Usage of Epidural Magnesium Sulphate to Reduce Postoperative Analgesics Requirements in Orthopedic Surgery

Thesis

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By

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List of Abbreviations

Abbrev.		Full-term
AMI	**:**	Acute Myocardial Infarction
ASA	**:**	American Society of Anesthesiology
ATP	**:**	Adenosine Tri Phosphate
AV	**:**	Atrioventricular
cAMP	**:**	Cyclic Adenosine Monophosphate
CgMP	**:**	Cylic Guanosine Monophosphate
Cm	**:**	Centimeter
CPB	**:**	Cardiopulmonary Bypass
CSF	**:**	Cerebrospinal Fluid
EAR	**:**	Estimated Average Requirement
ECG	**:**	Electrocardiogram
EPSP	**:**	Excitatory Postsynaptic Potentials
GABA	**:**	Y-Amino Butyric Acid
Gm	**:**	Gram
H	**:**	Hour
HOCM	**:**	Hypertrophic Obstructive Cardiomyopathy
IgE	**:**	Immunoglobulin E
Im	**:**	Intramuscular
Iv	**:**	Intravenous
KG	**:**	Kilogram
L	**:**	Lumbar Vertebra
LEA	**:**	Lumbar Epidural Anesthesia

MAP	**:**	Mean Arterial Pressure
Meq	**:**	Mili Equivilant
Mg	**:**	Milligram
$MgSO_4$	**:**	Magnesium Sulphate
mm	**:**	Millimeter
m mol	**:**	Milimole
M-opioid	**:**	Mieu-opioid
Nacl	**:**	Sodium Chloride
NHS	**:**	Neuronal Hyper-Excitability Syndrome
NMDA	**:**	N-methyl-d-aspartate
PCEA	**:**	Patient Controlled Epidural Analgesia
S	**:**	Sacral Vertebra
T	**:**	Thoracic Vertebra
TEA	**:**	Thoracic Epidural Analgesia
TKR	**:**	Total Knee Replacement
µg	**:**	Microgram
VAS	**:**	Visual Analogue Scale

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Introduction

Regional anesthesia is a safe, inexpensive technique and effective treatment of postoperative pain which blunts autonomic, somatic, and endocrine responses. It has become common practice to use a poly-pharmacological approach for the treatment of postoperative pain, because no drug has yet been identified that specifically inhibits nociception without associated side-effects ***(Sirvinskas and Laurinaitis, 2012).***

Intraoperative and postoperative noxious inputs may cause central sensitization, but analgesic interventions given before the noxious stimulus may attenuate or block sensitization (i.e. the analgesic agent given before occurrence of the noxious stimulus) ***(Vadivelu et al., 2014).***

The goals of analgesia are to decrease acute pain after tissue injury, to reduce intensity of pain and to inhibit the persistence of postoperative pain and the development of chronic pain ***(Grape and Tramer, 2007).***

A series of experimental data provide evidence that N-methyl-D-asartate (NMDA) receptors play a significant role in central sensitization to pain ***(Dickenson, 2014).***

NMDA antagonists have been shown to be useful in the reduction of acute postoperative pain, analgesic consumption, or both ***(Fisher et al., 2000).*** NMDA receptor is blocked by the presence of a centrally positioned magnesium ion ***(Dickenson et al., 2014).***

Aim of the Work

The current study was designed to evaluate the pre-emptive antinociceeptive effects of magnesium sulfate when given epidurally and to prove that the addition of magnesium sulfate to epidural bubivacaine decreases the postoperative narcotic requirements and improves the quality of analgesia.

Magnesium Physiology

Magnesium is the fourth most common cation in the body after potassium. It has a fundamental role as a cofactor in more than 300 enzymatic reactions involving energy metabolism and nucleic acid synthesis. It is also involved in several processes including hormone receptor binding, gating of calcium channels, trans-membrane ion flux and regulation of adenyl cyclase, musclecontraction neuronal activity, control of vasomotor tone, cardiac excitability, and neurotransmitter release. In many of its actions it has been linked to a physiological calcium antagonist ***(Vigil-De Gracia et al., 2015)***.

In humans, less than 1% of total body magnesium is found is serum and red blood cells. It is distributed principally between bone (53%) and the intracellular compartments of muscle (27%) and soft tissues (19%). Ninety percent of this intracellular magnesium is bound to organic matrices. Serum magnesium comprises only approximately 0.3% of total body magnesium, where it is present in three states: ionized (62%), protein bound (33%) mainly to albumin, and complexed to anions such as citrate and phosphate (5%) ***(Powell, 2014)***. Equilibrium between tissue pools is reached slowly with a half-life for the majority of radiolabeled magnesium varying between 41 and 181 days ***(Parmar et al., 2017)***. Thus serum

magnesium estimations may not provide representative information on the status of the other stores ***(Alday et al., 2005)***.

Magnesium units are commonly expressed in mg (milligrams), mmol or mEq. It should be noted that 1 gm of magnesium sulfate is equivatent to 4 mmol, 8 mEq or 98 mg of elemental magnesium ***(Fawcet et al., 1999)***. While there is an absolute requirement of magnesium, the daily estimated average requirement (EAR) is 200 mg for females and 250 mg for males ***(Humphrey et al., 2015)***. Rich sources of magnesium in the diet include cereals and legumes, but the processing of the former may lead to marked depletion of inherent magnesium, leaving only 3-28% of the original content ***(Jahnen-Dechent and Ketteler, 2012)***. Magnesium absorption is inversely proportional to intake and occurs principally from the ileum and colon. Excretion and serum magnesium control occur via the kidney. In common with other cations, magnesium is filtered at the glomerulus but differs in that re-absorption is predominantly in the ascending limb of the loop of Henle and not ion the proximal convoluted tubule ***(Dacey, 2001)***.

Actions of Magnesium

Magnesium has a suggested role in nearly every physiological system. Key underlying mechanisms of action are that of calcium antagonism via calcium channels, regulation of energy transfer (such as the production and function of ATP, and controller of glycolysis and the Krebs cycle in oxidative phosphorylation) and membrane sealing or stabilization. This has led to several studies on the central and peripheral nervous systems, and cardiovascular, respiratory, endocrine and reproductive systems ***(Gröber et al., 2015).***

A- Nervous System:

In the nervous system, magnesium has depressant effect at synapses and has been used as anticovulsant. The mechanism of action at synapses is related to competition between calcium and magnesium in the stimulus-secretion coupling processes in transmitter release ***(Isaev et al., 2012)***. The most well described of these is pre-synaptic inhibition of acetylcholine release at the neuromuscular junction. Its action as an anticonvulsant is secondary to N-methyl-D-aspartate (NMDA) receptors antagonism ***(Vink, 2016)***. This is a subgroup of glutamate receptors, stimulation of which is known to lead to excitatory postsynaptic potentials (EPSP) causing seizure; magnesium has been used successfully as an anti convulsant in eclampsia. However, in other circumstances it appears to be a much less