Original Research Article

Pre-emptive use of Gabapentine for Reducing Early Post-operative Pain and Analgesic Requirement in Laparoscopic Cholecystectomy

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Abstract

Background: Pain,the oldest symptoms of human existance,is thought to be inadequetly treated in most of the surgical patients. Surgical stimulation leads to peripheral sensitization(a reduction in the threshold of nociceptor afferent peripheral terminals) and central sensitization (an activity dependent increase in the excitability of spinal neurons) Prevention and treatment of postoperative pain is a major challenge in postoperative care and plays an important role in the early mobilization and well-being of the surgical patient.The optimal form of treatment is that applied pre,intra and postoperatively to preempt the establishment of pain hypersensitivity during and after surgery. Gabapentin, an anti-epileptic drug that has demonstrated analgesic effect in diabetic neuropathy, post-herpetic neuralgia and neuropathic pain, has shown anti-hyperalgesic properties, possibly by reducing central sensitization. Use of Gabapentin has more recently extended into the management of more acute conditions, particularly in the perioperative pain. **Objective**: To study the efficacy of gabapentin used preemptively for reduction of early post operative pain & analgesics requirement in laparoscopic cholecystectomy patients. **Materials & Methods**: A prospective randomised control trial was done in Department of Surgery,TUTH, on 121 consecutive patient selected for laparoscopic cholecystectomy.All patients were randomised into two groups. Study group (N=60) was given gabapentine 300mg orally 2 hrs before surgery and to control group (N=58) no preoperative drugs was given. All procedures were performed under general anesthesia. As a post operative analgesics both group were given inj. pethidine 1mg/kg/dose I.M. as when pain score 4 or more and on demand basis. Post-operative pain score was monitored by using numerical pain score, 0-10; 0= no pain, 10= worst possible pain. Pain score was taken at different time interval 2 hourly for 1st 6 hoursthen 6 hrly upto 24 hrs.Adverse effects of drugs were recorded in both groups. **Results**: Patients in gabapentine group had significantly lower pain scores (2.40±0.78, 2.91±1.14, 3.58±1.21, 3.58±1.11,2.13±0.85) in comparison to no preemptive drug group (5.33±1.77, 4.12±1.85, 5.28±1.25, 4.67±1.33, 3.45±1.11) at all time interval (0 hr,0-6hr,6-12hr,12-18hr.18-24hr).The requirement of pethidine also significantly less in study group (115±26.52 mg) compare to control group (198±31.21 mg) $p<0.05$. It was seen that Nausea, Vomiting and Retching were more in control group 36% (n=21) than in study group 31% (n=19). But dizziness and sedation were more common in study group 27% (n=16) than control group 20% (n=12). **Conclusion**: Preemptive use of gabapentine significantly decreases post-operative pain and pethidine requirement in laparoscopic cholecystectomy without any significant adverse effect.

Keywords: Pain, Peripheral sensitization, Central sensitization, Hypersensitivity, Preemptive analgesia, Gabapentin, Hyperalgesia, Laparoscopic cholecystectomy, Pethidine, Numerical pain score

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Introduction

Pain is as old a symptom as human existance itself. However its scientific basis remained unravelled until gate control theory of pain was postulated by Melzack and Wall in 1965 [1]. In the developed world, pain is recorded routinely as fifth vital sign in the post-operative ward.The International Association for the Study of Pain (IASP) published pain defination in 1979 as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described it interms of such a damage" [2]. Postoperative pain is typically regarded as a type of nociceptive pain involving peripheral mechano-receptor stimulation, inflammatory, and neurogenic and visceral mechanisms, with a transient, reversible type of neuropathic pain [3]. Surgical stimulation leads to sensitization of dorsal horn neurones, which are associated with augmentation of pain. Peripheral tissue injury provokes peripheral sensitization (a reduction in the threshold of nociceptor afferent peripheral terminals) and central sensitization(an activity dependent

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increase in the excitability of spinal neurons) [4, 5].These changes contribute to the post injury pain hypersensitivity state which manifests as an increase in the responsiveness to noxious stimuli and a decrease in the pain threshold, both at the site of injury and in the surrounding tissue [4, 5].Prevention and treatment of postoperative pain and complications such as nausea and vomiting, continues to be a major challenge in postoperative care and plays an important role in the early mobilization and well-being of the surgical patient.The optimal form of treatment is that applied pre, intra and postoperatively to preempt the establishment of pain hypersensitivity during and after surgery. Different treatment regimens could be used at different times relative to surgery to maximize the prevention of pain in response to different levels of sensory inputs. Many types of analgesics have been used alone or in combination for its treatment. Opioid analgesics, with their well-known side-effects, continues to represent a cornerstone in postoperative pain control, and testing new analgesics as well as combinations of analgesics in order to reduce the need for opioids, is a key area in acute pain research [6]. The rationale behind the preemptive use of analgesic is that antinociceptive treatment started before surgery is more effective in reducing postoperative pain than treatment started in the early postoperative period [7]. The preemtive treatment could be directed at the periphery,at inputs along the sensory axons and at central neurons. Surgery offers the most promising setting for preemptive analgesia because the timing of noxious stimuli is known.Laparoscopic surgery is intended to minimize the trauma without compromising the exposure of operative field, and even having a better exposure and better view. It gained popularity for smooth postoperative recovery,less morbidity and short hospital stay. Laparoscopic cholecystectomy is one of the commonly performed operation in general surgery. Studies are being performed for better patient compliance and to make postopeative recovery more comfortable.Gabapentin, an anti-epileptic drug that has demonstrated analgesic effect in both diabetic neuropathy, post-herpetic neuralgia and neuropathic pain [8-10], affects the nociceptive process by binding to the α2δ subunit of voltage dependent calcium channels [11. In pain models it has shown anti-hyperalgesic properties, possibly by reducing central sensitization, a prerequisite for postoperative hyperalgesia in clinical and preclinical studies [12, 13]. An increased number of randomised clinical trials indicate the effectiveness of gabapentine in reducing post-operative pain when used preemtively and also reduced opioid consumption,thus decreases its unpleasant side effects.The objective of this study was to make an evaluation of the efficacy of gabapentine as a pre-emptive analgesic.

Objectives

General Objective:To study the effects of gabapentin used preemptively on early post operative pain & analgesics requirement in laparoscopic cholecystectomy patients.

Specific Objectives:

To compare the post-operative pain scores at different time interval between preemptively used gabapentine group and preemptive no drug group.

To compare the total pethidine consumption over 24 hours in both group.

To compare the side effects in both groups.

Methodology

Patients & Methods

Design and setting

A prospective randomized controlled study was performed in the department of surgery, Tribhuvan University Teaching Hospital, Kathmandu, Nepal, between May 2008 and April 2009. Approval for the study was obtained from the Department of surgery, and permission was taken from the Institutional Review Board (Ethical committee).

Inclusion criteria

- Patients underwent laparoscopic cholecystectomy during the study period

Exclusion criteria

- Age older than 70 yr or younger than 18 yr
- Body weight exceeding 20% of the ideal body weight
- Known history of hypersensitivity to any drug
- History of drug or alcohol abuse;
- Patients with history of chronic pain conditions;
- Patients with impaired kidney or liver function;
- Laparoscopic cholecystectomy converted into open cholecystectomy;
- The administration of analgesics within 48hr of scheduled surgery.

All patients who were planned for elective laparoscopic cholecystectomy and fulfilled the selection criteria were included in the study. Informed consent was obtained from all patients.Thorough history, physical examination and investigations were reviewed and a proforma was filled. They were explained clearly about the numerical pain score on the day before surgery. Patients were randomized prospectively into one of two groups [study group and control group] in alternate patient basis. All patients received oral diazepam 5 mg in the evening before surgery and on the morning of surgery. Study group was given gabapentine 300mg orally 2 hrs before surgery and to control group no preoperative analgesics was given. All procedures were performed under general anesthesia by experienced laparoscopic surgeons.Laparoscopic cholecystectomy in this study was started with an open technique of trocar insertion through the infra-umbilical port and the creation of CO_2 pneumoperitoneum to the pressure of 10 to 15 mm of Hg with a flow rate of 3-5 liters per minute. Under laparoscopic view, further two port were made. After dissection of cystic duct and cystic artery, three metallic clips were applied on each and the cystic duct and artery were divided distal to the proximal two clips. Monopolar diathermy in a coagulation mode was used for the dissection of the gallbladder from the liver bed. The gallbladder was removed through the infra-umbilical port. Pneumoperitoneum was then evacuated and port sites were closed with umbilical port in two layers, fascial and skin, while the other ports are closed in one layer of skin only after infiltration with 0.5% bupivacaine in all cases.

The intra-operative parameters like the duration of surgery, operative findings and any difficulty during surgery were recorded.

After completion of surgery, neuromuscular blockade was reversed with atropine 0.02 mg/kg and neostigmine 0.04mg/kg and patients were extubated when adequate spontaneous ventilation was established. After surgery patient was kept initially in recovery ward and then shifted to postoperative ward. As a post operative analgesics both group were given inj. pethidine 1mg/kg/dose I.M. as when pain score 4 or more along with inj. phenergan 0.5 mg/kg/dose. Post operative pain score and analgesics given in recovery room was recorded and first dose of analgesic was given when pain score was 4 or more. Post-op pain score was monitored by using Numerical Pain Score, 0– 10; 0 = no pain, 10 = worst possible pain. Pain score was taken at different time interval 2 hourly for 1st 6 hours, then 6 hrly upto 24 hrs. All patients were monitored for 24 hrs. Side effects of drugs like nausea, vomiting, retching, respiratory depression, vertigo, dizziness and sedation were recorded in both groups.

Statistical tools used

SPSS software version 16.0 was used. Frequencies, percentages, means with standard deviations, range, odds ratios with their 95% confidence interval were calculated. Findings are presented as tables, bar diagrams, pie-charts and line diagram.

Statistical tests applied:

a. Chi-square test: used to compare the frequency/proportion between the ‘study’ and ‘control’ groups.
b. Independent samples t-test: used to compare the means between the ‘study’ and ‘control’ groups.

The 'p' value of less than 0.05 was regarded as significant

Results

Total number of patients operated in 1 year study period (May 2008 - April 2009) in one unit were 121. The patient were included in to two categories. One with pre-operative use of gabapentine was categorized as study group and other without pre-operative use of gabapentine was categorized as control group. From total number of study population, 3 were excluded for conversion to open cholecystectomy. Out of 118 patients, 60 were in study group and 58 in control group.

Age distribution

The mean age of the patients was 42.80± 12.67 (mean± SD) yrs in the study group (Group A) ranging from 20-68 yrs and 40.78 ± 13.37yrs in the control group (Group B) ranging from 19-70 yrs. The age difference in the two groups were not statistically significant (p >0.05). So the two groups were comparable [Table 1].

Table 1: Comparison of age distribution

Variables	Study Group (n=60)	Control Group (n=58)	P value
Mean Age(years)	42.80 ± 12.67	40.78 ± 15.34	> 0.05
Range	20 - 68	19 - 70	

Gender Distribution

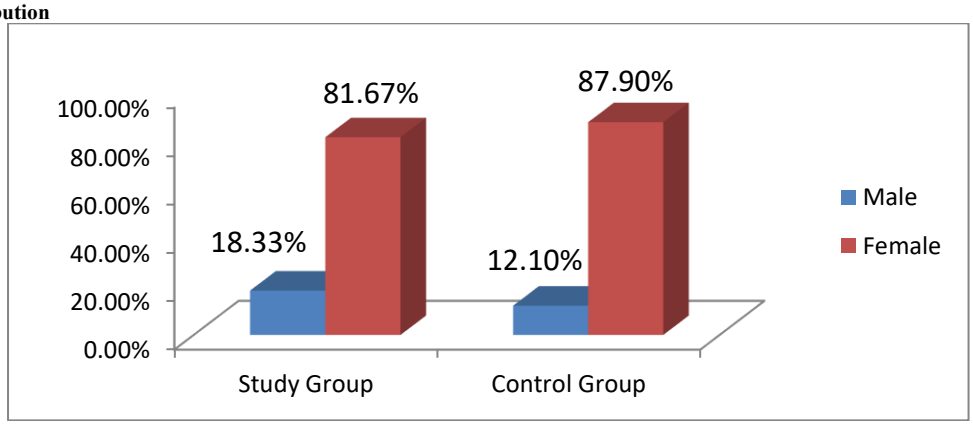

Fig 1: Gender distribution

Female was found to be more common in both of the groups. Female constituted 81.67% (n=49) of study group and 87.90% (n=51) of control group. Male constituted only 18.33% (n=11) of study group and 12.10% (n=7) of control group [Fig 1].

Distribution of body weight

The mean body weight was 55.65± 6.43 (mean± SD) Kg in the study group (Group A) ranging from 43-78 Kg and 57.21 ± 7.61 Kg in the control group (Group B) ranging from 42-75 Kg. The body weight in the two group were not statistically significant (p=0.234). So the two groups were comparable [Table 2].

Table 2: Comparison of distribution of body weight

Variables	Study Group (n=60)	Control Group (n=58)	P value
Body weight(kg)	55.65 ± 06.43	57.21 ± 07.68	0.234
Range	43 - 78	42 - 75	

Duration of surgery

The mean intra-oprative time was 48.75± 7.34 (mean± SD) minutes in the study group (Group A) ranging from 40-70 mins and 49.83± 8.53 mins in the control group (Group B) ranging from 35-80 mins.The intra-oprative time difference in the two groups were not statistically significant (p-value = 0.464). So the two groups were comparable [Table 3].

Table 3: Comparison of **d**uration of surgery

Variables	Study Group (n=60)	Control Group (n=58)	P value
Duration of surgery (Minutes)	48.75 ± 07.34	49.83 ± 08.53	0.464
Range	40 - 70	35 - 80	

Pain Scores

Table 4: Comparison of pain scores at different time interval

Group	Pain 0 hrs	Pain 0-6 hrs	Pain 12 hrs	Pain 18 hrs	Pain 24 hrs
Study Group (N=60)	2.40±0.78	2.91±1.14	3.58±1.21	3.58±1.11	2.13±0.85
Control Group (N=58)	5.33±1.77	4.12±1.85	5.28±1.25	4.67±1.33	3.45±1.11
Level Of significance	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001

Pain scores at different time interval were compared in the two groups. As shown in table-5,it was seen that pain score at 0 hour was 2.40±0.78 and 5.33±1.77 and 0-6 hour interval was 2.91±1.14 and 4.12±1.85 respectively in study and control group. Pain score at 12 hour,18 hour and 24 hour were recorded as 3.58±1.21 , 3.58±1.11, 2.13±0.85 in study group and 5.28±1.25, 4.67±1.33, 3.45±1.11 in control group respectively. It was seen that pain score at every time interval was lower in study group than control group which was statistically significant (p-value = <0.001) [Table 4/Fig 2].

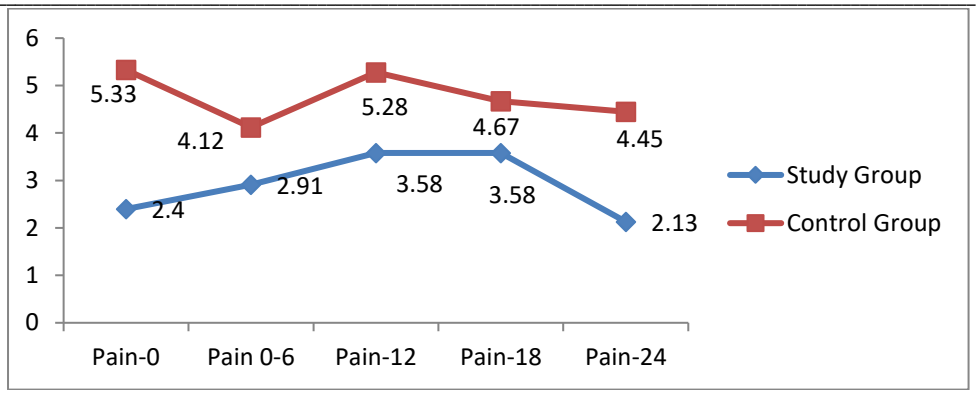

Fig 2: Pain scores in two groups at different time interval

Pethidine Consumption

Table 5: Comparison of total pethidine consumtion in 24 hours

Variables	Study Group(n=60)	Control Group(n=58)	P value
Total Pethine consumption (mg)	115.17 ± 26.52	198.71 ± 31.21	< 0.001
Range	100 - 200	150 - 300	

Total pethidine consumtion in study group was 115.17±26.52 mg while it was 198.71±31.21 mg in control group. The total amount of pethidine consumption in control group was significantly higher than study group in 24 hours (p<0.001) [Table 5].

Side Effects

Table 6: Comparison of side effects

Side effects	Study Group	Control Group	p value
Nausea/Retching/Vomiting	31% (n=19)	36% (n=21)	>0.005
Dizziness/sedation	27% (n=16)	20% (n=12)	>0.005
Respiratory Depression	0% (n=0)	0% (n=0)	

Side effects in both the group were also analyzed. It was seen that Nausea, Vomiting and Retching were more in control group 36%(n=21) than in srudy group 31%(n=19). But dizziness and sedation were more common in study group27% (n=16) than control group 20% (n=12). No case of respiratory depression was found in both of the groups [Table 6].

Discussion

A hospital based randomized, comparative, interventional study was done to evaluate the effect of gabapentine used preemptively on laparoscopic cholecystectomy. The study was conducted at Department of surgery of Institute of Medicine, Tribhuban University Teaching Hospital over the period of one year (May 2008-April 2009). Laproscopic cholecystectomy is one of the most commonly performed operation in general surgery. Early post-operative pain and related complications are most distressing and unwanted experiences noticed frequently after surgery making post-operative recovery less comfortable. Opioid analgesics, with their well-known side-effects, are the most commonly used drug to combat with the post-operative pain. Many studies have shown that preemptive use of analgesic reduces the early post-perative pain and related complications after surgery. Gabapentine has demonstrated analgesic effects in clinical trial when used preemptively to reduce the post operaive pain .Also it shows its efficacy in reducing post-operative opioid consumption and related side effects. Not much study has been performed at this setting to show the efficacy of such drug.This study was designed to evaluate the efficacy of preemptively used gabapentine interms of post-operative pain score, total pethidine consumption and related complications.Total number of cases included in the current study was 121. Three cases were excluded due to conversion into open cholecystectomy. The patient were randomized and grouped in to two categories. One with preemptive use of gabapentine,and other with no preemptive use of any drug. Alternate patient basis was selected for categorization.Out of 118 patients, 60 patients were given gabapentine preemptively regarded as study group and 58 patients were not given any preemptive drug regarded as control group.The mean age of the patients was 42.80± 12.67 (mean± SD) yrs in the study group (Group A) ranging from 20-68 yrs and 40.78 ± 13.37yrs in the control group (Group B) ranging from 19-70 yrs. This result was similar to result shown by Pandey et al [14] which showed 41.65±11.19 yrs and 43.49±11.14 yrs in study and control group respectively. In current study, female was found to be more common in both of the groups. Female constituted 81.67% (n=49) of study group and 87.90% (n=51) of control group. Male constituted only 18.33%(n=11) of study group and 12.10% (n=7) of control group.Total female : male ratio 5:1. Current study showed female were more prevalent,that co-relating other study where female : male ratio was about 4:1 [15].

The mean body weight was 55.65± 6.43 (mean± SD) Kg in the study group (Group A) ranging from 43-78 Kg and 57.21 ± 7.61 Kg in the control group (Group B) ranging from 42-75 Kg. The body weight in the two group were not statistically significant (p=0.234). In study shown by Pandey et al [14], the mean body weight in study group was 58.76± 7.80 Kg , and in control group it was 58.72± 7.81 Kg. The result in reference study was quite similar to current study. The duration of surgery in study group 48.75± 7.34 (mean± SD) minutes and control group 49.83± 8.53 minutes,which was similar (53.18±15.35 in study group and 49.00±12.86 in control group) with the previous study done by Dr Sidharth et al [16] in our institute. There was not much differance in age distribution,mean body weight and intra-operative time between the two groups,so these factors did not influence the outcome of study.

Pain scores at different time interval were compared in the two groups. It was seen that pain score at 0 hr was 2.40±0.78 and 5.33±1.77 respectively in study and control group. Similarly pain score at 0-6 hour interval was 2.91±1.14and 4.12±1.85 respectively (p <0.001).So,early post operative pain was significantly lower in study group in compare to control group. Also pain score at 12 hr, 18 hr and 24 hr were recorded as 3.58±1.21, 3.58±1.11, & 2.13±0.85 in study group and 5.28±1.25, 4.67±1.33, & 3.45±1.11 in control group respectively.It was seen that pain score at every time interval was lower in study group than control group which was statistically

significant. Reference study by pandey et al [14] showed similar result.

Total pethidine consumtion in study group was 115±26.52 mg while it was 198±31.21 mg in control group. The total amount of pethidine consumed in control group was significantly higher than study group in 24 hours($p<0.05$). Study by Pandey et al [14] showed 221.16±53.29 µg of fentanyl consumption in study group and 355.86±42.04 µg of fentanyl consumption in control group. In both studies, it was seen that opioid consumption was significantly higher in control than study group.

Side effects in both the group were also analyzed. It was seen that nausea, vomiting and retching were more in control group 36% (n=21) than in study group 31% (n=19). But dizziness and sedation were more common in study group 27% (n=16) than control group 20% (n=12). No case of respiratory depression was found in both of the groups. Study by Pandey et al [14] showed nausea, vomiting and retching were more in study group 24.8% than in control group 5.2%.Another study [17] of 250 patients underwent elective laparoscopic cholecystectomy who received either a single dose of 600 mg gabapentin or placebo 2 h before the operation found that the patients receiving gabapentin had a significantly lower incidence of PONV (37.8% vs 60%; P=0.04) though dizziness found to be more in this group. The mechanism of gabapentin in the prevention of PONV is unknown but it could possibly be due to the indirect effect of opioid sparing. The analgesic efficacy of gabapentin as well as concomitant decrease in opioid consumption when used preemptively has been demonstrated in surgical patients by differnt study (Table 7) which is co-relating the outcome of present study without any significant side effects.

Limitations: The study was not a double blind study,so some biasness could occure. There was no facility of patient control analgesia system in our institute,so all patient might not have complete pain free interval during post operative period.

Table 7: Similar studies

Reference	Surgical procedure	Gabapentine vs placebo(n)	Analgesic & delivery	Effect on analgesic consumption	Effect on pain score at 6 hr	Effect on pain score at 24 hr
Pandey et al.2004b [14]	Laparascopic chole-cystectomy	153/153	300 mg 2 h pre-op.	Fentanyl reduced from 356 to 221 ug	VAS lower with gabapentin (P < 0.05)	VAS lower with gabapentin (P < 0.05)
Dirks et al 2002 [12]	Radical mastectomy	31/34	1200 mg 1 h preop.	Morphine reduced from 29 to 15 mg	VAS lower with gabapentin (P < 0.018)	
Pandey 2004a [18]	Lumbar discoidectomy	28/28	300 mg 2 h pre-op.	Fentanyl reduced from 360 to 234 ug	VAS lower with gabapentin (P < 0.05)	VAS lower with gabapentin (P < 0.05)
Turan 2004c [19]	Ear-Nose-Throat Surgery	25/25	1200 mg 1 h pre-op..	Diclofenac reduced from 111 to 33 mg	VAS lower with gabapentin (P < 0.001)	VAS lower with gabapentin (P < 0.001)
Turan 2004 [20]	Abdominal hysterectomy	25/25	1200 mg 1 h pre-op.	Morphine reduced from 53 to 41 mg	VAS lower with gabapentin (P < 0.01)	VAS lower with gabapentin (P < 0.05)
Al-Mujadi 2006 [21]	Thyroid surgery	37/35	1200 mg 1 h pre-op.	Morphine reduced from 30 to 15 mg	VAS lower with gabapentin (P < 0.01)	VAS lower with gabapentin (P < 0.01)
Turan 2007 [22]	Hand surgery	20/20	1200 mg 1 h pre-op.	Diclofenac reduced from 63 to 30 mg	NS	NS

Conclusion

Gabapentine,a well tolerated drug,significantly decreases the incidence of post-operative pain and also decreases total pethidine consumption over 24 hours without any significant adverse effects.

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