ORIGINAL RESEARCH PAPER
Volume - 9 | Issue - 7 | July - 2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

COMPARATIVE STUDY BETWEEN GABAPENTIN AND CARBAMAZEPINE AS PRE-EMPTIVE ANALGESIA IN LAPAROSCOPIC CHOLECYSTECTOMY FOR POST OPERATIVE ANALGESIA REQUIREMENT

Anaesthesiology

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ABSTRACT

The treatment of choice for symptomatic gall stone is laparoscopic cholecystectomy. The antiepileptic drugs such as carbamazepine and gabapentin have also analgesic effect which can be used safely in laparoscopic cholecystectomy. This study is therefore aimed to compare pre-emptive analgesic effect between gabapentin and carbamazepine for patients undergoing laparoscopic cholecystectomy. A randomized, double blind prospective study was carried out on 120 patients with 40 patients in each group, Group G- Tablet gabapentin 300mg, Group C- Tablet carbamazepine 200 mg and Group P- Placebo. For comparing three groups mean and Student's t-test was used. For categorical data, Chi-square and Fischer's test were used. The postoperative VAS scores and the requirement of total rescue analgesic were recorded and it was found to statistically significant by comparing the three groups with minimum in Group G followed by group C and maximum in group P. This study suggests that for laparoscopic cholecystectomy, gabapentin is a better preemptive analgesic drug than carbamazepine.

KEYWORDS

Laparoscopic Cholecystectomy, Gabapentin, Carbamazepine

INTRODUCTION

Laparoscopic cholecystectomy is now the gold standard treatment for symptomatic gallstones and is the commonest operation performed laparoscopically world-wide.[1] Although, there are clear benefits compared with open surgery, but post-operative pain after laparoscopic cholecystectomy remains an issue.[1] In addition to the routine drugs for pain such as nonsteroidal anti-inflammatory drugs (NSAIDS), opioids, acetaminophen, anticonvulsants drugs: carbamazepine, clonazepam, gabapentin, lamotrigine, oxcarbazepine, phenytoin, topiramate and valproate are also used. Among these drugs carbamazepine is an antiepileptic agent that is generally used as a third-line treatment for neuropathic pain.[2,3] Although it is effective for trigeminal neuralgia, data on painful peripheral neuropathy are limited and inconsistent.[4] Previous research has reported that carbamazepine potentiated the analgesic effectiveness of morphine in animal models of neuropathic pain and postoperative pain.[4,5] Gabapentin, a newer anticonvulsant, has also demonstrated its efficacy in the treatment of neuropathic pain syndromes, including diabetic neuropathy, postherpetic neuralgia, multiple sclerosis, erythromelalgia, trigeminal neuralgia, and gulaain barre syndrome (GBS).[6,7,8] In addition to having an effect in neuropathic pain syndromes in human and animal models, studies have also demonstrated its effect in nociceptive pain syndromes.[9,10]

AIMS AND OBJECTIVES:

The present study was aimed to evaluate the safety and efficacy of two pre-emptive analgesic options: Gabapentin and Carbamazepine for patients undergoing laparoscopic cholecystectomy.

MATERIALS AND METHODS

After the study protocol was approved by local ethics committee a randomized, double blind prospective study was carried out on 120 patients with 40 patients in each group. The patients were divided randomly by computer generated numbers to one of the following groups and treatment allocation was done by 1:1:1 for all three groups. A sample size of 120 patients was calculated after pilot study ($\alpha = 0.05$, $\beta = 0.2$). The statistical analysis was done using SPSS for Windows version 16.0. For comparing three groups mean and Student's t-test was used. For categorical data, Chi-square and Fischer's Exact test were used. The critical value of 'p' indicating the probability of significant difference was taken as < 0.05 for comparisons. The patients were divided into three groups, Group G: Preemptive analgesia with Tab Gabapentin 300 mg, Group C: Preemptive analgesia with Tab Carbamazepine 200 mg, Group P: Preemptive analgesia with placebo. The inclusion criteria for the study was: Patients belong to American Society of Anaesthesiologists physical status I and II, patients undergoing elective laparoscopic cholecystectomy under general anaesthesia, anticipated duration of surgery less than 4 h, age group between 18 and 65 years, weight range up to 20% of the ideal body weight for either sex and haemodynamically stable The exclusion criteria was: Patients with a history of hypertension, diabetes, liver disease or renal disease, patients with known neurological or cardiovascular disease, pregnant patients,. patients with known psychiatric disorders, patients on antihypertensive drugs, sedatives, hypnotics, antidepressants, and drugs with effects on the nervous system, patients already taking oral gabapentin or carbamazepine, patients allergic to gabapentin or carbamazepine, patients not willing to participate and in patients in whom laparoscopic cholecystectomy was converted to open cholecystectomy.

At the time of pre-anaesthetic check-up patient's demography and other history were recorded to assess the fitness of patient for surgery and to exclude the patients not meeting the criteria as per defined criteria. Patients were examined for airway assessment, blood pressure (systolic, diastolic, and mean), heart rate and other relevant systems. Various laboratory investigations including haemoglobin, total leucocyte count, fasting blood sugar, E.C.G. and chest X-ray were analyzed and recorded. The patients were explained the procedure, possible side effects and potential benefits of drugs being used in study. Patient was also informed about the nature of study and that they can be allotted in any of the study groups and a written consent was obtained from them.

On the day of surgery, the selected patients were given oral tablets of Gabapentin, Carbamazepine or placebo 1 hour before the surgery depending on the selected group. In the operating room, a crystalloid infusion was started through an intravenous (IV) cannula. Mean artery blood pressure (MAP), heart rate (HR) and peripheral oxygen saturation (SpO_2) were monitored. IV dexamethasone 8 mg was given as antiemetic. Premedication with midazolam 30 g/kg and fentanyl 2 g/kg was administered intravenously on the table. After adequate pre-oxygenation for 3 min, anaesthesia was induced with propofol 2 mg/kg and vecuronium 0.1 mg/kg and maintained with 50% N_2O in O_2 on closed circle circuit, isoflurane and vecuronium 0.01 mg/kg. At the end of surgery, neuromuscular block was antagonized with neostigmine 0.05 mg/kg and glycopyrolate 0.01 mg/kg. Any increase in the HR and MAP when not settling down by deepening the pain of anaesthesia was given fentanyl 50 g/kg subsequently. After tracheal extubation, patients were observed in the PACU for 1 hr and then transferred to the surgical ward. Assessment of post-operative pain was made on the basis of the visual analogue score (VAS), where 0 cm – "no pain" and 10 cm – "Worst pain imaginable".[11] The VAS scores are taken immediately on extubation (0 hr) and at 1, 4, 8, 12 and 24 hours

postoperatively. Rescue analgesic used was Inj paracetamol 15 mg/kg body weight IV. Time to first analgesic requirement, total analgesic consumption in the first 24 hours post – operatively and occurrence of adverse events were also recorded. Patients were regularly asked about pain, retching and nausea and vomiting, sedation and any other complication if any. Blood pressure was regularly monitored for episodes of hypotension (MAP<60 mm Hg). Heart rate was regularly monitored for episodes of bradycardia (HR < 60). Total duration of surgery was recorded in all the cases. All observations such as post operative pain intensity on VAS score, analgesic request rate, total analgesic consumption, nausea, vomiting and any other adverse effects of preemptive medication were noted down. The immediate post operative sedation was assessed by the Richmond Agitation Sedation Scale.[12]

DISCUSSION

Preemptive analgesia can be achieved by administration of opioids, local anaesthetic blocks and other analgesic modalities before surgery in an attempt to decrease the intensity and duration of post operative pain as stated by Ng et al., and Hasaniya et al.[13,14]The present study was undertaken to compare the effect of Gabapentin and Carbamazepine on post operative pain and analgesic requirement within first 24 hours after laparoscopic cholecystectomy when used as a preemptive medication. The role of gabapentin for pain management was also established by various other studies such as by Sist et al in for reflex sympathetic dystrophy[8] whereas Rowbotham used it for trigeminal neuralgia and by Gilron for post herpetic neuralgia.[7,15]

The Demographic Data (table 1)

Demographic characteristics of subjects in the three study groups					
Variable		Group G	Group C	Group P	P value
		frequency (percentage)			
Gender	Male	14 (35)	13 (32.5)	13 (32.5)	0.963
	Female	26 (65)	27 (67.5)	27 (67.5)	
		Mean ± 2SD			
Age		40.08 ± 13.031	42.00 ± 12.954	37.22 ± 11.007	0.225
Weight		57.90 ± 14.270	61.50 ± 13.395	70.50 ± 11.968	0.000

showed that there was no significant difference among all the three groups however there was female preponderance. The post operative analgesia was measured for 24 hours post operatively by using Visual Analogue Scale. There was significant difference in VAS score in immediate post operative period when all the three groups were compared with the lowest pain score in Group G and the highest pain score in Group P (Table 2).

	Group G Mean±SD	Group C Mean±SD	Group P Mean±SD	f-value	p-value
VAS_Immediate_postop	2.42±0.675	3.50±1.281	5.30±1.137	74.717	<0.001
VAS_after_1hr	1.25±0.543	2.80±1.488	3.12±1.522	24.956	<0.001
VAS_after_4hr	1.58±0.712	3.30±1.285	3.05±1.395	25.405	<0.001
VAS_after_8hr	2.18±1.217	2.32±0.730	2.52±0.933	1.282	0.281
VAS_after_12hr	1.68±0.474	2.00±0.987	2.80±1.203	15.205	<0.001
VAS_after_24hr	1.40±0.496	1.42±0.501	1.90±0.632	10.621	<0.001

The VAS score was minimum in Group G was and maximum in Group P and was statistically significant (<0.001) in immediate, 1, 4, 12 and 24 hours. In the 8th hour the VAS score among all the groups was comparable (0.281).The result showed that patients who were given gabapentin (Group G) experienced less post operative pain in comparison to the patients who were given carbamazepine (Group C). Similar studies were done by Fassoulaki on breast surgeries[10], Rorarius in hysterectomy etc where gabepentin have shown significant pain relief.[16] There was significant difference in VAS score in immediate post operative period when all the three groups were compared with minimum in Group G and maximum in Group P (Table 3).

	Group G vs. C	Group G vs. P	Group C vs. P
VAS_Immediate_postop	<0.001	<0.001	<0.001
VAS_after_1hr	<0.001	<0.001	0.763
VAS_after_4hr	<0.001	<0.001	1.000
VAS_after_8hr	1.000	0.340	1.000
VAS_after_12hr	0.373	<0.001	0.001
VAS_after_24hr	1.000	<0.001	0.001

Gabapentin exerts its analgesic effect by acting on GABAergic system, as discussed in studies by Yoon, Nicholson and McLean [17,18,19] whereas Post RM et al found that Carbamazepine stabilizes membrane by inhibiting sodium channels.[5] In the immediate post operative period, maximum numbers of patients with requirement of rescue analgesia were in Group P and minimum in Group G (Table 4).

Analgesic given Immediate postop	Group G		Group C		Group P	
	No.	%	No.	%	No.	%
Yes	16	40.0	24	60.0	40	100
No	24	60.0	16	40.0	0	0.0
Total	40	100	40	100	40	100

All the patients of Group P required immediate post operative pain relief and more than half of the patients of Group C required rescue analgesia immediately after surgery. After the dose of analgesia, only few patients required analgesic till 12 hours of surgery in all the groups with maximum requirement in Group P at 4th and 8th hour and in Group C at 1st hour of surgery. At 12th hour of surgery there were significantly more number of patients requiring rescue analgesia as compared to Group G and Group C. At 24th hour of surgery, the pain was insignificant in all the three groups.

Most of the patients of Group G were calm and alert whereas the patients of Group C were drowsy. But the patients of Group P were combative. We did not notice any incidence of emergence delirium in any of the groups (Table 5).

Sedation Score Immediate postop	Mean±SD	p-value
Group G	-0.92±1.269	<0.001
Group C	-1.60±1.614	
Group P	2.65±0.893	

The incidence of post operative retching was significantly higher in placebo group in the immediate post operative period while no patient suffered retching in Group G. In vitro studies with radiolabeled Gabapentin have revealed a Gabapentin binding site in areas of rat brain including neocortex and hippocampus. This may be a mechanism of antiemetic effect of gabapentin. At 4th hour of surgery and after that very few patients in all the three groups had retching and all of them belonged to Group P. According to the Epilepsy Cooperative Study No. 264, the most common side effects of carbamazepine therapy included sedation, weight gain, nystagmus, gastrointestinal symptoms which included retching and nausea and vomiting, gait problems, changes in affect or mood, tremor, cognitive disturbance, rash and diplopia.[20] But in our study we found retching, nausea and vomiting to be lesser in Carbamazepine in comparison to placebo.

In this study, in the immediate post operative period nausea and vomiting was minimum in Group G and maximum in Group P. This was similar at different intervals viz. 4 hour, 8 hour, 12 hour and 24 hour except at 1 hour after surgery because of the use of rescue antiemetic drugs. This study shows the total requirement of rescue antiemetic drug in all the three groups. In the Immediate post operative period, maximum requirement of antiemetic was in Group P and minimum in Group G. The requirement was least in Group G at all time intervals. Only time when antiemetic given was maximum in Group C was at 1st hour after surgery due to previous anti emetic given in Group P at immediate post operative period.

Above finding suggest gabapentin as a better preemptive analgesic than carbamazepine and analgesia by both the above drugs was better than the placebo.

CONCLUSION-

This study suggested that for laparoscopic cholecystectomy, gabapentin is a better preemptive analgesic than carbamazepine with

lesser requirement of paracetamol as rescue analgesic and postoperative analgesia by both gabapentin and carbamzepine is better than the placebo.

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