Clinical Study Evaluating Pregabalin Efficacy and Tolerability for Pain Management in Patients Undergoing Laparoscopic Cholecystectomy

Thesis

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CONTENTS

Subject	Page
Acknowledgement	**i**
Contents	**ii**
List of Tables	**iii**
List of Figures	**iv**
List of Abbreviations	**v**
Abstract	**vii**
Introduction	**1**
Review of literature	**4**
1. Gallbladder disease: pathophysiology, diagnosis and treatment	**4**
Pathophysiology	**5**
Risk factors	**7**
Clinical Presentation	**8**
Diagnosis	**9**
Treatment	**11**
2. Laparoscopic Cholecystectomy .	**13**
3. Pain and postoperative pain	**14**
Pain	**14**
Postoperative pain	**16**
Management postoperative pain	**20**
4. Gabapentinoids	**27**
Gabapentin.	**27**
Pregabalin	**33**
5. Role of the pharmacist in pain management	**44**
Aim of the Study	**46**
Patients and Methods	**47**
Results	**53**
Discussion	**72**
Summary and Conclusion	**80**
Reference	**82**
Arabic Summary	**100**

LIST OF TABLES

No.	Table	Page
(1)	Diseases of the Gallbladder	5
(2)	Laboratory Values Associated With Cholelithiasis and Cholecystitis	9
(3)	Oral Bile Acid Dissolution Agents	12
(4)	The Assistive Tool for Determining Types of Pain	16
(5)	Major adverse effects of opioids analgesics	24
(6)	Comparisons of Gabapentin and Pregabalin	43
(7)	Patients' demographics and baseline data.	55
(8)	Visual Analogue scale score change at time 0, 12 & 24in the 3 groups	56
(9)	Visual Analogue scale score change over time in the 3 groups	58
(10)	The 24 hours- Pethidine consumption in the 3 groups	60
(11)	Numeric sedation scale score in the 3 groups.	65
(12)	Nausea and Vomiting score in the 3 groups	68
(13)	Dizziness score in the 3 groups	68
(14)	Pain Global satisfaction score in the 3 groups.	71

LIST OF FIGURES

No.	Figure	Page
(1)	Laparoscopic cholecystectomy procedure	14
(2)	The structural formulae of gabapentin	28
(3)	chemical structure of pregabalin	34
(4)	Schematic representation of pregabalin mode of action	35
(5)	Visual Analogue Scale (VAS)	50
(6)	Mean Visual Analogue Scale score change at time 0, 12 & 24 in the 3 groups	57
(7)	Visual Analogue scale score change over time in the 3 groups	59
(8)	The 24 hours Pethidine consumptionin the 3 groups	61
(9)	The mean numeric Sedation scale score in the 3 groups	66
(10)	The mean numeric Sedation scale score in the 3 groups over time	67
(11)	Nausea and vomiting occurrence and severity in the 3 groups	69
(12)	Dizziness score in the 3 groups	70
(13)	Pain Global satisfaction score in the 3 groups	71

LIST OF ABBREVIATIONS

ACEI	Angiotensin converting enzyme inhibitors
AEDs	Antiepileptic drugs
AMPA	a-amino-3 hydroxy-5-methyl-4-isoxazolepropionic acid
ASA	American Society of Anesthesiologists
AUC	Area under the curve
CBC	Complete blood count
CGRP	Calcitonin gene – related peptide
CLcr	Creatinin clearance
Cmax	Peak plasma concentrations
CNS	Central nervous system
CT	Computed tomography
ECG	Electrocardiogram
ERCP	Endoscopic retrograde cholangiopancreatography
FDA	Food and drug adminstration
FIQ	Fibromyalgia impact Questionnaire
GABA	Gamma Amino Butyric Acid
HDL	High density lipoprotein
HIDA	Hepatobiliary iminodiacetic acid
IASP	International association for the study of pain
IM	Intramuscular
IV	Intravenous
LC	Laparoscopic cholecystectomy
mcg	Micro gram
mg	Milli gram
N	Number of patient
NMDA	N-methyl-D-aspartate
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs

NSS	Numeric Sedation scale
P	Probability
P&T	Pharmacy and therapeutic committee
PACU	post anesthesia care unit
PCA	Patients controlled analgesia
PGIC	Patient global impression of change
PONV	postoperative nausea and vomiting
RBCs	Red blood cells
RCT	Randomized clinical trial
SD	Standard Deviation
SPSS	Statistical Package for Social Sciences
TENS	Transcutaneous electrical nerve stimulation
USP	United States Pharmacopeia
VAS	Visual analogue scale
V_d	Volume of Distribution
VGCCs	Voltage-dependent Calcum channels
WFSA	World Federation Of Societies Of Anesthesiologists

ABSTRACT

Abstract

Objectives: To evaluate the efficacy and tolerability of Pregabalin in postoperative pain management after laparoscopic cholecystectomy.

Methods A randomized, placebo, controlled study conducted at Anesthesia Department, Laparoscopy Surgery Unit, Ain Shams University Hospital. Ninety patients with ASA physical status I –II scheduled for elective laparoscopic cholecystectomy under general anesthesia were included. Patients were randomly assigned to the following groups (n=30 each); pregabalin group [P]; received 150mg pregabalin capsule two hours preoperative and 12 hours postoperative and twice daily for 2 days, Gabapentin group [G]; received 1200 mg gabapentin capsules (400 mg x3) two hours preoperative and 12 hours postoperative and 400mg three times daily for 2 days, Control group [C]; received placebo capsules. Postoperative pain scores were recorded on a visual analogue scale (VAS). The following data was recorded; total daily pethidine and diclofenac consumption, numeric sedation score and the postoperative nausea, vomiting and dizziness scores.

Results The 24 hour-pethidine consumption was significantly lower ($p<0.001$) in both Pregabalin and Gabapentin groups versus control. Both groups had significantly less ($p<0.001$) patients with postoperative nausea, vomiting, sedation and dizziness versus control. Overall patient satisfaction with pain management was significantly higher ($p<0.001$) in Pregabalin group versus gabapentin or control groups.

Conclusion Gabapentin 1200 mg and Pregabalin 150 mg, are effective and safe analgesics for reducing postoperative pain in laparoscopic cholecystectomy.

The perioperative oral administration of Pregabalin 150 mg in patients undergoing laparoscopic cholecystectomy is an effective and safe method of analgesia with a low incidence of adverse effects and reduces postoperative pethidine consumption.

Keywords; laparoscopic cholecystectomy, Pregabalin, Gabapentin, pain


INTRODUCTION

Introduction

Laparoscopic cholecystectomy is one of most popular surgical procedures however, pain after this surgery presents a major challenge. It is most intense on the day of surgery and on the following day and subsequently declines to lower levels within 3–4 days (Bisgaard et al., 2001a). Intense acute pain after laparoscopic cholecystectomy might predict the development of chronic pain (e.g. post-laparoscopic cholecystectomy syndrome) (Bisgaard et al., 2005).

Several medications have been used to treat postoperative pain (Khan and Dionne, 2002). Opioid are the most commonly used but has been associated with emesis, respiratory depression and altered mental status. Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used however; they are linked with the risk of allergy, kidney damage, bleeding and gastrointestinal dysfunction (Issioui et al., 2002). Another alternative is the use of local anesthetics though; they require interventional procedures and most of them are short or intermediate acting (Meyer, 2002). A multimodal approach has been suggested to improve postoperative analgesia and to reduce the above mentioned side effects (Woolf and Chong, 1993).

Both pregabalin and gabapentin are gamma-amino butyric acid (GABA) analogues (Woolf and Chong, 1993); they don't bind at the $GABA_A$ or $GABA_B$ receptor. However, they have a high binding affinity for the alpha-2-delta $\alpha_2\delta$ subunit of the presynaptic voltage-gated calcium channels (Ben-Menachem, 2004) which inhibits calcium influx and subsequent release of excitatory

neurotransmitters in the pain pathways that include glutamate, norepinephrine, substance P, and calcitonin gene-related peptide (CGRP) receptor (Ben-Menachem, 2004; Sarzi-Puttini et al., 2011). Hence, reducing the release of several excitatory neurotransmitters and blocking the development of hyperalgesia and central sensitization (Bryans and Wustrow, 1999; Belliotti et al., 2005). It is probable that this modulation of neurotransmitter release by pregabalin contributes to the drug's anticonvulsant, analgesic, and anxiolytic effects (Ben-Menachem, 2004).

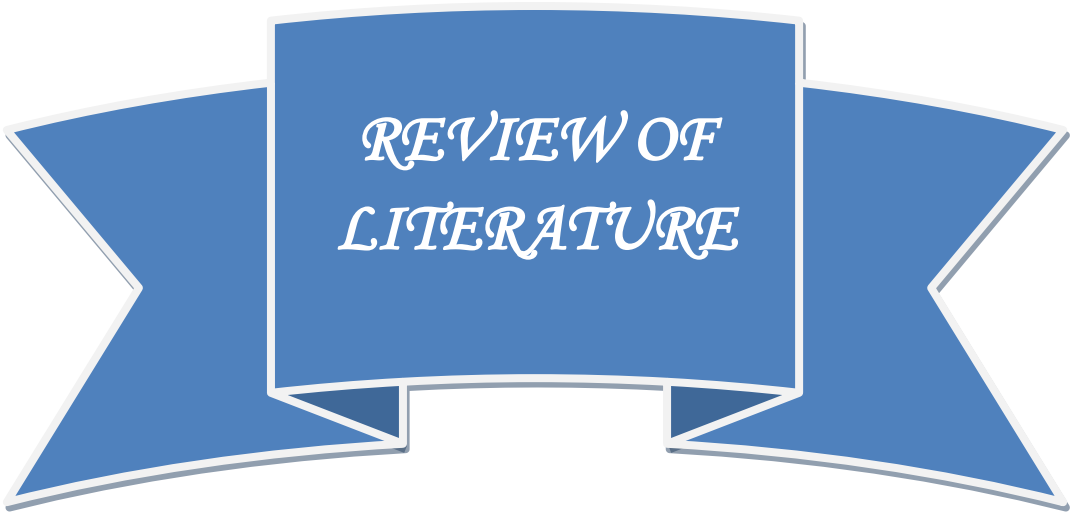
Pregabalin (S-[+]-3-isobutylgaba) as an anticonvulsant; is frequently used for treatment of neuropathic pain (Guay, 2005; Gajraj, 2007).Pregabalin is similar to gabapentin, but is more selective as it has a high-affinity ligand to the alpha-2-delta ($\alpha_2\delta$) binding site (Ben-Menachem, 2004). Moreover, it has a more favorable pharmacokinetic profile including dose-independent absorption and higher bioavailability (Ben-Menachem, 2004; Belliotti et al., 2005). The agent is also several times more potent than gabapentin with fewer adverse effects, lack of drug interactions, and linear dose-response characteristics (Sarzi-Puttini et al., 2011).

The use of pregabalin is increasing because of its efficacy for neuropathic pain associated with diabetic neuropathy, postherpetic neuralgia, and fibromyalgia and as an adjunctive therapy for partial-onset seizures (Zareba, 2005).

Several reports have indicated that the preoperative administration of pregabalin may have a role in the treatment of postoperative pain after different

surgical procedures (Tiippana et al., 2007). One trial observed that in patients undergoing lumbar laminectomy, pregabalin 150 mg given before and after surgery was effective in reducing the postoperative pain and decreasing the postoperative patient-controlled morphine consumption (Reuben et al., 2006). Yet, limited clinical trials have investigated the role of preoperative single-dose administration of pregabalin in attenuating postoperative pain after laparoscopic cholecystectomy (Agarwal et al., 2008).

To our knowledge till now, no study was done to compare the effects of pregabalin versus gabapentin in postoperative pain management in patients undergoing laparoscopic cholecystectomy.


REVIEW OF
LITERATURE