LAPAROSCOPIC CHOLECYSTECTOMY;

EFFECT IN **PREOPERATIVE GABAPENTIN** IN PREVENTION OF POSTOPERATIVE PAIN AFTER

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ABSTRACT… Background: shoulder pain after laparoscopic procedure is a frequent complication encountered in surgery ward. Several treatments have been proposed to reduce it. This study aimed to evaluate the efficacy of preoperative administration of gabapentin in preventing and attenuating Post Laparoscpoic Shoulder Pain (PLSP) after laparoscopic cholecystectomy. **Design:** In a randomised, double blinded placebo controlled study. **Setting:** Woman's Hospital, Kermanshah University of Medical Sciences**. Period:** April 2011 to March 2012. **Material and methods:** 90 patients of ASA physical status I-II undergoing elective laparoscopic cholecystectomy were randomly allocated to receive gabapentin 600 mg or placebo ,half an hour before surgery. The presence analgesia and side effects were recorded for 12h postoperatively in same times. **Results:** Incidence Verbal Rating Scale (VRS) ≥ 4 at different times after arrival to PACU were significantly lower in gabapentin group in arrival (P Value= 0.003) and then after 30 miniute (P Value= 0.02) and 2 (P Value= 0.003), 4 (P Value= 0.03) and 6 (P Value= 0.04) hours after arrival to Post Anesthesia Care Unit (PACU). But this sigificancy lost at 12 hours (P Value= 0.07) after arrival to PACU. Also there was a reduction in amounts of postoperative in ward analgesic consumption. Side effects were not different between two groups. **Conclusions:** 600 mg gabapentin as premedication is effective and safe for reducing post-laparoscopic shoulder pain intensity after general laparoscopy compared with placebo.

Key words: Laparoscopic cholecystectomy, gabapentin, Post Anesthesia Care Unit (PACU)

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INTRODUCTION

Postoperative pain management is an important challenge for anesthesiologists and surgeons[1]. Laparoscopy is being used as a current diagnostic and therapeutic approach in pelvic and abdominal surgeries. Compared with open surgery, laparoscopy causes less pain and reduces need for analgesics[2]. Shoulder pain after laparoscopic procedure is frequent[3,4] and in some cases it may causes more discomfort to the patient than the pain at the incision sites[5]. Post Laparoscpoic Shoulder Pain (PLSP) is provoked by irritation or injury of the phrenic nerve at the diaphragm surface during CO_2 pneumoperitoneum due to local acidosis[6] or distention of the diaphragm[6-9].

Gabapentin is a 3-alkylated analog of gamma-amino butyric acid (GABA). Its mechanism is modulation of alpha-2 delta calcium channel subunits. Gabapentin binds to the á-2 subunit of voltage-gated calcium channels, thus preventing the release of nociceptive neurotransmitters including glutamate, norepinephrine, substance P, and calcitonin gene-related peptide[10-12].

Several recent trials and multiple systematic reviews have evaluated the safety and efficacy of Gabapentin as an analgesic and its opioid-sparing effect in postoperative pain management in various surgical populations[13–17].

The aim of this clinical trial was to compare the efficacy of preoperative administration of gabapentin in preventing and placebo on attenuating PLSP after laparoscopic cholecystectomy.

MATERIAL AND METHODS

The protocol was approved by ethics and clinical studies committee of Kermanshah University of Medical Sciences and written consent was obtained from all patients who were in study.

This was a prospective double-blinded randomised placebo controlled study, involving 90 patients, ASA class I-II, scheduled for elective laparoscopic

cystectomy in Woman's Hospital, Kermanshah University of Medical Sciences, from April 2011 to March 2012.

Patients with at least one of the following criteria were not included in the study; patient refusing to give informed consent, Body Mass Index)BMI(<40, persistent preoperative pain, any analgesic intake daily or within 48 h preoperatively, drug abuse, a major psychiatric disorder, epilepsy or history of convulsion. Furthermore, when the laparoscopic surgery had to be shifted to an open laparotomy the patient had been excluded from the study.

Before surgery patients were instructed to rate their pain using an 11 point Verbal Rating Scale)VRS(,)0= no pain and 10=worst pain(. Patients were randomly assigned to two treatment groups)case and control groups(using a computer generated table. Patients were premedicated orally half an hour before surgery with placebo)control group(or gabapentin, 600 mg, PO)case group(. The study medications were prepared in capsules of identical colour and appearance and were packed by the pharmacy according to a computer generated randomised list, for placebo group the active gradients had been removed and replaced by glucose powder. The anesthesiologist, patient surgeon, nurses, and research assistants were blinded to the randomisation.

All patients were fasted overnight. After arrival in the operating room and intravenous access, patients received standardised general anesthesia at the decision of the attending anesthesiologist who was blinded to treatment. After administration of midazolam 2mg intravenously, remisufentanil infusion was initiated with a dose of 0.1- 0.2$\mu.kg^{-1}min^{-1}$. Induction of anesthesia was achieved with Tiopantal 5-7 mg/kg/h and subsequently tiopantal infusion was initiated in a maintenance dose of 0.1$mg.kg^{-1}min^{-1}$ during the surgery. Orotracheal intubation was facilitated by atracurium 0.5$mg.kg^{-1}$ and thereafter intermittent 0.15$mg.kg^{-1}$ bolus doses and the patient's lungs were mechanically ventilated with a 50% O_2. The Tidal Volume and/or Respiratory Rate were adjusted to keep the end tidal CO_2 at the level of 32-37mmHg. Abdominal Insuflatin was performed by CO_2 gas was to maintain the intra-abdominal pressure at maximum 12mmHg. The same surgical team performed all surgical procedures for the two groups using the same technical principles and was blinded to grouping of the study. Monitoring included intermittent noninvasive blood pressure monitoring, continuous electrocardiography, pulse oximetry, and capnography.

Surgery and anesthesia duration times were recorded for all patients. Patients requiring conversion to laparotomy were excluded from study. After the operation was completed, remisufentanil infusion was discontinued and immediately sufentanyl 5µg bolus IV was administered. After skin closure, tiopantal infusion was stopped. Neuromuscular block was antagonized with neostigmine 40-70$\mu g.kg^{-1}$ and atropine 40$\mu g.kg^{-1}$. The total amount of remisufentanil and tiopantal during anesthesia were recorded. After tracheal extubation and on awakening from anesthesia, patients were transferred to Post Anesthesia Care Unit)PACU(. In PACU, When patients requested an analgesic, a sufentanyl bolus at increment of 25-50µg was titrated according to patient's comfort. All patients received Diclofenac suppository 50 mg on the evening of the day of surgery and on the next morning. If patients requested for additional analgesic they received antianalgesic tablets combined of acetaminophen)325 mg(plus codeine)8mg(orally.

The presence, and intensity of PLSP using a Verbal Rating Scale)VRS, 0=no pain and 10=worst ever percepted pain(were recorded in arrival and then after 30 minutes and 2, 4, 6 and 12 hours after arrival to PACU by a blinded research nurse. If the patient

experienced sustained nausea or vomiting, lasting longer than 5 minutes ondansetron 4 mg intravenously was administered. The times to first request for analgesia and discharge from post anesthesia care unit were recorded. Total sufentanyl requirement and postoperative side effects such Post Operative Nausea and Vomiting)PONV(and drowsiness were recorded too.

The primary outcome was incidence and intensity of PLSP during the first and second postoperative days.

STATISTICAL ANALYSIS

Sample size estimation showed that 40 per treatment group would be adequate to detect a clinically relevant reduction of the level of pain by %25 with a power of 0.80 and a level of significance of %5, so we decided to randomise 45 patients into each group. Statistic tests were performed using SPSS 13.0 for windows)SPSS Chicago, Il, USA(. Continuous variables were analysed using student's T-test. Nominal parametric data were analysed using the fisher exact test or Mann-Whitney test. Results are reported as absolute value, means, or numbers.

RESULTS

After assessment for eligibility, 90 patients were enrolled into study, 4 patients were withdrawn from the trial within the first hour of surgery and excluded from the efficiency analysis the final analysis because of the need for converting to laparotomy. Therefore 86 patients)43 in gabapentin group and 43 in placebogroup(were included in the final analysis.

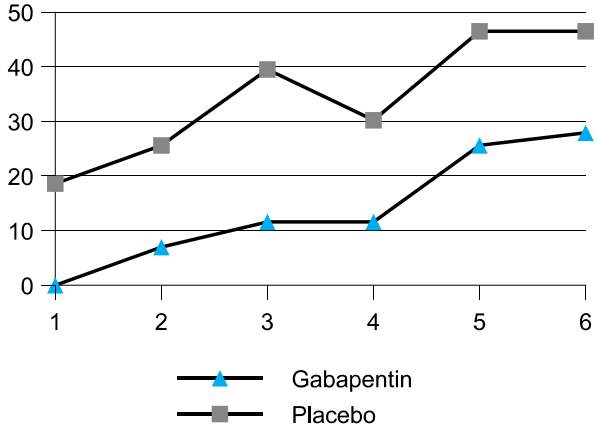
All patients had patients and were between 18-45 years old with a mean age of 27.5 years. Patients had weights between 50-78 kg and mean Body Mass Index was 24.5kg.m^{-2}.

There were no significant differences between the two groups with regard to patient's age (P value=0.27), BMI (P value=0.28), duration of surgery (P value=0.08)and duration of anesthesia(P value=0.18)(table I).

	Gabapentin	Placebo	P-value
Age	26.5 (±7.4)	28.5 (±9.2)	0.27
BMI	25.1 (±4.0)	23.9 (±5.9)	0.28
Duration of surgery	77.3 (±28.5)	67.9 (±20.2)	0.08
Duration of anesthesia	90.1 (±25.2)	83.5 (±20.3)	0.18

Table-I. Comparison the independent variables between groups of study

Incidence VRS ≥ 4 at different times after arrival to PACU were significantly lower in gabapentin group in arrival (P value= 0.003) and then after 30 minute (P value= 0.02) and 2 (P value= 0.003), 4 (P value= 0.03) and 6 (P value= 0.04) hours after arrival to Post Anesthesia Care Unit (PACU). But this significance difference lost at 12 hours (P value= 0.07) after arrival to PACU (Table-II, Figure 1).



Gabapent>	0	7	11.6	11.6	25.6	27.9
Placebo	18.6	25.6	39.5	30.2	46.5	46.5

Figure 1: Comparison the patients with a Visual Rating

1) Percentage of patients with a VRS Score ≥4 at arrival to Post Anesthesia Care Unit

2) Percentage of patients with a VRS Score ≥4 at 30 minute after arrival to Post Anesthesia Care Unit
3) Percentage of patients with a VRS Score ≥4 at 2 hours after arrival to Post Anesthesia Care Unit
4) Percentage of patients with a VRS Score ≥4 at 4 hours after arrival to Post Anesthesia Care Unit
5) Percentage of patients with a VRS Score ≥4 at 6 hours after arrival to Post Anesthesia Care Unit
6) Percentage of patients with a VRS Score ≥4 at 12 hours after arrival to Post Anesthesia Care Unit

The mean VRS during first 12 hours after surgery had increased in both groups of study of the highest degree in 12 hours after surgery (Figure 2).

	Gabapentin	Placebo	P value[3]
Incidence VRS[1] ≥ 4 at arrival to PACU[2]	-	8 (18.6%)	0.003
Incidence VRS ≥ 4 at 30 min after arrival to PACU	3 (7.0%)	11 (25.6%)	0.02
Incidence VRS ≥ 4 at 2 hours after arrival to PACU	5 (11.6%)	17 (39.5%)	0.003
Incidence VRS ≥ 4 at 4 hours after arrival to PACU	5 (11.6%)	13 (30.2%)	0.03
Incidence VRS ≥ 4 at 6 hours after arrival to PACU	11 (25.6%)	20 (46.5%)	0.04
Incidence VRS ≥ 4 at 12 hours after arrival to PACU	12 (27.9%)	20 (46.5%)	0.07

Table-II. Incidence VRS ≥ 4 at different times after arrival to Post Anesthesia Care Unit (PACU)
[1] VRS: Verbal Rating Scale [2] PACU: Post Anesthesia Care Unit [3] P Value more than 0.05 are significant

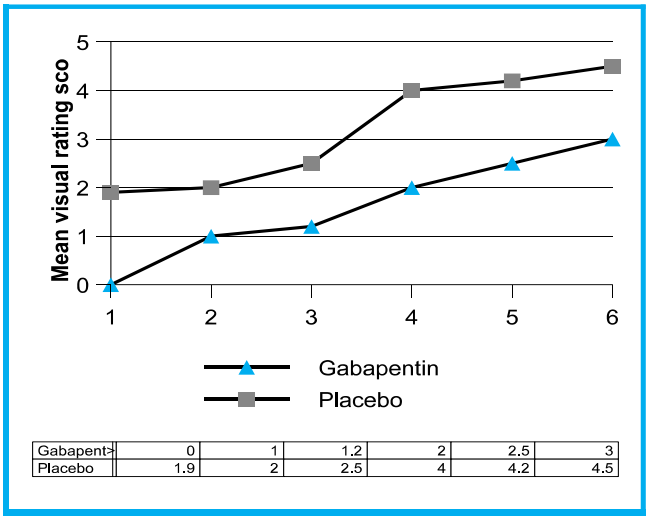


Figure-2. Comparison the mean Visual Rating Scale

1) Mean VRS at arrival to Post Anesthesia Care Unit
2) Mean VRS at 30 minute after arrival to Post Anesthesia Care Unit
3) Mean VRS at 2 hours after arrival to Post Anesthesia Care Unit
4) Mean VRS at 4 hours after arrival to Post Anesthesia Care Unit
5) Mean VRS at 6 hours after arrival to Post Anesthesia Care Unit
6) Mean VRS at 12 hours after arrival to Post Anesthesia Care Unit

Sufentanyl consumption in recovery room was similar among two groups (P=0.157), meanwhile, the number of patients who request additional analgesia in ward was lower significantly in gabapentin group versus placebo group in the operation day (P=0.0009) and first post-operation day (P= 0.01) (Table III).

Side effects including drowsiness, nausea and vomiting were not significantly different between two groups (Table III).

	Gabapentin	Placebo	P value[1]
Mean dose of sufentanyl in PACU[2]	15	23	0.157
Acetamiophen use in operation day	9 (20.9%)	24 (55.8%)	0.0009
Acetamiophen use in first post-operative day	2 (4.7%)	10 (23.3%)	0.01
Nausea in operation day	6 (14.0%)	5 (11.6%)	0.74
Nausea in first post-operative day	2 (4.7%)	2 (4.7%)	1.00
Vomiting in operation day	5 (11.6%)	5 (11.6%)	1.00
Vomiting in first post-operative day	1 (2.3%)	-	0.32
Drowsiness in operation day	2 (4.7%)	1 (2.3%)	0.54

Table-III. Analgesic request and Side effects in gabapentin and palcebo groups
[1] P Value more than 0.05 are significant [2] Post Anesthesia Care Unit

DISCUSSION

Post surgical pain is an important challenge for anesthesiologists and surgeons[1].

As the role of laparoscopy in operative management of general conditions developed in past decades, the post laparoscopic shoulder presents as a frequent and challenging type of pain after this surgeries[2,18]. Although laparoscopy compared with laparotomy causes less post-operative pain and less opioid need, but post-laparoscopic shoulder pain in some patients may be moderate to severe, so opioid administration would be necessary to reduce pain.

Pathophysiology of pain after laparoscopy is different from laparotomy. Pain after laparotomy has somatic or parietal origin, where as post laparoscopic pain is caused by visceral irritation[19].

Gabapentin is a 3-alkylated analog of gamma-amino butyric acid (GABA) which is used to reduce post laparoscopic pain. Gabapentin was first introduced as antiepileptic agent[20]. Studies have shown that Gabapentin is effective in pain reduction of many diseases including post-herpetic neuralgia syndrome, diabetic neuropathy, and sympathetic reflex dystrophy. According to ability of Gabapentin to affect on central nervous system, its use in practice had been increased. The results of previous studies showed that Gabapentin is effective for reduce postoperative pain especially during the first hours post operation[21].

A majority of the published placebo controlled, double blind and randomised trials have demonstrated postoperative analgesic efficacy with gabapentin, and a small number of the comparative trials suggest that its analgesic and opioid sparing efficacy are roughly comparable to that of NSAIDS[22].

In most of studies, only one dose of Gabapentin had been prescribed, and plasma level of Gabapentin reaches to maximum after 2-3 hours. In one study, there was a reverse association between plasma level of Gabapentin and opiod use, and which could be the consequence of dose dependent response to Gabapentin and diminish need to opioid administration with elevated the Gabapentin dose[23].

The results of these studies showed that gabapentin has reduced post-operative pain, especially during the first hours post operation. Hoseinsen and

colleagues studied the effect of 1200mg gabapentin 1hour preoperation for relieving pain of hysterectomy[24]. In their study dose of gabapentin was higher than us, maybe because the pain of laparotomy is more intensive than laparoscopy. They concluded gabapentin is effective in improving early pain control. Ian Gilron and colleagues studied the effect of combination of gabapentin and refecoxib on decreasing pain after hysterectomy[25] (Gilron, 2005 #5). In their study, gabapentin was significantly effective but sedation was more frequent with it than other groups. Amount of administration of gabapentin in their study was higher than us (1800mg/day). R. Jakela and colleagues studied usefulness of pregabalin with Diclofenac to control pain after gynaecological laparoscopy[26]. They showed analgesia was better after pregabalin 150mg than diazepam 5mg (as an active placebo).

Seong-Hwan Chang and colleagues found pregabalin 300mg BD perioperative is not effective for prevention and attenuation of PLSP after laparoscopic cholecystectomy compared to placebo and over-sedation[27]. The most common dose of gabapentin is 1200mg in the trials performed on operative pain and this dose has been found to be effective in three systemic review published during the past.

We studied efficacy of gabapentin 600mg orally 0.5 hr before surgery on incidence and intensity of PLSP after laparoscopic cholecystectomy and showed this drug with such dose was significantly effective especially during the first hours post operative compared with placebo and because of using almost low dose of gabapentin ,we did not see any significant side effects.

Pain intensity was increased in first 12 hours postoperatively, which decreased its differences in two groups gradually. Pain intensity was higher in placebo group during this period. This could be discussed by analgesic effects of Gabapentin and further diminish in its plasma level. Continuing the analgesic effect of a single dose of gabapentin is an interesting finding of this study, which could partially, discussed by remaining plasma level of the primary dose or in other ways including preemptive analgesia.

LIMITATION

One of the major limitations of our study is that the study population involved patients, undergoing lower abdominal surgery, and furthermore comparative studies including male patients and other laparoscopic surgeries are necessary.

CONCLUSIONS

Gabapentin 600mg as premedication is significantly effective in reducing the intensity of post-laparoscopic shoulder pain after cholecystectomy laparoscopy. The side effects, such as PONV and drowsiness are not significantly higher than placebo at this dose.

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