Original Article

Preemptive Analgesia with Pregabalin: It's Effect on Postoperative Analgesia after Abdominal Hysterectomy

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Abstract

Background: *Preemptive administration of single dose pregabalin reduces postoperative narcotic analgesic consumption after abdominal hysterectomy under sub-arachnoid block.*

Objectives: *The present study was designed to evaluate the effect of pregabalin as a preemptive agent to reduce postoperative pain.*

Methodology: *This randomized double-blind placebo-controlled clinical trial was conducted in the Department of Anesthesia, Analgesia and Intensive Care Medicine at Banghabandhu Sheikh Mujib Medical University, Dhaka from July 2010 to June 2012 for a period of two years. Women aged between 40 to 60 years scheduled for abdominal hysterectomy under sub-arachnoid block were selected as study population. A total of one hundred and twenty women were randomly allocated into two equal groups by card sampling. 120 cards, 60 for each group were prepared by another person who was not aware of the study. Group A was known as study group who were received 300mg oral pregabalin one hour before performance of SAB and group B was known as control group who were received matching placebo one hour before SAB.Pain in the postoperative period was assessed on visual analogue scale and managed with PCA using morphine. Patients were visited by the investigators at ½, 1, 2, 4, 12, and 24 h after operation. At each visit, outcomes were measured in the following order: heart rate, mean arterial pressure, respiratory rate, SpO2, and VAS pain score, sedation score, and any side effects which would develop. Finally, total amount of morphine administered in 24 hour was recorded. The time since spinal anaesthesia to first dose of analgesic was also recorded.*

Result: *The mean 24hrs morphine consumption was 13.3 (±1.5) mg in Group-A, whereas in Group-B was 29.1(±2.1) mg. The Group-A showed a significant reduction in morphine consumption then the Group-B (P<0.001). The time interval of first dose of analgesic was 5.2(±0.4) hrs in the Group-A, whereas in the Group-B was 2.3(±0.2) hrs.The difference was significant (P<0.05).It was seen that side effects like respiratory depression more in Group-B, dizziness and somnolence was more in Group-A than Group-B.Sedation score was higher in Group-A than Group-B. Incedence of nausea/vomotting was same in both groups.*

Conclusion: *It is demonstrated that preemptive use of Pregabalin led to significant reduction in narcotic analgesic requirement and thereby a significant reduction in morphine related side effects. Beside this, pregabalin caused increased levels of sedation which may be beneficial for certain patients in early postoperative periods.*

Keywords: *Pregabalin; abdominal hysterectomy; preemptive analgesia; morphine consumption*

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Introduction

Postoperative pain is one of the common problems of the postoperative ward care. The pain relief is associated with alleviation of endocrine-metabolic response to surgery, inhibition of surgery related autonomic reflexes. These problems lead to muscle spasm and many other undesirable side effects (Kehlet, 1994). So, in addition to the subjective comfort, postoperative pain management is provided to reduce pain induced autonomic and somatic responses. It allows the patients to breath, cough and to move more easily (Kehlet & Dah, 1993).These are essential for the prevention of pulmonary and thromboembolic consequences (Atkinson et al, 1993).

Under- treatment of pain has been identified as one of the most common cause of failure in postoperative patient management. Traditional method of postoperative pain management has been the nurse-administered intramuscular injection of narcotic analgesic, when the pain threshold has been exceeded. This method of pain management either leads to poor control of pain or associated with opioid related complications such as postoperative nausea & vomiting, delay recovery of bowel function, urinary retention and respiratory depression (White & Kehlet, 2007). Now a days, there is increasing emphasis on the use of multimodal regimen to modulate pain either peripherally at the nociceptor or centrally at spinal and supraspinal structure (White, 2005; White, 2008; Morgan & Mikhail, 2006).

One of the classical ways of achieving multimodal regimen of analgesia is to administer analgesics pre-emptively, instead of waiting for the patient's complaint. Preemptive analgesia, an analgesic treatment initiated before, as opposed to after the surgical procedure. It prevents the central sensitization (neuronal hyper excitability) from deleterious effects of peripheral noxious stimuli (Woolf & Chong, 1993).In preemptive analgesia altered processing of input, which amplifies postoperative pain, are prevented. This concept was formulated by Circle (Circle-1913) at the beginning of 19^{th} century on the basis of clinical observation. Preemptive analgesia strategies have involved interventions at one or more sites along the pain pathway (Figure-13). These strategies have included infiltration with local anesthetics, nerve block, epidural block, subarachnoid block, opioid analgesics, anti-inflammatory drugs, and N-methyl-D-aspartate antagonist. All which are associated with variety of problems such as infiltration with local anaesthetics only reduces somatic pain but inadequate for visceral pain (Leung CC, et al. 2000)., nerve block and subarachnoid block are associated with short duration of analgesia, which doesn't cover postoperative analgesia for first 24hr, incremental dose of epidural local anaesthetic and opioid may cover postoperative analgesia for first 24hr but often associated with side effects such as itching, respiratory depression, bowel and bladder retention, lower limb paresis, low back pain, epidural haematoma and epidural abscess formation(Christie IW, 2007 and Susan M Nimmo, 2012), non-steroidal anti- inflammatory drugs and paracetamol are often associated with multiple organ related side effects including gastrointestinal, renal, cardiovascular, hepatic, pulmonary and haematological and the clinical use of ketamine is limited due to its potential to cause hallucinations and a dissociative mental state. (Buvanendran A, Kroin JS. 2007).

Traditionally, the pathophysiology and treatment of acute (postoperative) and neuropathic pain have been considered as separate entity. Opioids, non-steroidal anti-inflammatory drugs(NSAIDs) and local anesthetics are the tools for dealing acute pain. On the other hand, neuropathic pain is managed with anticonvulsant and tricyclic antidepressant drugs. But several recent studies have suggested overlapping in the pathophysiology of acute and neuropathic pain. Sensitization of the neurons in the dorsal horns, which is a mechanism for neuropathic pain, has been demonstrated in acute pain models (Lascelles et al., 1995).

Pregabalin, a structural analogue of gama-amino-buteric acid(GABA), binds potently with alpha-2-delta subunit of presynaptic voltage- dependent calcium channels (N-type). These type of channels are present throughout the nervous system (Arikkath & Campbell, 2003; Gee et al., 2006; Taylor, 2004). The European commission and food and drug administration first approved pregabalin in 2004 for the treatment of neuropathic pain and in 2005 for an adjunctive therapy in epilepsy. In 2006, the European Commission approved

pregabalin for the treatment of generalized anxiety disorder (Forde, 2007; Gilron et al., 2006, Frampton et al 2004).The available literatures also suggested its efficacy in the management of acute pain (Reuben et al 2006, Agarwal et al2008,Saraswat et al 2008, Mathiesen2008). By acting as a Ca^{+} channel blocker, it blocks release of certain excitatory neurotransmitter, like-glutamate, substance-P and CGRP etc (Garaj, 2005). In this way pregabalin causes inhibitory modulation of neuronal hyper excitability and can be used as an adjuvant to a multimodal analgesic regimen to achieve opioid sparing effects (Agarwal et al., 2008; Mathiesen et al., 2008). Common side effects of pregabalin are less, which is comparable to other agents used for preemptive analgesia.

It is already mentioned that pregabalin acts by blocking the N-type Ca+ channel in central nervous system (CNS) which absolutely different from mechanism of action of morphine, which exarts its analgesic action by acting on opioid receptors. So there is no obviating chance of chemical interaction.

The pregabalin has proven efficacy in epilepsy, neuropathic pain and fibromyalgesia. There is yet-no specific evidence of its efficacy in post-operative pain management when pain is already established.So, the present study is designed to investigate the opioid-sparing effect of pregabalin after its preemptive administration.

Methodology

Study Population and Study Design: This randomized double-blind placebo-controlled clinical trial was conducted in the Department of Anesthesia, Analgesia and Intensive Care Medicine, Banghabandhu Sheikh Mujib Medical University, Dhaka from July 2010 to June 2012 for a period of two years. Women aged between 40-60 years scheduled for abdominal hysterectomy under sub-arachnoid block were selected as study population for this study. The study populations were divided into group A and group B. The eligibility criteria of the patients were the age group between 40 to 60 years and ASA physical status I - II. scheduled for abdominal hysterectomy under sub-arachnoid block, and Patietns with chronic pain syndromes and epilepsy, patients getting treatment with pregabalin for chronic pain, impaired renal function, bleeding diathesis, local skin infection, pre-existing neurological or spine disease were excluded from this study.

Group A was known as study group who were received 300mg oral pregnabin one hour before performance of SAB and group B was known as control group who were received matching placebo one hour before SAB.

Anesthesia procedure: The patients were examined preoperatively and preoperative baseline parameters including: heart rate, respiratory rate, mean arterial pressure, and SpO_2 were recorded immediately before sub- arachnoid block (SAB). During preoperative assesment patients were explained about the visual analogue scale (VAS).In the operating room, all patients were preloaded with Ringers lactate solution 10 ml/kg before administration of spinal anesthesia. The spinal anesthesia were administered at lumbar interspaces between L3-L4 in a mid line approach with 0.5% hyperbaric bupivacaine (3-3.5 ml). After SAB, patients were immediately placed in supine position. After completion of operation, all patients were taken to the recovery ward where patients were continuously monitored and managed for first 24 hours. The time interval of onset of pain in the postoperative period was recorded. Pain was managed with the initial loading dose of morphine, 3mg intravenously when the visual analogue scale (VAS) score was >3.Then pain management was continued with PCA with morphine, in which a 30ml syringe was filled with morphine where the concentration was 1mg/ml of 0.9% NaCl. Then programming of the PCA device was done with single dose of 1 mg, maximum dose being 15 mg/ 4hr, lockout time was 10 min. The patients used a PCA machine by pushing a button which delivers the equi-analgesic concentration of morphine in each volume according to the programme mentioned above. The postoperative nausea and vomiting (PONV) was managed with antiemetic drugs likes Ondansetron. Time of first dose of inj. Morphine in the post-operative ward was recorded and total dose of analgesic administered in the first 24 hrs was then calculated.

Outcomes Measure and Follow up: The intensity of pain was assessed with visual analogue scale (VAS: 0-10 cm) which was explained to patient during preoperative visit. The time interval of onset of pain in the postoperative period was recorded. The postoperative nausea and vomiting (PONV) was managed with antiemetic drugs. Time of first dose of inj. Morphine in the post-operative ward was recorded and total dose of analgesic administered in the first 24 hrs was then calculated. Patients were visited by the investigators at ½, 1, 2, 4, 12, and 24 h after operation. In each visit, the following parameters were measured and recorded SpO2, heart rate, respiratory rate, mean arterial pressure, and VAS pain score, sedation score, and the side effects developed. Finally, total 24 hours consumption of Morphine and time interval of first dose of Morphine from SAB were recorded.

Statistical analysis: Data are presented as mean ± SD. **Unpaired Student's t-Test** was used for comparison of the two groups regarding baseline characteristics, haemodynamic status, VAS score and the morphine consumption. The incidence of side effects was compared using **Chi-square (c^2)** Test and occurrence of somnolence in both group were analysed using **Fischer's Exact Test.** A p value >0.05 was interpreted as an indication of statistical significance, where confidence interval was 95%

Observation & Result

The present study was conducted on 120 women undergoing abdominal hysterectomy. Of them, 60 received preemptive single oral doses (300mg) Pregabalin (Group A) and the rest 60 received matching placebos (Group B) 1hr before surgery. The data was recorded immediately before SAB and at 30 minutes, 1 hr. 2 hrs, 4 hrs, 12 hrs and 24 hrs intervals in postoperative period.

5.1 Demography:

The groups were similar for age, weight, and ASA physical status (Table-I).

Table-I

Distribution of patient baseline characteristics.

Baseline characteristics	Group A (n = 60)	Group B (n = 60)	p-value
Age(in yrs)# (mean ± SD)	43.9 ± 4.7	44.7 ± 6.1	0.341
Weight(in kg)# (mean ± SD)	53.7 ± 7.2	54.2 ± 5.5	0.668
ASA Status*			
ASA Grade-I	42(70.0)	36(60.0)	0.251
ASA Grade-II	18(30.0)	24(40.0)	

Figures in the parenthesis denote corresponding %. **#** Data was analyzed using **Student's t-Test** and was presented as **mean ± SD. Chi-square (χ^2) Test** was employed to analyze the***** data; p-value < 0.05 is significant.

5.2 Haemodynamic Status: Heart Rate: Heart rate of both groups is displayed in Table-II. Mean values of the heart rate in the Group-A varies from the Group-B, which is statistically significant (P<0.05).

Table-II

Changes in heart rate in different period.

Group	Before SAB	Post-operative parameters					
		After 30 min	After 1hr	After 2hrs	After 4hrs	After 12hrs	After 24hrs
GroupA(n=60)	79.4 ± 4.7	67 ± 2	69 ± 3	70 ± 1.6	71 ± 4	71 ± 4	73 ± 5
GroupB(n=60)	90.5 ± 5.7	83 ± 2	90 ± 4	99 ± 3	88 ± 3	88 ± 3	85 ± 4
P-value	0.011	0.032	< 0.001	<0.001	0.04	0.024	0.043

Data was analyzed using Student's t-Test and was presented as mean ± SD

5.3 Haemodynamic Status: Mean Arterial Pressure:

Mean arterial pressure of both groups is displayed in Table-III. Mean values of MAP in the Group-A varies from that of the Group-B, which is statistically significant (P<0.05).

Table-III

Changes in MAP in different period

Group	Before SAB	Post-operative parameters					
		After 30 min	After 1hr	After 2hrs	After 4hrs	After 12hrs	After 24hrs
GroupA(n=60)	94.3±5.32	86.8 ± 2.9	88.45 ± 3.19	89.25 ± 3.91	89.05 ± 2.93	88.95± 5.85	89.42±4.45
GroupB(n=60)	95.8 ± 20.4	96.1 ± 5.1	96.8± 2.2	104.2 ± 8.07	93.95± 6.17	92± 15.6	96.15±2.56
P-value	0.569	<0.001	<0.001	<0.001	0.003	<0.001	<0.001

Data were analyzed using **Student's t-Test** and were presented as **mean ± SD.**

5.4 HAEMODYNAMIC STATUS: SpO2

Oxygen saturation of both groups is displayed in Figure-1. Mean values of the SpO2 in the Group-A varies from that of Group-B, which is significant at 2hr in postoperative period (P<0.05).

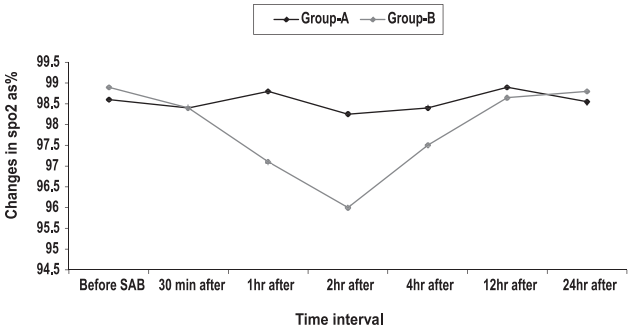

Fig.-1: *Changes in SpO2 from baseline to end-point of the study.*

5.5 Haemodynamic Status: Respiratory Rate:

Respiratory rate of both groups is displayed in Figure-2. Mean values of the respiratory rate in the Group-A varies from that of the Group-B, which is significant (P<0.05).

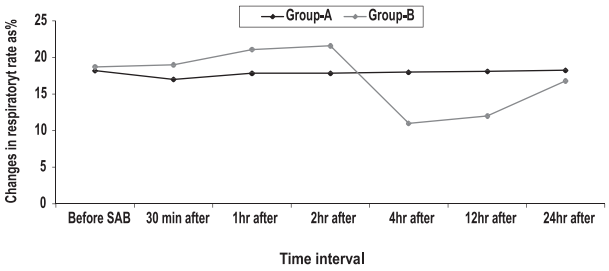

Fig.-2: *Changes in respiratory rate from baseline to end-point of the study.*

5.6 Changes in Vas Score:

VAS score of both groups is displayed in Figure-3. Mean values of the VAS score in the Group-A varies from that of the Group-B, which is significant (P-<0.05).

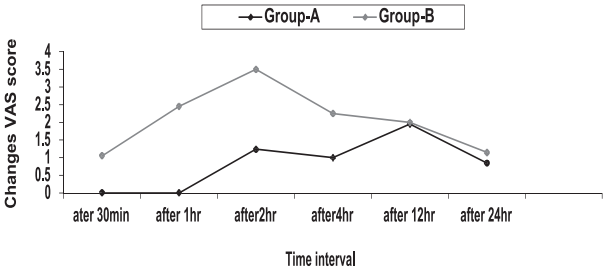

Fig.-3: *Changes in VAS score from baseline to end-point of the study.*

5.7 Changes in Sedation Score:

Sedation score of both groups is displayed in Table-IV. Mean values of the Sedation score in the Group-A varies from that of the Group-B, which is significant (P<0.05).

Table-IV

Changes in Sedation score in different period.

Group	Post-operative parameters					
	After 30 min	After 1hr	After 2hrs	After 4hrs	After 12hrs	After 24hrs
Group-A (n=60)	2.8 ± 0.4	2.75 ± 0.45	2.4 ± 0.49	2.10 ± 0.45	2.05 ± .59	1.2 ±0.55
Group-B (n=60)	0.1± .013	0.1 ± 0.03	0.15 ± 0.36	0.55 ± 0.48	1.06 ± 0.38	1.25 ± 0.6
P-value	0.003	0.003	0.004	0.013	0.021	0.432

Data were analyzed using Student's t-Test and were presented as mean ± SD.

5.8 Side Effects:

10% of the patients in the Group-A developed somnolence as opposed to none in the Group-B (P-0.014). More than one-quarter (26.7%) in the Group-A and only 6.7% in the Group-B experienced dizziness. There was no significant difference between the groups in terms of nausea/vomiting but respiratory depression was significantly more (P-0.0052) in Group-B than Group-A (Fig.-4).

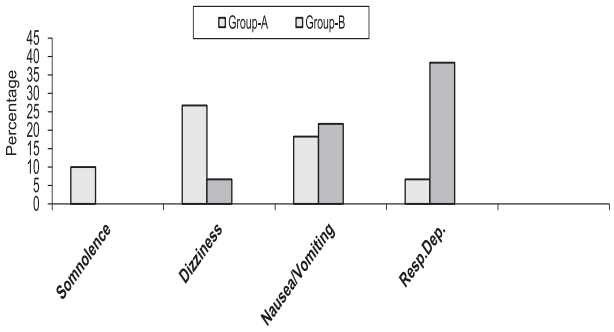

Fig.-4: *Side effects encountered by the patients*

5.9: Time interval of first dose of inj. morphine and the amount of morphine required in the postoperative period for 24 hours:

The time interval of first dose of Inj. morphine required in the postoperative ward by the patients of Group-A was on an average 5.2(± 0.4) hours from subarachnoid block which was 2.3 (± 0.4**)** hours in the Group-B ($p < 0.05$). The total amount of morphine was much less in the Group-A than that in the Group-B 13.3 (± 1.5) mg vs. 29.1 (± 2.1mg) (<P-0.05) (Figure-5).

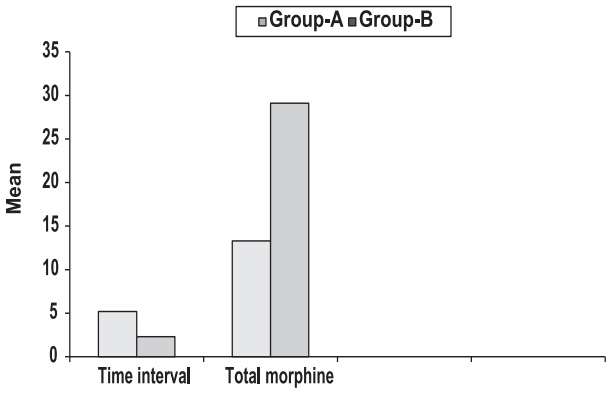

Fig.-5: *Showing morphine doses and time interval of first dose of morphine*

Discussion

During the last decade, there has been increasing interest in the use of preemptive analgesia for postoperative pain relief. Preemptive analgesia has been shown to be more effective in control of post operative pain by protecting the central nervous system from deleterious effect of noxious stimuli (Kelly et al 2001).

Pregabalin is a gabapentinoid drug useful for treating neuropathic pain. It has no effect on nociceptors but by blocking the CNS N-type calcium channel it may reduce the release of excitatory neurotransmitter and thereby it can reduce the hyper excitability of dorsal horn neurons which are induced by tissue damage. So it may also be beneficial in acute post-operative pain. Several studies have reported its usefulness as adjuvant analgesic to opioid in acute pain management where opioid related side effects are reduced with higher patient satisfaction (Tiippana EM et al, Hillem et al, Evr J Pain 2001, Jokela R. etal and Agarwal A et al).

This study was designed to evaluate the effect of pregabalin after its preemptive administration in reducing postoperative pain. In Group-A, the patients received 300mg pregabalin 1 hour before abdominal hysterectomy under sub-arachnoid block with 0.5% hyperbaric bupivacaine. More intensive analgesia (VAS scores less than 3cm) was observed in pregabalin group than placebo group. In a large number of studies similar analgesic effect was obtained, where the were type of surgery and mode of anesthesia was different (Hiil et al, Ritva et al). The duration of analgesia following SAB was longer in Group-A (5.2 ± 0.4) as compared to Group-B (2.3 ± 0.2).The difference was highly significant and somewhat different from previous studies (Saraswat et al, Kohli M et al).

This study also compared the total morphine consumption within 1st 24 hrs of postoperative period between pregabalin group and placebo group. This was 13.3(±1.5) mg in pregabalin group vs. 29.1(±2.1) mg in placebo. We observed that pregabalin was effective in terms of morphine consumption (more than 50%).This finding is comparable to the studies done in Agarwal et al. In Agarwal's study they use 150mg of pregabalin one hour before laparoscopic cholecystectomy and usePCA device with fentanyl for postoperative

analgesia. Result of that study show that PCA fentanyl consumption was reduced in the pregabalin group than control group but which is not as much as 300mg of pregabalin.

Garaj (Garaj et al) revised the pharmacology of pregabalin and found that somnolence (29.2%) and dizziness (22.2%) were the most common side effects. In the present study dizziness 26.7% and somonolence10% were the leading side effects. Incidence of nausea & vomiting (P= **0.648**) were present in both groups but the difference was not significant.

Respiratory depression was more in placebo group (38.3%) than the pregabalin group (6.67%). It signifies more consumption of morphine in Group-B to control pain which cause respiratory depression.

We observed that, the sedation score is more in pregabalin group than the placebo group in early postoperative period. The clinical relevance is that sedation in early postoperative period may be beneficial for some surgical patients. In other studies using 100mg, pregabalin (Michael et al) shows that sedation score was less than the current study but no reduction of pain score and analgesic consumption in post operative period. Therefore we used 300mg of pregabalin.

The limitation of this study design was that the single dose of pregabalin had been used. The half-life of pregabalin is 5-7 hrs and can not provide as a sole agent for covering postoperative pain management. Further studies are needed to determine the long term benefits, if any. The real challenge in the clinical setting is not simply to minimize the dose of morphine consumption but to minimize long-term side effects and occurrence of chronic pain syndromes within week or month after surgery.

Conclusion:

It can be concluded that pregabalin can be an effective tool in the armamentarium of anaesthesiologist in the treatment of postoperative pain. Despite some side effects like somnolence and dizziness, preemptive pregabalin reduces postoperative morphine consumption and thus morphine related side effects. It can be recommended that preemptive administration of 300mg oral pregabalin, can act as an adjuvant to multimodal analgesic regimen during post surgical periods.

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