16.32 (0.18098)                           |
| 30 min after the induction            | 119.05±11.32 (0.4771)                            | 119.2±8.76 (0.0001)                                | 123.28±8.48 (0.0001)                             |
| 60 min after the induction            | 116.72±12.58 (0.5375)                            | 115.46±16.12 (0.0001)                              | 120.93±14.28 (0.0001)                            |
| 90 min after the induction            | 119.95±12.82 (0.2519)                            | 120.26±7.42 (0.0001)                               | 122.20±10.26 (0.0001)                            |
| 120 min after the induction           |                                                 | 122.26±4.32 (0.0001)                               |                                                  |
| Just prior to shifting                | 123.96±11.72 (0.6371)                            | 1198.54±11.42 (0.0001)                             | 121.65±16.82 (0.0012)                            |
### TABLE 3: Duration of post-operative analgesia (in mins)

| Group                  | Duration (mean ± SD) |
|------------------------|----------------------|
| Group I (Control)      | 61.92±8.38 min       |
| Group II (Gabapentin)  | 124.62±16.41 min     |
| Group III (Clonidine)  | 87.23±12.46 min      |

### TABLE 4: Duration of post-operative Statistical comparison of duration of postoperative analgesia.

|   | B/W Group I (Control) & II (Gabapentin) | B/W Group I (Control) & III (Clonidine) | B/W Group II (Gabapentin) & III (Clonidine) |
|---|----------------------------------------|----------------------------------------|-------------------------------------------|
| Difference | 62.7 | 25.31 | 7.39 |
| Standard error of sample | 2.128 | 1.734 | 2.379 |
| 95% Confidence Interval | 58.496 to 66.904 | 21.884 to 28.736 | 42.092 to 32.688 |
| Test statistic z | 29.26 | 14.49 | 15.61 |
| Degree of freedom | 148 | 148 | 148 |
| Significance level P-Value | P < 0.0001 | P < 0.0001 | P < 0.0001 |

### Verbal analgesia scale at different time interval

| Analgesia score relevance | VAS | Verbal analgesia scale at 0-6 hrs. | Verbal analgesia scale at 6-12 hrs. |
|---------------------------|-----|----------------------------------|-----------------------------------|
|                          | No. | %                               | No. | %                             | No. | %                                  | No. | %                                   |
| 1 No pain                 | 30  | 40%                             | 54  | 72%                           | 40  | 53%                                | 18  | 24%                                |
| 2 Mild pain               | 16  | 21.3%                           | 25  | 33.3%                         | 15  | 20%                                | 22  | 29.3%                             |
| 3 Moderate pain           | 8   | 10.6%                           | 8   | 10.6%                         | 24  | 32%                                | 8   | 10.6%                             |
| 4 Sever pain              | 2   | 2.6%                            | 2   | 2.6%                          | 18  | 24%                                | 6   | 8%                                 |
| Total                     | 75  | 100%                            | 75  | 100%                          | 75  | 100%                               | 75  | 100%                               |

### Verbal analgesia scale at different time interval (Continued)

| Analgesia score relevance | VAS | Verbal analgesia scale at 12-18 hrs. | Verbal analgesia scale at 18-24hrs |
|---------------------------|-----|-------------------------------------|-----------------------------------|
|                          | No. | %                                  | No. | %                             | No. | %                             |
| 1 No pain                 | 10  | 13.33%                             | 8   | 10.67%                        | 3   | 4%                             |
| 2 Mild pain               | 8   | 10.67%                             | 20  | 26.7%                         | 4   | 5.33%                          |
| 3 Moderate pain           | 19  | 25.33%                             | 24  | 18.67%                        | 22  | 29.33%                         |

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4 Sever pain | 71-100 | 38 | 50.67% | 17 | 22.67% | 27 | 36% | 46 | 61.33% | 22 | 29.33% | 38 | 50.67%  
Total | 75 | 100% | 75 | 100% | 75 | 100% | 75 | 100% | 75 | 100% | 75 | 100%  

**TABLE 5**: Degree of postoperative pain (as assessment by visual analogue scale) 
VAS at different time interval of post-operative period.

| Group | Amount (mean ± SD) |
|-------|---------------------|
| Group I(Control) | 98.0±15.34mg |
| Group II(Gabapentin) | 72.0±18.23 mg |
| Group III(Clonidine) | 84.0 ±12.56 mg |

**TABLE 6**: Total rescue analgesic requirement (i/v inj diclofenac) in 24 hrs. into post-operative period.

| B/W Group I (Control) & II (Gabapentin) | B/W Group I (Control) & III (Clonidine) | B/W Group II (Gabapentin) & III (Clonidine) |
|------------------------------------------|----------------------------------------|------------------------------------------|
| Difference | 25.61 | 13.77 | 11.84 |
| Standard error of sample | 2.751 | 2.289 | 2.556 |
| 95% Confidence Interval | 20.173 to 31.047 | 9.246 to 18.294 | 6.789 to 16.891 |
| Test statistic Z | 37.2 | 41.89 | 56.3 |
| Degree of Freedom | 148 | 148 | 148 |
| Significance level P-Value | P < 0.0001 | P < 0.0001 | P < 0.0001 |

**TABLE 7**: Statistical comparison of total rescue analgesic Requirements (i/v inj diclofenac) in 24 hrs. into postoperative period.

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