DOI: 10.36347/sjams.2017.v05i02.042

Scholars Journal of Applied Medical Sciences (SJAMS) **ISSN 2320-6691 (Online)**
Sch. J. App. Med. Sci., 2017; 5(2C):517-522 **ISSN 2347-954X (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublishers.com

Original Research Article

Effect of Different Doses of Pre-Emptive Pregabalin for Attenuation of Postoperative Pain after Cholecystectomy

Dr. Tarangini Das[1] , Dr. Ramakanta Mohanty[2], Dr. Sidharth Sraban Routray[3], Dr. Debasis Debata[4]
[1,3,4]Assoc prof, Department of Anaesthesiology and critical care, SCB Medical College, Hospital, Cuttack, Odisha, India
[2]Asst prof Department of Surgery. SCB Medical college,Hospital. Cuttack, Odisha, India

***Corresponding author**
Dr Sidharth Sraban Routray
Email: drkitusraban@gmail.com

Abstract: Postoperative pain management has become a challenge as no drug has been found to be ideal. Many authors have studied the effect of neuropathic pain killer like pregabalin as preemptive analgesic for management of acute postoperative pain. The dose of preemptive pregabalin for the same has not yet been optimized. The present study has been undertaken to find out optimal dose of pregabalin as pre-emptive analgesic. It was a randomized double blind prospective study with 80 patients of American society of anaesthesiology (ASA) Grade I and II, aged between 30 to 65 years. All patients were divided into 4 groups with Group M7.5 received 7.5mg midazolam, Group P75 received 75mg pregabalin, Group P150 received 150mg pregabalin and Group P300 received 300mg pregabalin orally. VAS score, total dose of rescue analgesic and hemodynamic was compared in all 4 groups. VAS was significantly low in group P300 and group P150 than group I and II. The total dose of nalbuphine consumed in 24 hours duration was significantly less in group P300 and group P150 than group M7.5 and P75. Sedation scores were more in patients of group P300. Side effects like dizziness were more in Group P300 than other groups. Preemptive oral pregabalin 300mg is most effective in providing good postoperative analgesia compared to other doses but has side effects like dizziness. So pregabalin 150 mg may be ideal instead of 300mg.
Keywords: Preemptive analgesia, Pregabalin, Spinal Anaesthesia

INTRODUCTION

Pre-emptive analgesia is one of the treatment modality used to manage pain in postoperative period. It reduces the physiological consequences of nociceptive transmission provoked by surgery. Owing to this 'protective' effect on the nociceptive pathways, pre-emptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery [1, 2]. Postoperative pain management can be improved by finding exact molecular mechanisms, new pharmaceutical products and other routes and modes of analgesic delivery. For the years, opioids have been the mainstay of postoperative pain management but they have their own side effects [3, 4]. For this purpose the multimodal approach and non-opioid drugs have been suggested to improve postoperative analgesia. Gabapentanoids (gabapentin and pregabalin) were originally introduced as antiepileptics but have analgesic, anticonvulsant, and anxiolytic effects [5, 6]. These drugs have limited side-effects. Pregabalin is a structural analog of gamma-aminobutyric acid (GABA). It acts by presynaptic binding to the α -2δ subunit of voltage-gated calcium channels that are widely distributed in the spinal cord and brain [7]. By this mechanism, pregabalin modulates the release of several excitatory neurotransmitters, such as glutamate, norepinephrine, substance P, and calcitonin gene-related peptide. It leads to inhibitory modulation of "overexcited" neurons and returning them to a "normal" state [8]. By acting centrally, pregabalin could reduce the hyper excitability of dorsal horn neurons that is induced by tissue damage**.** Pregabalin has efficacy of varying degree in neuropathic pain conditions such as post herpetic neuralgia, painful diabetic neuropathy, central neuropathic pain, and fibromyalgia [9]. But the ideal dose of drug is not known. We have done the study to evaluate the optimal pre-emptive dose of oral pregabalin for postoperative pain control by comparing the different doses of pregabalin and to study its impact on post operative VAS, requirement of rescue analgesia and hemodynamic.

METHOD

The study entitled was conducted at S.C.B. Medical College & Hospital, Cuttack, Odisha during the period from July 2016 to September 2016. Following approval by ethical committee of SCB Medical College & Hospital, eighty patients of ASA class 1 and 2, of age range between 30- 65 years and free from co-morbid conditions like hepatic dysfunction, renal dysfunction, bronchial asthma and coagulopathies were included in the study. All the patients were undergone cholecystectomy of duration less than 2 hours under general anaesthesia. The study was conducted in a double blind prospective randomized design. The patients were divided into four groups basing on doses of drugs pregabalin 75mg, 150mg, 300mg and midazolam 7.5mg. Thorough airway and systemic examination of cardiac, respiratory, renal, hepatic system, abdomen and spine was carried out in every patient. After thorough assessment eighty patients were selected and explained about the procedure and informed consent was taken. Patients were randomly divided into four groups of each 20 patients. Group M7.5-Patients were given tablet midazolam 7.5mg.Group P75-Patients were given tablet pregabalin 75mg.Group P150-Patients were given tablet pregabalin 150mg.Group P300-Paients were given tablet pregabalin 300mg.All drugs were given 1 hour before surgery with a sip of water. All the patients were given Tab ranitidine 150mg orally in the previous night and overnight fasting was advised in all patients for at least 8 hrs before surgery to prevent aspiration. All patients were explained about the Visual analogue scale for pain during a preoperative visit one day prior to study. Routine vital monitors like ECG, pulse oximetry, noninvasive blood pressure were attached to the patient. Preoperative baseline study parameters were recorded. Intravenous access was secured with an 18 G cannula & an infusion of ringer's lactate was started. All patients were premedicated with iv inj. Glycopyrrolate 0.2mg i.v. and inj. pentazocine 0.5mg/kg 15minutes before induction. In all cases, preoxygenation was done with 100% oxygen via face mask prior to induction of anaesthesia to prevent hypoxic crisis during laryngoscopy and intubation. Immediately after premeditation HR and MABP was recorded and considered as baseline value. Then patients were induced with Propofol 2mg/kg iv followed by inj. Rocuronium 0.6 mg/kg iv. All the patients were intubated with appropriate size cuffed endotracheal tube .Tube was fixed and ventilation was carried out with a mixture of N_2O (50%) and O_2 (50%). Thereafter heart rate(HR) & mean arterial blood pressure(MABP) was recorded after intubation, 5min, 15min, 30min, 45min, 60min, just before extubation and immediately after extubation**.** Anaesthesia was maintained with N2O: O2 (50:50) & Isoflurane 1%. Muscle relaxation was maintained with rocuronium bromide 0.15 mg/kg every 15 minutes.

At the end of the surgery, when patients' respiratory efforts were perceived slowly, residual neuromuscular block was reversed with Neostigmine 2.5mg IV and Glycopyrolate, 0.4mg IV. After extubation, patients were shifted to post anaesthetic care unit (PACU) and kept under observation till 24 hours. Then patients were monitored for SPO_2, PR and B.P. Pain was assessed for 24 hours on VAS. Injection Nalbuphine 5mg was administered intravenously as rescue analgesia when pain intensity as described by the patient was more than equal to 4 in visual analogue scale. Statistical analysis was performed by using SPSS version 19.0 for windows. The result were presented in numbers, percentage, mean and standard deviation. One-way ANOVA test were used as per applicability to analyse the observations. $p<0.05$ was considered as statistically significant. $p<0.001$ was considered as highly significant

RESULTS

All the groups were comparable in respect to age, weight & duration of surgery.(Table-1)

Table-1: Demographic variable

Variable	M7.5 Mean ± SD	P75 Mean ± SD	P150 Mean ± SD	P300 Mean ± SD	P Value
Age(years)	51.05±5.93	48.5±5.44	51.65±6.37	49.25±4.50	0.25
Weight(kg)	54.25±7.07	52.4±4.9	55.7±4.94	52.9±6.18	0.29
Duration of surgery(min)	89.55±9.25	90.9±7.39	91.1±8.28	93±10.7	0.70

VAS on rest was low in P150 and P300 group compared to other two group which was statistically significant. VAS on exertion was comparable in all 4 group which was statistically not significant (Table-2,3)

Table-2: Post-operative mean pain score on VAS at rest

Time in hour	M7.5 Mean±SD	P75 Mean±SD	P150 Mean±SD	P300 Mean±SD	P value
0hr	3.1±0.44	3.0±0.32	0.4±0.503	0.02±0.47	<0.001
1hr	2.95±0.51	2.75±0.44	0.45±0.605	0.3±0.47	<0.001
2hr	3.0±0.45	2.7±O.47	1.05±0.76	0.65±0.49	<0.001
4hr	2.2±0.41	2.15±0.671	1.85±0.58	1.4±0.5	<0.001
8hr	2.1±0.308	1.9±0.55	1.6±0.50	0.9±0.31	<0.001
16hr	1.8±0.52	1.8±0.52	1.25±0.44	0.8±0.41	<0.001
24hr	1.55±0.51	1.5±0.51	1.09±0.302	0.7±0.47	<0.001

Table-3: (Post-operative mean pain score on VAS on exertion)

Time in hour	M7.5 Mean±SD	P75 Mean±SD	P150 Mean±SD	P300 Mean±SD	P value
0hr	5.85±0.36	5.55±O.75	5.45±0.68	5.35±0.75	0.10
1hr	4.75±0.44	4.55±0.60	4.4±0.68	4.7±0.86	0.34
2hr	4.15±0.36	3.85±0.48	3.8±0.52	4±0.56	0.11
4hr	4.1±0.30	3.9±0.55	3.9±0.44	3.7±0.57	0.08
8hr	4.1±0.55	3.8±0.52	3.7±0.57	3.55±0.51	0.1
16hr	2.95±0.39	2.95±0.52	2.85±0.48	2.75±0.55	0.51
24hr	2.8±0.41	2.75±0.51	2.65±0.48	2.5±0.51	0.14

Dizziness and Drowsiness was more in P300 and P150 group compared to other groups.(Table-3)

Table-3: Side effects

Side effects	M7.5 n (%)	P75 n(%)	P150 n(%)	P300 n(%)	P value
Nausea	4(20%)	5(25%)	7(35%)	6(30%)	0.758
Vomiting	5(25%)	6(30%)	7(35%)	5(25%)	0.822
Dizziness	0	3(15%)	6(35%)	9(45%)	0.004
Drowsiness	0	0	5(30%)	12(60%)	0.001

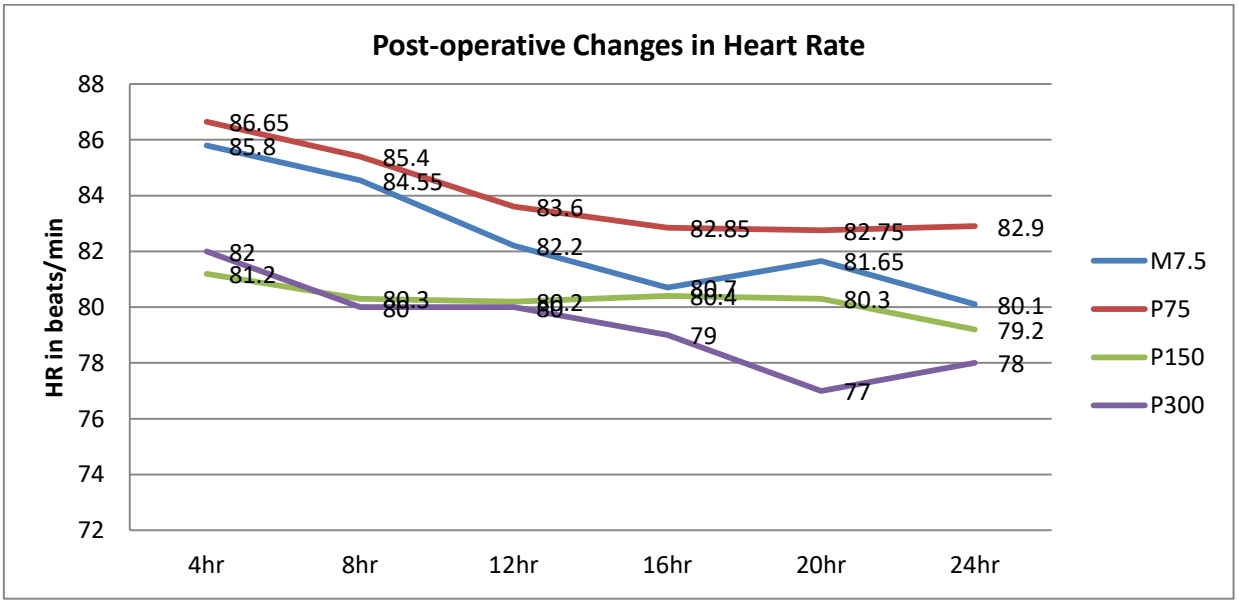

Fig 1: Changes in HR

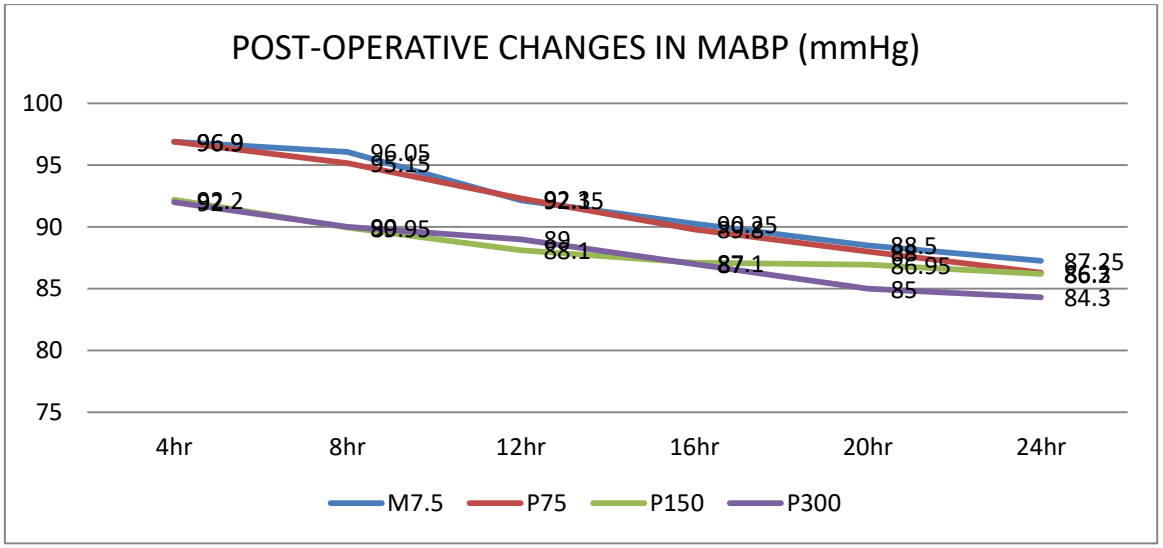

Fig 2: Changes in MABP

Hemodynamic parameters like MABP and HR was comparable in all 4 groups (Graph-1,2). Total amount of analgesia (inj. nalbuphine) required postoperatively in groupP300 was 14.3mg, in P150 group 16.5mg, in P75 group 18.75mg and in M7.5 group 19.5mg.This showed significant difference of group P150 &P300 than M7.5&P75 ($p<0.001$).(Graph-3)

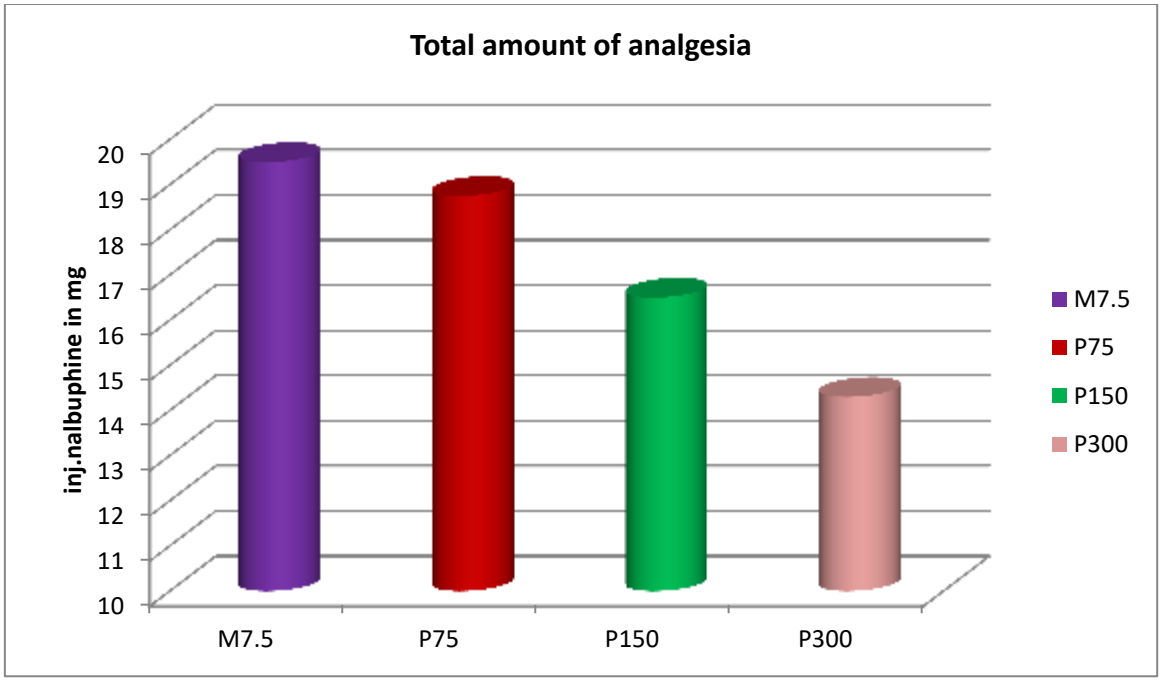

Fig 3: Total amount of rescue analgesia required in 24 hrs

DISCUSSION

Postoperatively VAS score at rest were significantly reduced in pregabalin 150 & 300 group when compared with midazolam & pregabalin 75mg group at different time interval i.e 0hr,1hr, 2hr,4hr, 8hr,16hr,24hr as described by 'p' value <0.001.There was also significant difference between P150 & P300 group as 'p' value <0.05. But while comparing the VAS score on exertion we found there was no significant difference in all the four groups. Preoperative single dose pregabalin 150mg and 300mg was effective in reducing the rest pain postoperatively compared to midazolam and P75 group, but did not reduce the exertion pain. In a study conducted by R. Jokela *et al.;* they found that 300mg pregabalin was more effective than pregabalin 150mg.The incident of dizziness; headache and blurred vision were higher in the 300mg pregabalin group [10]. Our observation is supported by

the study conducted by A. Agarwal et al who showed that a single dose of pregabalin 150mg was effective in reducing postoperative pain after laparoscopic hysterectomy [11]. Hill *et al.;* compared pregabalin (50 and 300mg) to placebo and 400mg of ibuprofen in 198 patients who had undergone elective surgery for one or two third molars extraction in terms of pain relief and pain intensity. Pain relief and pain intensity were significantly better in the 300mg pregabalin group [12]. In a study conducted by Krzysztof Przesmycki *et al.;* 300mg pregabalin administered 1hr preoperatively before abdominal hysterectomy with/without salpingo-oophorectomy significantly reduced verbal rating numerical scale (VNRS) pain score and improved satisfaction score at 24 hr post operatively [13]. Our finding was similar to other studies [14, 15].

Total amount of analgesia (inj. nalbuphine) required postoperatively in groupP300 was 14.3mg, in P150 group 16.5mg, in P75 group 18.75mg and in M7.5 group 19.5mg.This showed significant difference of group P150 &P300 than M7.5&P75 ($p<0.001$). Amjad Ali *et al.;* conducted a study on 65 patients undergoing elective open cholecystectomy. Patients were randomly divided into two groups of 30 each, to receive either pregabalin 150mg or celecoxib 200mg orally 1hr before surgery. They compared postoperatively pain intensity & total amount of nalbuphine requirement. Cumulative consumption of inj. nalbuphine over 24hr was 13.5±7.4mg for pregabalin group and 13.67±6.7mg for celecoxib group. No significant difference was found in pain relief [16].

Patient satisfaction in our study was good with pregabalin 300mg group than 150mg. This is supported by the study Kohli et al who conducted study upon150 patients undergoing hysterectomy under spinal anaesthesia. All patients were divided into three groups - Group I (PO) - Control group, Group II (P150) received 150 mg pregabalin and Group III (P300) received 300 mg pregabalin and found pregabalin significantly reduced anxiety level, requirement of supplementary analgesic, than placebo group. Complications like sedation, dizziness was more with 300mg than 150mg, and patient satisfaction showed almost equal between 150 and 300mg group [17]. On comparing the complications like sedation, dizziness, nausea and vomiting , the incidences of dizziness and sedation in patients receiving pregabalin 300mg was more than those who receiving 150mg, 75mg & midazolam group. Incidence of the nausea and vomiting showed no significant difference between the groups which is correlated with the study conducted by R. Jokela *et al.;* They found that 300mg pregabalin was more effective than pregabalin 150mg.The incident of dizziness; headache and blurred vision were higher in the 300mg pregabalin group [18].

CONCLUSION

From this study we concluded that oral pregabalin 150 mg would be the optimal pre-emptive dose for cholecystectomy under general anaesthesia for postoperative pain relief and can reduce postoperative opioid consumption. A higher dose of pregabalin though reduces postoperative pain intensity but can produce higher incident of side-effects. Further studies should be carried out to find out the optimal dose of pregabalin for other surgical procedures under general anaesthesia

REFERENCES

1. Kissin I. Preemptive analgesia. The Journal of the American Society of Anesthesiologists. 2000 Oct 1; 93(4):1138-43.
2. Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia II: recent advances and current trends. Canadian Journal of Anesthesia. 2001 Dec 1; 48(11):1091.
3. Reuben SS, Buvanendran A, Kroin JS, Raghunathan K. The Analgesic Efficacy of Celecoxib, Pregabalin, and Their Combination for Spinal Fusion Surgery: Retracted. Anesthesia & Analgesia. 2006 Nov 1; 103(5):1271-7.
4. Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety, AnesthAnalg. 2007 Jun; 104(6):1545-56,
5. Saraswat V, Arora V. Preemptive gabapentin vs pregabalin for acute postoperative pain after surgery under spinal anaesthesia. Indian journal of anaesthesia. 2008 Nov 1; 52(6):829.
6. Mathiesen O, Jacobsen LS, Holm HE, Randall S, Adamiec-Malmstroem L, Graungaard BK, Holst PE, Hilsted KL, Dahl JB. Pregabalin and dexamethasone for postoperative pain control: a randomized controlled study in hip arthroplasty. British journal of anaesthesia. 2008 Oct 1; 101(4):535-41.
7. White PF, Tufanogullari B, Taylor J, Klein K. The effect of pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. Anesthesia & Analgesia. 2009 Apr 1; 108(4):1140-5.
8. Mahmoud M. El Sayed El-Gohary MD & Mohamed A. Fatthallah MD, Pregabalin single dose in functional endoscopic sinus surgery analgesic and antiplatelet effect, Ain Shams Journal of Anaesthesiology 2011 oct; 4(3).
9. MahzadAlimian, Farnad Imani, and Saeid Safari, Effects of Single-Dose Pregabalin on Postoperative Pain in Dacrocystorhinostomy Surgery, Anesthesiology and Pain Medicine. 2012 October; 2(2): 72-76.

10. Jokela R, Ahonen J, Tallgren M, Haanpää M, Korttila K. Premedication with pregabalin 75 or 150 mg with ibuprofen to control pain after day-case gynaecological laparoscopic surgery. British journal of anaesthesia. 2008 Jun 1; 100(6):834-40.
11. Agarwal A, Gautam S, Gupta D, Agarwal S, Singh PK, Singh U. Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. British journal of anaesthesia. 2008 Nov 1; 101(5):700-4.
12. Hill CM, Balkenohl M, Thomas DW, Walker R, Mathe H, Murray G. Pregabalin in patients with postoperative dental pain. European Journal of Pain. 2001 Jun 1; 5(2):119-24.
13. Przesmycki K, Wiater-Kozioł E, Kotarski J, Czuczwar M, Jaskowiak R, Zabek M, Kołacz A, Fijałkowska M, Kotus M. Effect of pre-emptive pregabalin on pain intensity and morphine requirement after hysterectomy. Anestezjologia intensywna terapia. 2010 Dec; 43(1):14-7.
14. Pradeep Jain, Annu Jolly, Vaibahav Bholla, Sweta Adatia, and Jayashree Sood, evaluation of efficacy of oral pregabalin in reducing postoperative pain in patients undergoing total knee athroplasty: Indian J Orthop. 2012 Nov-Dec; 46(6): 646–652
15. Sundar AS, Kodali R, Sulaiman S, Ravullapalli H, Karthekeyan R, Vakamudi M. The effects of preemptivepregabalin on attenuation of stress response to endotracheal intubation and opioid-sparing effect in patients undergoing off-pump coronary artery bypass grafting. Ann Card Anaesth. 2012 Jan-Mar;15(1):18-25.
16. Jain P, Jolly A, Bholla V, Adatia S, Sood J. Evaluation of efficacy of oral pregabalin in reducing postoperative pain in patients undergoing total knee arthroplasty. Indian journal of orthopaedics. 2012 Nov 1; 46(6):646.
17. Kohli M, Murali T, Gupta R, Khan P, Bogra J. Optimization of subarachanoid block by oral pregabalin for hysterectomy, J Anaesthesiol Clin Pharmacol. 2011 Jan; 27(1):101-5.
18. Jokela R, Ahonen J, Tallgren M, Haanpää M, Korttila K. A randomized controlled trial of perioperative administration of pregabalin for pain after laparoscopic hysterectomy. Pain. 2008 Jan 31; 134(1):106-12.