Ain Shams University- Faculty of Medicine
Department of Anesthesia, Intensive Care & Pain Management

Comparative study between the effect of pre-emptive use of oral Gabapentin and Pregabalin on acute post-operative pain after elective gynecological surgeries performed under spinal anesthesia

Thesis
Submitted For Partial Fulfillment of M.D. Degree in Anesthesiology

By
Omnia Mohamed Mostafa Helwa
M.B.B.Ch., M.Sc. Ain Shams University

Under Supervision of
Prof. Dr. Gehan Seif El-Nasr Mohamed
Professor of Anesthesia, Intensive Care and Pain Management
Faculty of Medicine, Ain Shams University

Dr. Noha El-Sayed Hussein
Ass. Professor of Anesthesia, Intensive Care and Pain Management
Faculty of Medicine, Ain Shams University

Dr. Dina Salah El-Din Mahmoud
Ass. Professor of Anesthesia, Intensive Care and Pain Management
Faculty of Medicine, Ain Shams University

Dr. Saymon Haleim Armanious
Lecturer of Anesthesia, Intensive Care and Pain Management
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2017

Acknowledgement

Above and before all, I would like to thank ***Allah*** *the all Mighty, the most Merciful for the support, guidance he granted me throughout my life.*

No words can express my deepest appreciation and profound respect to ***Prof. Dr. Gehan Seif El-Nasr Mohamed,*** *Professor of Anesthesia, Intensive Care and Pain Management, Ain Shams University, for her continuous guidance and support. She has generously devoted much of her time and her effort for planning and supervision of this study.*

Also, my profound gratitude to ***Dr. Noha El-Sayed Hussein,*** *Assistant Professor of Anesthesia, Intensive Care and Pain Management, Ain Shams University, for her kind supervision and support. It was great honor to work under her supervision.*

I would like also to thank ***Dr. Dina Salah El-Din Mahmoud,*** *Assistant Professor of Anesthesia, Intensive Care and Pain Management, Ain Shams University, for her support, help and constructive criticism during this work.*

I would like also to thank ***Dr. Saymon Haleim Armanious,*** *Lecturer of Anesthesia, Intensive Care and Pain Management, Ain Shams University, for his help during this work.*

Last but not least, I dedicate this work to my family, whom without their sincere emotional support, pushing me forward this work would not have ever been completed.

Omnia Mohamed Mostafa

Contents

List of Abbreviations

Abb.	Full Term
ASA	American society of anesthesiologists
BMI	Body mass index
BP	Blood pressure
$Ca_V\alpha_2$-δ	Calcium channel alpha$_2$-delta
CBC	Complete blood count
CGRP	Calcitonin gene-related peptide
CLcr	Creatinine clearance
DPN	Diabetic peripheral neuropathy
ECG	Electrocardiogram
FDA	Food and Drug Administration
GABA	γ-aminobutyric acid
GLM	General linear model
HS	Highly significant
IM	Intramuscularly
IV	Intravenous
KFT	Kidney function tests
LFT	Liver function tests
NIBP	Non-invasive blood pressure
NS	Non-significant
PACU	Post-anesthesia care unit
PHN	Postherpetic neuralgia

Abb.	Full Term
PONV	Postoperative nausea and vomiting
POP	Pelvic organ Prolapse
PT	Prothrombin time
PTT	Partial thromboplastin time
RBS	Random blood sugar
RSS	Ramsay sedation scale
S	Significant
SD	Standard deviation
SpO_2	Pulse oximetry
SPSS	Statistical package of social science
TAH BSO	Total abdominal hysterectomy and bilateral salpingo-oophorectomy
TOT	Trans-obturator vaginal tape
USAN	United states adopted names
VAS	Visual analog scale
VH	Vaginal hysterectomy
$\alpha 2$-δ	$Alpha_2$- delta

List of Tables

List of Figures

Introduction

Pain is defined by International Association for Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. The relief of postoperative pain is a subject, which has been receiving an increasing amount of attention in the past few years **(Fassoulaki et al., 2012)**. Pre-emptive analgesia is the administration of analgesics prior to onset of noxious stimuli, which modifies peripheral and central nervous system processing of noxious stimuli, thereby reducing hyperalgesia (increased pain from a stimulus that usually provokes pain) and allodynia (pain due to a stimulus that does not usually provoke pain) **(Kelly et al., 2001) (Jensen and Finnerup, 2014)**.

The goals of pre-emptive analgesia are to decrease acute pain after tissue injury and to inhibit the persistence of post-operative pain and the development of chronic pain **(Levaux et al., 2003)**. Various drugs such as local anesthetics, opioids, non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitor, gabapentin, pregabalin, clonidine and dexmedetomidine have been used as pre-emptive analgesics **(Zhang et al., 2011)**.

Central neuronal sensitization contributes to postoperative hypersensitivity to pain **(Dirks et al., 2002)**. As such, postoperative pain may be considered as a transient type of "neuropathic" pain and, consequently there is a rationale for the exploitation of antihyperalgesic drugs for postoperative analgesia **(Dahl et al., 2004)**.

Gabapentin is a structural analog of gamma amino butyric acid **(Bafna et al., 2014)**, that was introduced as an antiepileptic drug in 1993. It has been extensively used to treat painful neuropathies in patients with diabetic polyneuropathy, postherpetic neuralgia, and neuropathic pain in general **(Dworkin et al., 2003)**. It mainly has an antihyperalgesic and antiallodynic properties with only a minor effect on normal nociception **(Iannetti et al., 2005)**. Pregabalin is another structural analog of γ-aminobutyric acid, which shows analgesic, anticonvulsant, and anxiolytic effects **(Shneker and McAuley, 2005**).

The mechanism of action of gabapentin and its successor, pregabalin is likely mediated by binding to the 21 subunits of the presynaptic voltage-gated calcium channels, which are up-regulated in the dorsal root ganglia and spinal cord after surgical trauma. Gabapentin may produce antinociception by inhibiting calcium influx via these channels, and subsequently inhibiting the release of

excitatory neurotransmitters (e.g., substance P, calcitonin gene-related peptide) from the primary afferent nerve fibers in the pain pathway **(Rose and Kam, 2002)**. Hence, reducing the hyperexcitability of dorsal horn neurons induced by tissue injury **(Gilron, 2002)**. Central sensitization of these neurons is important in chronic neuropathic pain, but also occurs after trauma and surgery. Reduction in central sensitization by an antihyperalgesic drug like gabapentin may reduce acute postoperative pain. Gabapentin may also prevent opioid tolerance **(Gilron et al., 2003)**. Both gabapentin and pregabalin have anxiolytic properties **(Menigaux et al., 2005)**.

Some clinical trials of gabapentin, given before a variety of surgical procedures producing visceral and somatic injury, have found significant reduction in postoperative analgesic requirements and others have found a reduction in early and late postoperative pain **(Dahl et al., 2004)**.

Pregabalin which is several times more potent than gabapentin and rapidly absorbed orally with more than 90% bioavailability **(Frampton and Foster, 2005)**, was also shown to have a significant analgesic effect on acute postoperative pain according to other placebo-controlled studies **(Hill et al., 2001), (Reuben et al., 2006)**.

Aim of the Work

The aim of this work is to compare the effect of pre-emptive single dose of oral gabapentin and oral pregabalin on acute postoperative pain after elective gynecological surgeries performed under spinal anesthesia, in order to omit the possible analgesic effects of general anesthetics on the results of this study.

Mechanism of Postoperative Pain and Pre-emptive Analgesia

In recent decades, major progress has been made in reducing perioperative morbidity and mortality. As anesthesia and surgery have become safer, there has been an increasing emphasis toward the improvement of secondary outcome measures including perioperative pain **(Hurley et al., 2006)**.

Pain is more than a simple bodily reaction to noxious stimuli; rather, it is a complicated and individualized experience. Patients undergoing a surgical procedure are predisposed to pain postoperatively for a number of reasons. For example, pre-existing pain (both acute and chronic), psychological influences, fear of recurring additional pain, neurovascular tissue damage from a prior operation, in addition to the extent of the surgery which can all contribute to major postoperative discomfort **(Kissin, 2000)**.

Systemic opioids are the most common medications administered for postoperative pain relief. However, opioids have many adverse effects including respiratory depression, constipation, nausea, vomiting, urinary

retention, and pruritus. Alternative treatments such as medications delivered via epidural catheters, peripheral nerve catheters, or given as single-administration peripheral nerve blocks are attractive choices but may not be possible in all patients or types of surgery **(Hurley et al., 2006)**.

Unfortunately, inadequate treatment of postoperative pain persists, despite the presence of postoperative pain guidelines and advanced technologies **(Block et al., 2003)**. Post operative pain which occurs as a consequence of tissue trauma, may further result in physical, cognitive, and emotional discomfort **(Parsons et al., 2013)**.

In addition to poor patient satisfaction, the outcome of a surgical procedure can be affected by inadequate perioperative pain control. The pain-related changes can affect insulin, cortisol, catecholamine, and other hormone levels **(Dunwoody et al., 2008)**. Also, it is associated with increased cytokine and acute-phase reactant release, activation of the renin-angiotensin- aldosterone cascade, impaired coagulability, and an altered immune response **(Cohen et al., 2004)**.

Decrease in physical mobility due to postoperative pain can predispose an individual to pneumonia **(Pessaux et al., 2013)**, and muscle splinting has the potential to

decrease blood flow to an extremity, resulting in thrombosis or embolism **(Bader et al., 2010)**. Muscles can be further damaged by spasm, atrophy, and impairment of metabolism **(Dunwoody et al., 2008)**. Muscles controlling urinary bladder motility can become impaired, resulting in urinary retention. Coronary vasoconstriction from activation of the sympathetic nervous system can result in cardiovascular effects such as angina or ischemia. Furthermore, unresolved postoperative pain may give rise to sleep deprivation, anxiety and depression **(Bader et al., 2010)**.

Almost a century ago, researchers first described a possible relationship between intra-operative tissue damage and an intensification of acute pain and long-term postoperative pain, now referred to as central sensitization **(Crile, 1916)**. Nociceptor activation is mediated by chemicals that are released in response to cellular or tissue damage **(Vadivelu et al., 2014)**.

Numerous neurophysiologic or neurochemical mechanisms are involved in postoperative pain including peripheral nerve and central sensitization. These changes can contribute to enhanced pain sensitivity experienced by the patient and can include hypersensitivity of spinal cord neurons **(Woolf & Salter, 2000)**, hypersensitivity of

peripheral pain transmitting C-fibers **(Banik & Brennan, 2004)**, or changes in periphery surrounding the immediate area of the incision **(Woo et al., 2004)**. These postoperative changes may therefore represent a corollary of neuropathic pain in the acute setting and may be responsive to treatments used in the palliation of neuropathic pain **(Hurley et al., 2006)**.

It has been refined and evolved to a broader concept that surgical incision alone is not the trigger for central sensitization **(Katz, 1995)**. Other factors, such as preoperative pain, additional noxious intraoperative inputs such as retraction, postoperative inflammatory processes, related peripheral and central neuromodulators, as well as ectopic neural activity can all cause an intensification of acute pain and development of long-term postoperative pain as a result of central sensitization **(Vadivelu et al., 2014)**.

Hence, Central sensitization can occur for a variety of reasons, ranging from preoperative pain to intraoperative tissue injury and postoperative inflammatory processes that can occur immediately after surgery up to several weeks later **(Katz et al., 2011)**.