

# **THE EFFECT OF EPIDURAL MAGNESIUM SULFATE AS ADJUVANT TO FENTANYL FOR POSTOPERATIVE ANALGESIA**

Thesis

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**To**

**My Family**

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## LIST OF CONTENTS

Title	Page No.
<b>Introduction</b> .....	١
<b>Aim of the work</b> .....	٥
 <b>Review of Literature</b>	
- A brief history of pain .....	٦
- Anatomy and physiology of pain .....	١٠
- Opioid system.....	٢٦
- Epidural analgesia .....	٤٠
- The NMDA receptor.....	٦٢
- Magnesium sulfate.....	٨١
 Patients and methods.....	١١٧
Results.....	١٢٤
Discussion.....	١٥٨
Summary .....	١٧٨
Conclusion .....	١٨٢
References .....	١٨٣
Arabic Summary .....	—

## LIST OF TABLES

Tab. No.	Title	Page No.
Table (١):	Opioid receptors.....	٣٠
Table (٢):	causes of magnesium deficiency .....	٨٤
Table (٣):	Benefits and Adverse Effects of the Perioperative I.V. Administration of Magnesium Sulfate .....	٩٧
Table (٤):	Modified bromage scale: .....	١٢٣
Table (٥):	Comparison between the study groups as regard sex of the patients: .....	١٢٤
Table (٦):	Age of the study group: .....	١٢٥
Table (٧):	The weight, height and BMI of the study group .....	١٢٦
Table (٨):	Comparison between the study groups as regard ASA classification: .....	١٢٩
Table (٩):	Comparison between the study groups as regard different types of operations: .....	١٣٠
Table (١٠):	The systolic blood pressure of the study groups:.....	١٣١
Table (١١):	The diastolic blood pressure of the study groups:.....	١٣٣
Table (١٢):	The pulse rate of the study group: .....	١٣٥
Table (١٣):	The Spo <sub>٢</sub> of the study groups:.....	١٣٧
Table (١٤):	The respiratory rate of the study groups:.....	١٣٩
Table (١٥):	The time to ١ <sup>st</sup> analgesic requirement:.....	١٤١
Table (١٦):	Comparison between the fentanyl consumption in the control, FM١٠٠ and FM٥٠٠ study groups .....	١٤٣

Table (١٧): Comparison of fentanyl consumption between the FM١٠٠ group and the FM٥٠٠ group .....	١٤٦
Table (١٨): Comparison between the study groups as regard The Visual analogue score:.....	١٤٨
Table (١٩): Comparison of VAS between the FM١٠٠ group and the FM٥٠٠ group:.....	١٥١
Table (٢٠): Comparison between the study groups as regard sedation scores:.....	١٥٣
Table (٢١): The Bromage scale for assessment of motor block:.....	١٥٥
Table (٢٢): Adverse effect:.....	١٥٧

## LIST OF FIGURES

Fig. No.	Title	Page No.
Figure (١):	Descartes' Boy with Foot in Fire .....	٦
Figure (٢):	Spinal and supraspinal pathways of pain. ....	١٢
Figure (٣):	Location of Rexed's laminae at the L <sup>٥</sup> level of the spinal cord.....	١٣
Figure (٤):	The “pain matrix” .....	١٧
Figure (٥):	Peripheral inflammatory mediators .....	٢٠
Figure (٦):	Epidural space .....	٤١
Figure (٧):	Vertebral venous plexus .....	٤٢
Figure (٨):	The vertebral ligament.....	٤٤
Figure (٩):	Glutamate receptors.....	٦٣
Figure (١٠):	NMDA receptor & its subunits .....	٦٥
Figure (١١):	NMDA receptor binding site.....	٧٢
Figure (١٢):	Vascular effect of magnesium sulfate .....	٨٨
Figure (١٣):	Effect of magnesium on blood brain barrier ..	٩٢
Figure (١٤):	١٠ point scale visual analuge scale .....	١٢١
Figure (١٥):	Height of the three study groups .....	١٢٧
Figure (١٦):	Weight of the three study groups .....	١٢٧
Figure (١٧):	BMI of the three study groups.....	١٢٧
Figure (١٨):	Distribution of patient's according to ASA classification. ....	١٢٩
Figure (١٩):	Distribution of patients according to the type of operation .....	١٣٠
Figure (٢٠):	Systolic blood pressure in the three study groups at different time point of the study.....	١٣٢
Figure (٢١):	diastolic blood pressure in the three study groups at different time point of the study.....	١٣٤
Figure (٢٢):	pulse rate in the three study groups at different time point of the study. ....	١٣٦

Figure (٢٣): oxygen saturation in the three study groups at different time point of the study.....	١٣٨
Figure (٢٤): Respiratory rate in the three study groups at different time point of the study.....	١٤٠
Figure (٢٥): fentanyl consumption in the three study groups at different time point of the study.....	١٤٤
Figure (٢٦): comparison of the fentanyl consumption in the two study groups at different time point of the study. ....	١٤٧
Figure (٢٧): VAS in the three study groups at different time point of the study. ....	١٤٩
Figure (٢٨): comparison between the FM١٠٠ and FM٥٠٠ as regard the VAS at different time point of the study. ....	١٥٢



## LIST OF ABBREVIATIONS

Abbrev.	Meaning
<b>ACC</b>	Anterior cingulate cortex
<b>ACH</b>	Acetylcholine
<b>ACTH</b>	Adrenocorticotrophic hormone
<b>ALS</b>	Amyotrophic lateral sclerosis
<b>AMI</b>	Acute myocardial infarction
<b>AMP</b>	Adenosine monophosphate
<b>AMPA</b>	$\alpha$ -amino- $\gamma$ -hydroxy- $\delta$ -methyl- $\epsilon$ -isoxazolepropionate
<b>ASA</b>	American society of anaesthesiologist
<b>ATP</b>	Adenosine triphosphate
<b>AV</b>	Atrio-ventricular
<b>BBB</b>	Blood brain barrier
<b>BDNF</b>	Brain-derived neurotrophic factor
<b>BTS</b>	British Thoracic Society
<b>CABG</b>	Coronary artery bypass graft
<b>CGRP</b>	Calcitonin gene- related peptide
<b>CL</b>	centrolateral nucleus
<b>CNS</b>	Central nervous system
<b>COX</b>	Cyclooxygenase
<b>CPB</b>	Cardiopulmonary bypass surgery
<b>CSF</b>	Cerebrospinal fluid
<b>CSF</b>	Cerebrospinal fluid
<b>DAGO</b>	[D-Ala $\gamma$ ,N-methyl-Phe $\epsilon$ ,Gly $\delta$ -ol]enkephalin
<b>DPDPE</b>	[D-Pen $\gamma$ , D-Pen $\delta$ ]enkephalin
<b>DPLPE</b>	[D-Pen $\gamma$ , L-Pen $\delta$ ]enkephalin
<b>DRG</b>	Dorsal root ganglion
<b>EAR</b>	Estimated average requirement
<b>ECC</b>	Extracorporeal circulation
<b>GABA</b>	Gama aminobutyric acid
<b>GMP</b>	Guanosin monophosphate
<b>i.v.</b>	Intravenous
<b>ICU</b>	Intensive care units
<b>iGlu-Rs</b>	Ionotropic glutamate receptor
<b>IL</b>	Interleukins
<b>LOX</b>	Lipoxygenase (LOX
<b>LOX</b>	Lipooxygenase
<b>MDA</b>	Malondialdehyde
<b>MDvc,</b>	Ventrocaudal part of medial dorsal nucleus

<b>Abbrev.</b>	<b>Meaning</b>
<b>mGlu-Rs</b>	Metabotropic glutamate receptor
<b>MgSO<sub>4</sub></b>	Magnesium sulfate
<b>MLC</b>	Myosin light chain
<b>mu-OR</b>	Mu-opioid receptors
<b>NGF</b>	Nerve growth factor
<b>NMDA</b>	N-methyl-d-aspartate
<b>nNOS</b>	Nitric oxide synthase
<b>NS</b>	Nociceptive specific neurons
<b>O/B</b>	Octanol:buffer partition coefficient
<b>PAG</b>	Periaqueductal grey matter
<b>PCA</b>	Patient controlled analgesia
<b>PCEA</b>	Patient controlled epidural analgesia
<b>Pf</b>	Parafascicular nucleus
<b>PFC</b>	Prefrontal cortex
<b>PKA</b>	Protein kinase A
<b>PKC</b>	Protein kinase C
<b>PLC</b>	Phospholipase C
<b>PNS</b>	Peripheral nervous system
<b>POMC</b>	Proopio-melanocortin
<b>PSD-95</b>	Post-synaptic density-95
<b>RVM</b>	Rostroventral medulla
<b>SAP97</b>	Synapse associated protein 97
<b>SCT</b>	Spinal cord trauma
<b>SI</b>	Primary somatosensory cortex
<b>SIGN</b>	Scottish Intercollegiate Guidelines Network
<b>SII</b>	Secondary somatosensory cortex
<b>SKF-38393</b>	Sigma N-allylnormetazocine
<b>SN</b>	Sinus nodal
<b>SP</b>	Substance P
<b>TBI</b>	Traumatic brain injury
<b>TOF</b>	Test of four
<b>TRPV1</b>	Transient receptor potential channel V1
<b>VAS</b>	Visual analogue scales
<b>VMpo,</b>	Posterior part of ventromedial nucleus
<b>VPI,</b>	Ventral posterior inferior nucleus
<b>VPL</b>	Ventral posterior lateral nucleus
<b>VPM</b>	Ventral posterior medial nucleus
<b>WDR</b>	wide dynamic range neurons

## INTRODUCTION

Regional anesthesia is a safe, inexpensive technique, with the advantage of postoperative pain relief. Effective treatment of postoperative pain blunts autonomic, somatic, and endocrine responses. It has become common practice to use a polypharmacological approach for the treatment of postoperative pain, because no drug has yet been identified that specifically inhibits nociception without associated side effects. Research continues concerning different techniques and drugs that could prolong the duration of regional anesthesia and postoperative pain relief (*Bilir et al.*, 2004).

It was found that the sole use of local anesthetics is less common than local anesthetic-opioid combinations because of the relatively high incidence of motor blockade and hypotension (*Wheatley et al.*, 2004).

Epidural analgesia is most commonly provided using a combination of local anesthetic and an opioid (typically a lipophilic opioid). Compared with opioids or local anesthetic alone, a local anesthetic-opioid combination provides superior postoperative analgesia with lower local anesthetic doses (*Jorgensen et al.*, 2005).

Epidural opioids confer several benefits compared with epidural local anesthetics, related primarily to the absence of sensory and motor blockade as well as the absence of sympathetic blockade (*Jeffrey and Christopher*, 2006).

Unfortunately, intra-spinal and epidural opioid can be associated with dose dependant side effect including nausea, vomiting, urinary retention, respiratory depression, pruritis and development of tolerance and physical dependence (*Chaney, 1998; Tan et al., 2004*).

As these adverse effects is depending on the dose or the concentration, these adverse effect may be minimized by using epidural solutions of low drug concentration, so it would appear that higher concentration of epidural fentanyl may increase the likelihood of opioid-related side effects. On the other hand, low concentration of epidural fentanyl does not provide analgesia of high quality (*Tan et al., 2004*).

A variety of other classes of drugs have been studied more recently to try to improve the quality of neuroaxial blockade, both in the epidural space and in the subarachnoid space (*Pushparaj and John, 2006*).

In the 1980s, two groups of scientists first provided evidence for the role of N-methyl-D-aspartate (NMDA) receptors in nociception and their potential as analgesic targets reporting that spinal delivery of NMDA receptors antagonists inhibited the hyper-excitability of the spinal cord nociceptive neurons induced by C-fiber stimulation (*Boyce et al., 1999; Medvedev et al., 2004; Massey et al., 2004 and Ultenius et al., 2006*).

Studies suggested a role for N-Methyl D-Aspartate (NMDA) receptor antagonists (such as magnesium and ketamine) in the management of postoperative pain. NMDA receptor antagonism inhibits induction and maintenance of central sensitization after peripheral nociceptive stimulation by blocking dorsal horn N-methyl-D-aspartate (NMDA) receptor activation induced by excitatory amino acid transmitters, such as glutamate and aspartate (*Fawcett et al., 1999*).

Magnesium is the fourth most plentiful cation in the body. It has antinociceptive effects in animal and human models of pain, it has also been reported that they can reveal the analgesic properties of opioids (*Kroin et al., 2000 and Begon S. et al., 2000*), these effects are primarily based on the regulation of calcium influx into the cell that is natural physiological calcium antagonism and antagonism of NMDA receptor (*Sirvinskas and Laurinaitis, 2000*).

Numerous clinical studies investigating the effects of intravenously injected magnesium sulfate ( $\text{MgSO}_4$ ) on intra-operative and post-operative pain perception have shown that  $\text{MgSO}_4$  reduces the intra-operative consumption of hypnotic agents and analgesics (*Altan et al., 2000 and Arcioni et al., 2000*), and reduces postoperative analgesic requirements (*Levaux et al., 2000 and Apan et al., 2000*).

The intravenous administration of  $\text{MgSO}_4$  does not seem to be associated with a corresponding increase in cerebrospinal

fluid (CSF) ion concentrations (*Ko et al., 2001*), Although this is probably its true site of action (*Xiao et al., 1994*), precisely how  $Mg^{+2}$  pass through the blood– brain barrier remains unclear (*Fuchs-Buder et al., 1994*).

To obtain a meaningful and clinically effective action of  $Mg^{+2}$  on spinal cord NMDA receptors, some have hypothesized the injection of  $MgSO_4$  directly into the subarachnoid space, Direct intrathecal administration of  $MgSO_4$  prolongs the action of subarachnoid anesthesia in animal experiments (*Xiao and Bennett, 1994; McCarthy et al., 94 and Kroin et al., 2000*) and in humans, This administration route has been shown to be clinically safe in humans (*Buvanendran et al., 2002 and Ozalevli et al., 2009*) and its safety profile has been evaluated in several experimental settings, including histopathologic analysis (*Simpson et al., 1994 and Chanimov et al., 1994*)

So this study was intended to shed more light on this topic and to study the effect of epidural magnesium sulfate infusion on post operative analgesia. And study its effect as adjuvant to fentanyl for postoperative analgesia.

## **AIM OF THE WORK**

The aim of this work was to study the effect of epidural magnesium sulfate infusion in various concentrations on post operative analgesia in patients undergoing lower extremities orthopedic surgery.