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

Thesis
Submitted for Partial Fulfillment of the
M.D. Degree in Anaesthesiology

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Acknowledgment

First of all thanks to "Allah"

I would like to express my greatest and cordial thanks to ***Prof. Dr. Mahmoud Sherif Moustafa*** *Professor of Anesthesia and Intensive Care, Faculty of Medicine, Ain Shams University, for his encouragement, advice and unlimited support have guided me through every step of this work.*

I would like to express my highest appreciation and gratitude to ***Prof. Dr. Nehal Gamal El-Din Nooh*** *Professor of Anesthesia and Intensive Care, Faculty of Medicine, Ain Shams University, for her generous support and continuous encouragement.*

I would like to express my deepest and profound respect to ***Prof. Dr. Hoda Omar Mahmoud Aly,*** *Professor of Anesthesia and Intensive Care, Faculty of Medicine, Ain Shams University, for her endless patience and co-operation attitude were of great help to complete this work.*

Very special thanks should go to ***Dr. Adel Mekhail Fahmy Shenouda,*** *Assistant Professor of Anesthesia and Intensive Care, Faculty of Medicine, Ain Shams University, for his sincere help and valuable advice through the whole work.*

Ahmed Agwa

To
My Family
Ahmed Agwa

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Abbrev.	Meaning
ACC	Anterior cingulate cortex
ACH	Acetylcholine
ACTH	Adrenocorticotrophic hormone
ALS	Amyotrophic lateral sclerosis
AMI	Acute myocardial infarction
AMP	Adenosine monophosphate
AMPA	α-amino-٣-hydroxy-٥-methyl-٤-isoxazolepropionate
ASA	American society of anaesthesiologist
ATP	Adenosine triphosphate
AV	Atrio-ventricular
BBB	Blood brain barrier
BDNF	Brain-derived neurotrophic factor
BTS	British Thoracic Society
CABG	Coronary artery bypass graft
CGRP	Calcitonin gene- related peptide
CL	centrolateral nucleus
CNS	Central nervous system
COX	Cyclooxygenase
CPB	Cardiopulmonary bypass surgery
CSF	Cerebrospinal fluid
CSF	Cerebrospinal fluid
DAGO	[D-Ala٢,N-methyl-Phe٤,Gly٥-ol]enkephalin
DPDPE	[D-Pen٢, D-Pen٥]enkephalin
DPLPE	[D-Pen٢, L-Pen٥]enkephalin
DRG	Dorsal root ganglion
EAR	Estimated average requirement
ECC	Extracorporeal circulation
GABA	Gama aminobutyric acid
GMP	Guanosin monophosphate
i.v.	Intravenous
ICU	Intensive care units
iGlu-Rs	Ionotropic glutamate receptor
IL	Interleukins
LOX	Lipoxygenase (LOX
LOX	Lipooxygenase
MDA	Malondialdehyde
MDvc,	Ventrocaudal part of medial dorsal nucleus

Abbrev.	Meaning
mGlu-Rs	Metabotropic glutamate receptor
$MgSO_4$	Magnesium sulfate
MLC	Myosin light chain
mu-OR	Mu-opioid receptors
NGF	Nerve growth factor
NMDA	N-methyl-d-aspartate
nNOS	Nitric oxide synthase
NS	Nociceptive specific neurons
O/B	Octanol:buffer partition coefficient
PAG	Periaqueductal grey matter
PCA	Patient controlled analgesia
PCEA	Patient controlled epidural analgesia
Pf	Parafascicular nucleus
PFC	Prefrontal cortex
PKA	Protein kinase A
PKC	Protein kinase C
PLC	Phospholipase C
PNS	Peripheral nervous system
POMC	Proopio-melanocortin
PSD-٩٥	Post-synaptic density-٩٥
RVM	Rostroventral medulla
SAP٩٠	Synapse associated protein ٩٠
SCT	Spinal cord trauma
SI	Primary somatosensory cortex
SIGN	Scottish Intercollegiate Guidelines Network
SII	Secondary somatosensory cortex
SKF-١٠,٠٤٧,	Sigma N-allylnormetazocine
SN	Sinus nodal
SP	Substance P
TBI	Traumatic brain injury
TOF	Test of four
TRPV١	Transient receptor potential channel V١
VAS	Visual analogue scales
VMpo,	Posterior part of ventromedial nucleus
VPI,	Ventral posterior inferior nucleus
VPL	Ventral posterior lateral nucleus
VPM	Ventral posterior medial nucleus
WDR	wide dynamic range neurons

INTRODUCTION

Regional anesthesia is 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., ٢٠٠٧)***.

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., ٢٠٠١)***.

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., ٢٠٠٠)***.

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, ٢٠٠٥)**.

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, ١٩٩٥; Tan et al., ٢٠٠٤).***

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., ٢٠٠٤)***.

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, ٢٠٠٦)***.

In the ١٩٨٠s, 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., ١٩٩٩; Medvedev et al., ٢٠٠٤; Massey et al., ٢٠٠٤ and Ultenius et al., ٢٠٠٦)***.

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., ١٩٩٩)***.

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., ٢٠٠٠ and Begon S. et al., ٢٠٠٢)***, 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, ٢٠٠٢)***.

Numerous clinical studies investigating the effects of intravenously injected magnesium sulfate ($MgSO_4$) on intra-operative and post-operative pain perception have shown that $MgSO_4$ reduces the intra-operative consumption of hypnotic agents and analgesics ***(Altan et al., ٢٠٠٥ and Arcioni et al., ٢٠٠٧)***, and reduces postoperative analgesic requirements ***(Levaux et al., ٢٠٠٣ and Apan et al., ٢٠٠٤)***.

The intravenous administration of $MgSO_4$ does not seem to be associated with a corresponding increase in cerebrospinal

fluid (CSF) ion concentrations ***(Ko et al., ٢٠٠١)***, Although this is probably its true site of action ***(Xiao et al., ١٩٩٤)***, precisely how $Mg^{+٢}$ pass through the blood– brain barrier remains unclear ***(Fuchs-Buder et al., ١٩٩٧)***.

To obtain a meaningful and clinically effective action of $Mg^{+٢}$ on spinal cord NMDA receptors, some have hypothesized the injection of $MgSO_٤$ directly into the subarachnoid space, Direct intrathecal administration of $MgSO_٤$ prolongs the action of subarachnoid anesthesia in animal experiments ***(Xiao and Bennett, ١٩٩٤; McCarthy et al.,٩٨ and Kroin et al., ٢٠٠٠)*** and in humans, This administration route has been shown to be clinically safe in humans ***(Buvanendran et al., ٢٠٠٢ and Ozalevli et al., ٢٠٠٥)*** and its safety profile has been evaluated in several experimental settings, including histopathologic analysis ***(Simpson et al., ١٩٩٤ and Chanimov et al., ١٩٩٧)***

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.