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EFFECT OF MAGNESIUM SULPHATE INFUSION ON PAIN RELIEF AFTER LOWER ABDOMINAL SURGERY

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In

ANAESTHESIOLOGY AND INTENSIVE CARE

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LIST OF ABBREVIATIONS

Acronyms	Definition
A.F	Atrial Fibrillation
Ach	Acetylcholine
ACT	Activated Clotting Time
ACTH	Adreno-Cortico-Trophic Hormon
ADH	Anti-Diuretic Hormone
ADP	Adenosine Diphosphate
ALT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
AMP	Adenosine Mono Phosphate
ANOVA	Analysis Of Variance
AQP4	Aquaporin 4
ASA	American Society Of Anesthesiology
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
BEAM	Beneficial Effects Of Antenatal Magnesium Sulphate
CABG	Coronary Artery Bypass Graft
c-AMP	Cyclic Adenosine Monophosphate
CPB	Cardiopulmonary Bypass
CSE	Combined Spinal Epidural
CSF	Cerebral Spinal Fluid
CVS	Cardio Vascular System
db	Double-Blind
DCT	Distal Convoluted Tubule
FAST-MAG	Field Administration Of Stroke Therapy-Magnesium
FFA	Free Fatty Acids
GA	General Anesthesia
Glu	Glutamate

GPCR	G-Protein-Coupled Receptors
HE	Hysterectomy
IHD	Ischemic Heart Disease
I.M	Intra Mascular
IMAGES	Intravenous Magnesium Efficacy In Stroke
iP	Inorganic Phosphate
IP_3	Inositol Triphosphate
IR	Ischemia Reperfusion
ISIS	International Study Of Infarct Survival
I.V	Intravenous
LCCE	Laparoscopic Cholecystectomy
LIMIT	Leicester Intravenous Magnesium Intervention Trial
LVRS	Lung Volume Reduction Surgery
MAC	Minimal Alveolar Concentration
MAGIC	Magnesium In Coronaries
MAP	Mean Arterial Pressure
MASH	Magnesium Sulphate In Aneurysmal Subarachnoid Hemorrhage
MAT	Multifocal Atrial Tachycardia
MFI	Micro Vascular Flow Index
Mg^{+2}	Magnesium
$MgSO_4$	Magnesium Sulphate
MVO_2	Myocardial Oxygen Consumption
NMDA	N-Methyl-D-Aspartat
NO	Nitric Oxide
NSAID	Non Steroidal Anti-Inflammatory Drug
PACU	Post Anesthetic Care Unit
PCA	Patient Controlled Analgesia
PCEA	Patient Controlled Epidural Analgesia
PEFR	Peak Expiratory Flow Rate
PLC	Phospholipase C

PRCT	Prospective Randomized Placebo-Controlled Trial
PTH	Parathyroid Hormone
SAH	Subarachnoid Hemorrhage
SNP	Single Nucleotide Polymorphism
SVT	Supraventricular Tachycardia
VAS	Visual Analogue Scale
VC	Vasoconstriction
VD	Vasodilatation
VF	Ventricular Fibrillation
VOCC	Voltage-Operated Calcium Channels
VT	Ventricular Tachycardia
ECF	Extra cellar fluid

CHAPTER 1

INTRODUCTION

1.1 Introduction

Many patients still suffer from moderate to severe pain after lower abdominal surgery, treatment have been used to relieve pain, including NSAID, Opioids, an anesthetics, but none has been consistently satisfactory. This may be because postoperative pain results from combination of inflammatory, incisional, somatic and visceral components **(Laurila et al., 2006)**.

Magnesium is essential for the formation of strong bones and healthy teeth, the transmission of nerve signals and the contraction of muscles. It activates several enzymes and is important in the conversion of blood sugar into energy. It also helps regulate the body's temperature. Magnesium founded naturally in green, leafy vegetables, nuts whole meal cereals, soya beans and seafoods. Drinking water in hard water areas is also source of magnesium. Supplements are only necessary for magnesium deficiency associated with impairment of absorption from the intestines such as repeated vomiting or diarrhea, advanced kidney disease, severe alcoholism or prolonged treatment with certain diuretic medicines.

It is also to treat abnormal heart rhythms, especially in situations when the levels of potassium are low. In this situation, the levels of magnesium are often also low. Adding magnesium can correct the abnormal heart rhythms by resetting the normal electrical activity in the heart. Magnesium sulphate may be given for the treatment of high blood pressure and fits (convulsions) in the later stages of pregnancy (eclampsia). It reduces the electrical excitability of the brain and thereby reduces the chance of fitting **(Keus et al, 2007)**.

Uncontrolled post-operative pain is associated with a number of adverse sequels that can lead to post-operative morbidity. Greater understanding of these phenomena would help to motivate staff provide better analgesia. A long line of publications continue to highlight an ongoing inadequacy in modern acute pain management with up to 30% of patients still suffering moderate to severe pain following surgery **(Ko et al., 2001)**.

Details of the mechanisms underlying the anesthesia-enhancing effects of magnesium remain unknown. A competitive antagonism on hippocampal presynaptic calcium channels that regulate neurotransmitter release in the central nervous system has been suggested. Volatile anesthetics, such as isoflurane, are thought to partially induce anesthesia by inhibition of these channels. Attenuation of catecholamine release from the adrenal medulla and calcium antagonistic effects on vascular smooth muscle cells also may contribute to the anesthetic effects of magnesium. In terms of neuromuscular blockade, the inhibition of calcium-mediated release of acetylcholine from the presynaptic nerve terminal at the neuromuscular junction plays an important role. A decrease of postsynaptic sensitivity to acetylcholine and direct effects on the membrane potential of myocytes also may contribute **(Hollmann et al., 2001)**.

Magnesium is the fourth most plentiful cation in the body. It has antinociceptive effects in animal and human models of pain. These effects are primarily based on the regulation of calcium influx into the cell and that is the natural physiological antagonism of the N-methyl-D-aspartate (NMDA) receptor. These effects have prompted the investigation of magnesium as an adjuvant for postoperative analgesia **(Kara et al., 2002)**.

The NMDA receptor is an excitatory amino acid receptor that has been implicated in the modulation of prolonged pain states in animal models. NMDA antagonists have been shown to be useful in the reduction of acute post-operative pain, analgesic consumption, or both when they are added to more conventional means of providing analgesia in the Perioperative period **(Bhatia et al., 2004)**.

AIM OF THE WORK:

The aim of this work is to study the effect of the preoperative Magnesium Sulphate (by IV infusion) on the postoperative pain relief, analgesic consumption(by measuring the time to the 1st analgesic dose requested by the patient), shivering scale and so the postoperative hospital stay in patients undergoing lower abdominal surgery.

CHAPTER 2

PHYSIOLOGY OF PAIN

2.1 Pain

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage **(Pasero and McCaffrey, 2005)**. Pain can be classified according to the followings:

- **According to the Clinical Status:**
  - Acute pain
  - Chronic pain
- **According To Pathophysiology:**
  - Nociceptive pain
  - Neuropathic pain
- **According to Etiology:**
  - For example, postoperative pain and cancer pain
- **According to the Affected Area:**
  - For example, headache or low back pain

2.2 Pain Pathway

- **First Order Neurons (primary afferent fibers):** Conduct impulses from the nociceptors to the spinal cord (at dorsal horn)
- **Second Order Neurons:** Conduct impulses from dorsal horn in spinal cord and ascend in the contra lateral spinothalamic tract to reach thalamus.
- **Third Order Neurons:** Conduct impulses from thalamus and send fibers through internal capsule to somato sensory areas I and II in the post central gyrus of the parietal cortex, and through corona radiate to the superior wall of the Sylvain fissure (**Pasero and McCaffrey, 2005)**.

2.3 Association (Complication) (Neuro-Endocrine Stress Response)

2.3.1 Mechanism of Response

The stress response to surgery consists of main component; the neuro-endocrine response and cytokine response.

(a) The Neuro-Endocrine Response (Central Response):

- The stimulus: painful afferent neural stimulus,
- The afferent limb: pain pathway,
- The efferent limb:

  A. Neural response: sympathetic system stimulation that causes:
  - An increase in the sympathetic tone to all viscera,
  - Catecholamine release from the adrenal medulla,
  - Renin-angiotensin-aldosterone stimulation,
  - Increased glucagon,
  - Decreased insulin and testerone,
  - Increased acute-phase proteins of liver

  B. Endocrinal response:

  Hypothalamic-pitutary adrenal stimulation that causes increased secretion of Adreno-Cortico-Trophic Hormon (ACTH), Growth hormone, antidiuretic hormone, B-endorphin, and prolactin

(b) The Cytokine Response (The Peripheral Response):

- The stimulus: local tissue damage at site of surgery itself. It is not associated with pain per se (without tissue damage).
- The response:

  A. Cytokine and inflammatory mediator release:
  - Increased IL-1, IL-6, and TNF that cause platelet adhesion

- Increased prostaglandins that increase coagulation and hypothalamic-pituitary-adrenal activity
- Increased neutrophils (that cause local inflammation and pain) and decreased lymphocytes.

B. Pyrexia (due to release of IL-I) it increase metabolic rate.

2.3.2 Degree of Response

The neuro-endocrinal stress response is proportional to pain intensity. Minor or superficial operations are associated with little or no stress, whereas major upper abdominal and thoracic procedures produce major stress (**Jacobi et al., 2002)**.

2.3.3 Effect of Neuro-Endocrinal Stress Response

1. Cardiovascular Effects:

- Increased blood pressure, heart rate, arrhythmias, and systemic vascular resistance which cause Increase myocardial O_2 demand and cause coronary vasoconstriction that predispose to ischemia and infarction.
- Increased cardiac output.

2. Respiratory Effects:

- Increased O_2 consumption and CO_2 production,
- Increased work of breathing,
- Pain due to abdominal or thoracic incisions causes guarding which:
  - Reduces TV and FRC, which causes atelectasis, intrapulmonary shunting V/Q mismatching, hypoxia and hypoventilation.
  - Impairs coughing and clearance of secrations.

3. **Gastrointestinal Effects:**
   - Increased sphincter tone,
   - Decreased intestinal motility,
   - Both predispose to ileus,
   - Increased gastric acid secretion, which predispose to stress ulceration,
   - Increased nausea and vomiting,
   - Constipation and abdominal distention,
   - All of these predispose to aspiration pneumonitis.

4. **Urinary Effects:**
   - Increased sphincter tone,
   - Decreased urinary motility,
   - Both predispose to urinary retention.

5. **Metabolic Effects (Hormonal Response):**
   - Increased catabolic hormones (catecholamins, cortisol, and glucagon),
   - Decreased anabolic hormones (insulin and testosterone),

   Both cause:
   - Protein catabolism,
   - Hyperglycemia and insulin intolerance,
   - Lipolysis,
   - Sodium and water retention.

6. **Hematological Effects:**

- Increased platelet adhesiveness,
- Decreased fibrinolysis,
- Hypercoagulability,
- All of these cause thrmbo-embolic phenomena and DVT.

7. Immune Effects:

- Leukocytosis with lymphopenia,
- Depressed reticulo-endothelial system,
- Both decreased the immunity and predispose to infection.

8. Psychological Effects:

- Anxiety,
- Sleep disturbances,
- Depression,

9. Chronic pain:

There is some evidence that patients who suffer acute pain are more likely to develop chronic pain (**Jacobi, et al., 2002)**.

2.3.4 Effects of Anesthesic Agents on Stress Response

- **General anesthesia** (intravenous and inhalational) **does not attenuate** the stress response irrespective of dose. To lesser extent, very high dose of doses of inhalational may have an effect.
- **High dose opioids** e.g., morphine 4mg/kg or fentanyl 50-100 mg/kg inhibit the neuro-endocrine stress response. If the opioid is given after

the surgical incision, it does not prevent the emergence of the stress response.

- **Local and regional anesthesia** greatly attenuates the neuro-endocrine stress response by blocking the non-nociceptive pathways **(Jodka and Heard, 2005)**.

2.4 Postoperative Pain

It is one of the most important acute types of pain. It produces neuro-endocrine stress response as any acute pain. Postoperative pain is the most concern and frightening aspect for the patients undergoing surgical procedures. Acute postoperative pain considered as the 5^{th} vital sign of the patient.

Postoperative pain control is generally **best managed by anesthesiologists** because they:

- offer regional anesthetic techniques,
- are experienced in the analgesic drugs, and
- have an idea about the patient's response to analgesics during anesthesia .

Selection of analgesic techniques is generally based on three factors; the patient, the procedure, and the setting (inpatient versus outpatient) **(Portenoy, 2003)**.

Postoperative pain management should begin preoperatively to:

- get the benefit of preemptive analgesia and so decreases the dose of analgesic requirement.

- **decrease the patient's anxiety and fear** of unrelieved pain which in turn decreases the postoperative pain **(Chong and Bajwa, 2003)**.

Mechanism of Acute Postoperative Pain: There is difference between postoperative pain and that from inflammation. It is mainly studied in animals. There is sensitization of nerve endings leading to spontaneous firing of nerve fibers, which constantly drive a pain system in the spinal cord after surgery whereas this is not the case with simple inflammation.

Some drugs are effective to treat either surgery whereas others can only treat one type of pain. Glutamate receptors of the NMDA subtype are essential to drive pain after inflammation but are not involved in pain after surgery. Some other authors say that NMDA receptor antagonists may prevent central sensitization which occurs following surgical trauma and tissue injury.

The isoenzyme cyclo-oxygenase-2 (COX-2) is activated during inflammation while cyclo-oxygenase-1 (COX-1) is activated during surgery, so cyclo-oxygenase inhibitors are effective analgesics in both inflammation and surgery **(Keogh and Herdenfeldt, 2002)**.

CHAPTER 3

MAGNESIUM SULPHATE

3.1 Physiological Properties

Magnesium (Mg^{+2}) plays a fundamental role in many cellular functions, such as storage, metabolism and energy utilization. It serves as a cofactor for various biologic processes including protein synthesis, neuromuscular function and nucleic acid stability (**Fawcett et al., 1999)**.

3.1.1 Sites and Mechanisms of Action for Magnesium

Magnesium is an intrinsic component of many adenosines 5'-triphosphatases and an endogenous regulator of several electrolytes **(Toyoshima and Mizutani, 2004)**. Being a noncompetitive inhibitor of inositol triphosphate-gated calcium channels, magnesium functions as an endogenous calcium antagonist by affecting its uptake and distribution. Magnesium also shows modulatory effects on sodium and potassium currents, thus influencing membrane potential. In the central nervous system, magnesium exerts depressant effects, acting as an antagonist at the N-methyl-D-aspartate (NMDA) glutamate receptor and an inhibitor of catecholamine release (Figure 3.1) **(Herroeder et al., 2011)**.

(1) Total Body Amount of Mg^{+2}:

A human adult body contains an average of 24 g (1 mol), (approximately 1000 mmol of magnesium) **(Herroeder et al., 2011)**.

(2) Magnesium Distribution in Adults:

- **Bone** (60%): With a half-life of 25 days. Bone Mg^{+2} is considered to be un-exchangeable,
- **Muscle** (20%): Exchangeable Mg^{+2},
- **Soft tissues** (20%): Exchangeable Mg^{+2},
- **ECF** (1%): Comprises 9% of all exchangeable Mg^{+2}, including 0.3% found in plasma.

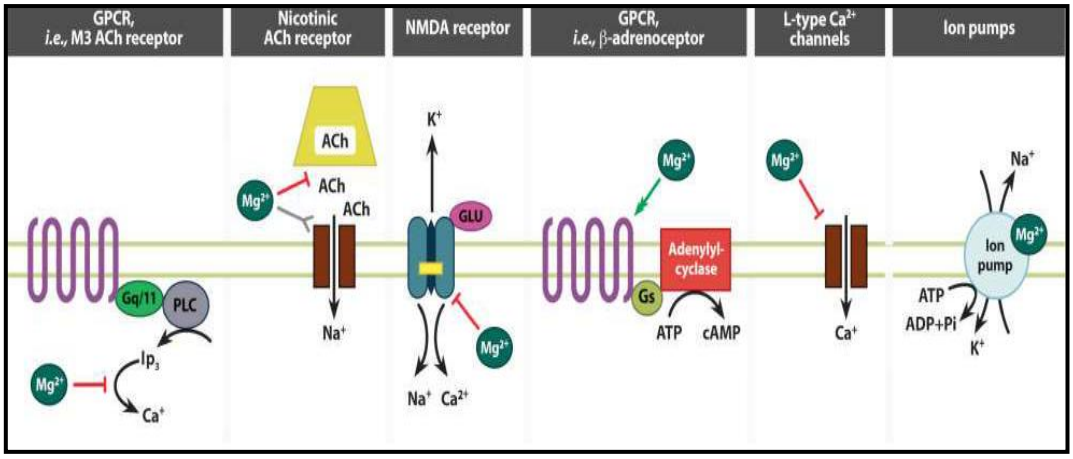

Figure 3.1: Sites and mechanisms of action for magnesium (Herroeder et al., 2011).

By modulating not only ion channels and ion pumps, but also receptor signalling, magnesium affects numerous cellular processes. Ach = acetylcholine; ADP = adenosine diphosphate; ATP = adenosine triphosphate; c-AMP = cyclic adenosine monophosphate; Glu = glutamate; GPCR = G-protein-coupled receptor; IP_3 = inositol triphosphate; NMDA = N-methyl-D-aspartate; iP = inorganic phosphate; PLC = phospholipase C.

3.1.2 Serum Magnesium

Serum is favoured over plasma for magnesium assay because the anticoagulant used for plasma samples can be contaminated with citrate or other anions that bind Mg^{+2} **(Elin, 1988)**. The normal range for serum magnesium depends on the daily magnesium intake, which varies according to geographic region. The normal range for healthy adults residing in The United States is shown in (Table 3.1) **(Elin, 1988)**.

Table 3.1: Reference ranges for serum Mg^{+2} pertain to healthy adults residing in the united states.

	Total	Ionized	Urinary
Traditional Units	1.4-2.0 mEq/L	0.8-1.1 mEq/L	5-15 mEq/day
SI Units	0.7-1.0 mmol/L	0.4-0.6 mmol/L	2.5-7.5 mmol/day

3.1.3 Ionized Magnesium

Only 60% of the magnesium in plasma in the ionized (active) form that regulates intracellular magnesium homeostasis, and the remaining 40% is either bound to plasma proteins (33% of the total) or chelated with divalent anions such as phosphate and sulphate (7% of the total) **(Mc Lean, 1994).**

The standard assay for magnesium (i.e., spectrophotometry) measures all three fractions of magnesium. Therefore, when the serum magnesium is abnormally low, it is impossible to determine whether the problem is a decrease in the ionized (active) fraction or a decrease in the bound fractions (e.g. Hypoproteinemia) **(Mc Lean, 1994)**.

The level of ionized magnesium can be measured with an ion-specific electrode or by ultra-filtration of plasma, but these techniques are not routinely available for clinical use. However, because the total amount of magnesium in plasma is small, the difference between the ionized and bound magnesium content may not be large enough to be clinically relevant **(Mc Lean, 1994)**.

3.2 Magnesium Homeostasis

Maintenance of magnesium homeostasis is largely regulated by intestinal absorption and renal excretion as below:

3.2.1 Intestinal Absorption of Magnesium

Magnesium is mainly absorbed in the small intestine via two different pathways depending on dose and formula of dietary intake: at low intraluminal concentrations predominantly by a saturable active transcellular

transport and with rising concentrations through nonsaturable passive diffusion (Table 3.2) **(Fine et al., 1991)**.

Table 3.2: GIT Absorption of Mg^{+2}. Data represented refer to a normal dietary intake of 300 mg/day. Approximately 40–50% of the dietary magnesium is absorbed (Fine et al., 1991).

Anatomical Site	Mg Absorption (mg/day)	% Absorption of Intake
Stomach	0	0
Duodenum	15	5
Jejunum	30	10
Proximal ileum	45	15
Distal ileum	30	10
Colon	15	5
Total	135	45

Little is known about the mechanisms underlying magnesium reabsorption in the distal convoluted tubule (DCT). As demonstrated for the small intestine, an active transcellular transport involving (TRPM6), a member of the transient receptor potential family of cation channels, localized along apical DCT membranes and at brush-border membranes of the duodenum, seems to play a role. Patients with mutation in the TRPM6 gene experience severe hypomagnesaemia and secondary hypocalcaemia **(Walder et al., 2002)**.

In Figure 3.2, **A** is intestinal absorption that follows a curvilinear kinetic resulting from two transport mechanisms: a saturable transcellular transport (dotted line) which is of functional importance at low intraluminal concentrations and a paracellular passive transport (dashed line) linearly rising with intraluminal magnesium concentrations **(J Physiol, 2005)**.

While **B,** in the thick ascending limb, magnesium is reabsorbed via the paracellular route. Here, a specific tight junction protein, paracellin-1 or

claudin-16, permits the selective paracellular flux of calcium and magnesium. Defects in paracellin-1 lead to combined calcium and magnesium wasting **(J Physiol, 2005)**.

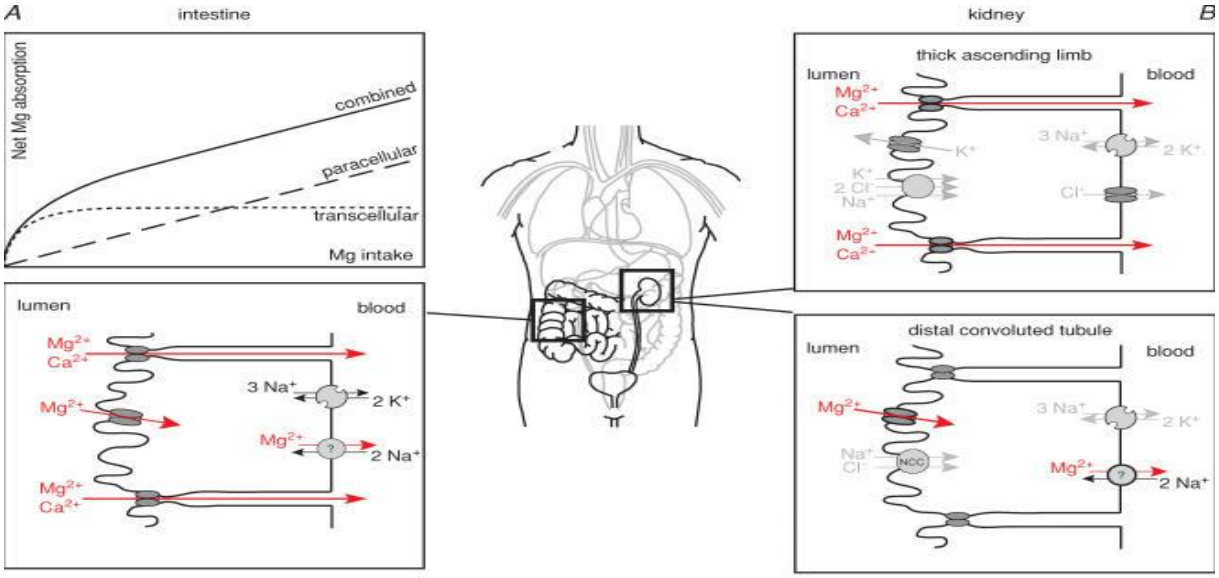

Figure 3.2: Epithelial magnesium transport in intestine and kidney (J Physiol, 2005).

The DCT reabsorbs magnesium in a transcellular fashion, consisting of an apical entry into the DCT cell through a magnesium-selective ion channel, and a basolateral extrusion of unknown molecular identity **(J Physiol, 2005)**.

3.2.2 Renal Handling of Magnesium

Under normal circumstances, only small quantities of magnesium are excreted in the urine. Urinary excretion of magnesium is normally 5 mmol/day if renal function is adequate but it can be decreased to less than 0.5% (~ 0.03 mmol/day) in the event of magnesium deprivation caused by extra renal losses. However, individuals are highly vulnerable to hypermagnesemia with loss of renal function **(J Physiol, 2005)**.

When magnesium intake is deficient, the kidneys conserve magnesium and urinary magnesium excretion falls to negligible levels and the serum magnesium remains in the normal range. This illustrates the relative value of urinary magnesium over serum magnesium levels in the detection of magnesium deficiency (**J Physiol, 2005)**.

In the kidneys, approximately 80% of plasma magnesium is ultrafiltered through the glomerulus, with more than 95% being reabsorbed by the consecutive segments of the nephron (Figure 3.3) **(J Physiol, 2005)**.

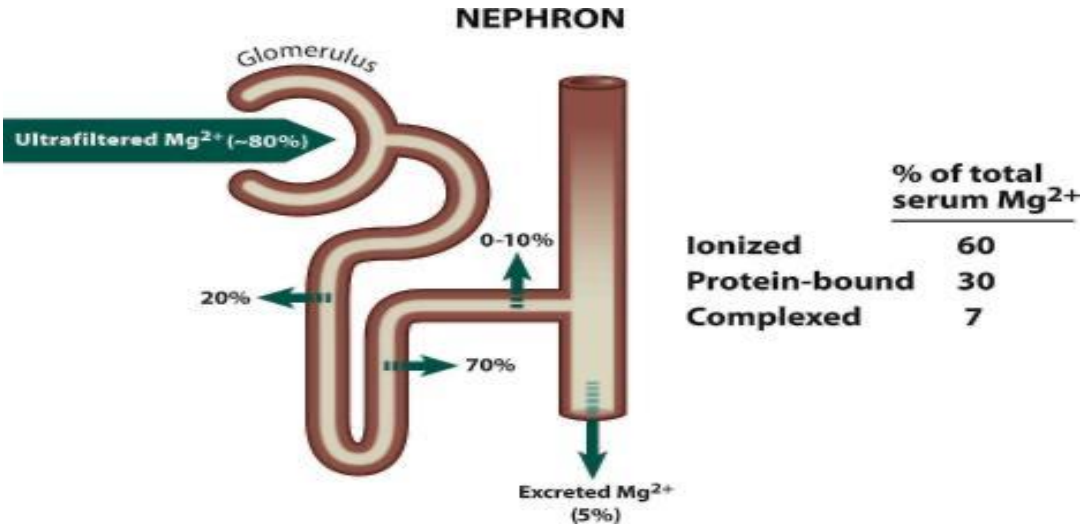

Figure 3.3: Schematic representation of the renal handling of magnesium. Normally 95% of the filtered magnesium is reabsorbed by the nephron (J Physiol, 2005).

The predominant site is the cortical thick ascending limb of the loop of Henle (70%), with the proximal and DCT accounting for only 15–25% and 5-10% of reabsorption, respectively. In the loop of Henle, magnesium is passively reabsorbed via paracellular diffusion, driven by an electrochemical gradient, resulting from reabsorption of sodium chloride. The tight junction protein Claudine 16 is believed to facilitate paracellular magnesium reabsorption because mutations in its encoding gene paracellin-1 cause a human hereditary magnesium-wasting syndrome (**Kausalya et al.**, **2006)**.

Factors that Affect Mg^{+2} Handling by the Kidney:

(1) Plasma Magnesium Concentration:

The most striking changes in magnesium excretion occur in response to alterations in plasma magnesium concentration. With marked acute or chronic hypermagnesemia due to high dietary intake or intravenous magnesium infusion, urinary magnesium excretion can approximate the filtered load of magnesium. Conversely, severe hypomagnesemia results in almost complete renal conservation of magnesium.

Thus, a major determinant of renal magnesium excretion appears to be the plasma magnesium concentration. **Quamme, 1986,** has suggested that the large increase in magnesium excretion occur following hypermagnesemia due to**:**

- Increased filtered load,
- Reduction in fractional reabsorption in the proximal tubules,
- Reduction in reabsorption in the ascending limb of loop of Henle **(Kausalya et al., 2006)**.

(2) Parathyroid Hormone (PTH):

The interrelationship between magnesium and PTH is complex. Parathyroid hormone secretion may be modulated by changes in plasma magnesium concentration as it is by changes in calcium concentration. Parathyroid hormone may enhance renal magnesium reabsorption and the resulting effects may depend on the opposing forces of elevated serum calcium and magnesium concentrations **(Kausalya et al., 2006)**.

(3) Adenosine Mono Phosphate (AMP) Mediated Hormones:

Including PTH, Anti-Diuretic Hormone (ADH), calcitonin and glucagon, **Costanzia and Windheget, 1980,** observed that all four hormones generally enhance Na^{+}, CI^{-}, K^{+} and Mg^{+2} reabsorption in the loop of Henle and distal tubule. This observation suggested that these might not be specific regulator mechanisms at least for magnesium **(Kausalya et al., 2006)**.

Accordingly, control of renal magnesium excretion by these factors is a combination of the independent hormonal effects apparently acting in concert with each other to provide electrolyte balance **(Kausalya et al., 2006)**.

(4) Thyroid Hormone:

Thyrotoxic patients often have a decreased serum magnesium concentration with increased urinary magnesium excretion. This is usually associated with an increase in plasma calcium concentration and hypercalcuria. Hypothyroidism on the other hand is consistently associated with a mean increase in plasma magnesium concentration possibly due to renal magnesium retention **(Kausalya et al., 2006)**.

(5) Adrenocortical Steroids:

Chronic administration of glucocorticoids usually leads to an increase in urinary excretion of both magnesium and calcium in animals and humans. This may be related to its catabolic effect on the bone with release of magnesium, or to the rise in glomerular filtration rate, which is often observed in this situation **(Konrad et al., 2004)**.

Chronic administration of aldosterone increased calcium and magnesium excretion and this effect was reversed by spironolactone administration or adrenal insufficiency **(Konrad et al., 2004)**.

The modest increase in magnesium excretion with chronic mineralocorticoid administration probably reflects a degree of volume expansion with an increase in the delivery of sodium, calcium and magnesium to the distal tubule **(Konrad et al., 2004)**.

(6) Other Hormones:

A variety of other hormones is thought to influence renal magnesium handling. Although their specific roles are not well understood, growth hormone has been reported to increase urinary magnesium as well as calcium. Infusion of angiotensin or catecholamines increases the urinary excretion of magnesium in proportion to calcium and sodium. Excretion of estrogens and androgens has been reported to either increase or have little effect on magnesium excretion **(Konrad et al., 2004)**.

(7) Plasma Calcium Concentration:

Hypocalcaemia of any etiology markedly increases magnesium excretion. **Shareghi and Agus, 1982,** observed that the increase in plasma calcium and magnesium affects the reabsorption of each other in the loop of Henle and this observation strongly supports the existence of calcium magnesium membrane interaction.

Hypocalcaemia may lead to enhanced mg^{+2} reabsorption. It may be that hypocalcaemia permits more complete calcium and magnesium reabsorption in the loop of Henle as the result of reduced competition for the transport system at the basolateral membrane **(Konrad et al., 2004)**.

(8) Sodium Balance and Extracellular Fluid Volume:

Extracellular volume expansion with saline or ringer solution produces an immediate increase in magnesium excretion. The high fractional magnesium excretion rate secondary to volume expansion persists despite reduction in renal artery perfusion pressure. The fractional reabsorption falls from 30 to 15% when the extracellular volume is expanded to 5% of the body weight.

Quamme, 1986, has found that the increased amount of magnesium delivered to the loop is largely excreted unchanged in the urine due to concomitant increase in distal salt delivery from the proximal tubule **(Kausalya et al., 2006)**.

(9) Phosphate Depletion:

The syndrome of phosphate depletion results in marked hypercalcuria and hypermagnesemia. In fact, the renal magnesium wasting may be sufficient to lead to overt Hypomagnesaemia. This defect may be corrected by the acute administration of parathyroid hormone or neutral phosphate infusion **(Kausalya et al., 2006)**.

(10) Acidosis and Alkalosis:

Acute metabolic acidosis in experimental animals uniformly results in an increase in urinary magnesium excretion. The changes observed in metabolic alkalosis are more consistent. Acute and chronic bicarbonate infusion leads to a fall in urinary magnesium excretion **(Kausalya et al., 2006)**.

(11) Drugs:

The homeostatic role of the kidney in maintaining the magnesium balance can be interfered by a number of drugs that affect the renal handling of magnesium and produce renal wasting of magnesium. **J Physiol, 2005,** reported these drugs that cause renal losses of magnesium as:

- Diuretics especially loop blockers, Factors influencing the effects of diuretics on the renal handling of magnesium **(J Physiol, 2005).**
  - Type of diuretic, including:
    - Site of action,
    - Duration of action,
  - Dose of diuretic,
  - Duration of diuretic treatment,
  - Underlying disease,
  - Nutritional intake of magnesium.
- Antibiotics especially aminoglycoside,
- Anticancer especially cisplatin,
- Immunosuppressive drugs especially cyclosporine,
- Alcohol,
- Nephrotoxic drugs:

  Cyclosporine produces nephrotoxic lesions such as amino glycosides, the anticancer drug cisplatin and the immunosuppressive agent, which are associated with renal wasting of magnesium.

3.2.3 Hormonal Control of Mg^{+2} Homeostasis

Regulation of magnesium transport lacks a specific endocrine control, although several hormones have been suggested to alter magnesium homeostasis. Parathormone and vitamin D stimulate magnesium renal and intestinal reabsorption respectively, whereas insulin may decrease renal excretion of magnesium and enhance its cellular uptake. The human body is not able to rapidly mobilize magnesium stores and exchange them with circulating magnesium to keep plasma concentrations within normal limits **(Saris et al., 2000)**.

3.2.4 Relation of Magnesium with Electrolytes

The relationship between magnesium and calcium has been the best documented. Absorption of both magnesium and calcium appears to be interrelated, with concomitant deficiencies of both ions is well described. A common link is that parathyroid hormone (PTH) and secretion of both is enhanced by hypocalcaemia.

Hypomagnesaemia impairs hypocalcaemia induced PTH release, which is corrected within minutes after infusion of magnesium. The rapidity of correction of PTH concentrations suggests that the mechanism of action of magnesium is enhanced release of PTH.

Magnesium is also required for the sensitivity of the target tissue to PTH and vitamin D metabolites. In contrast, calciotrophic hormones (PTH and calcitonin) have a profound effect on magnesium homeostasis, with PTH release enhancing magnesium reabsorption in the kidney, absorption in the gut and release from bone **(Saris et al., 2000)**.

A more fundamental interaction between magnesium and other ions occurs at the cellular level. Intracellular calcium concentrations are controlled

within narrow limits, with transient increases rapidly giving way to a return to normal levels. The release of intracellular calcium plays a key role in many cell functions, both basic (cell division and gene expression) and specialized (excitation, contraction and secretion).

A common pathway for the release of intracellular calcium from many stimuli such as hormones; growth factors and neurotransmitters is phospholipase C activation and hydrolysis of phosphatidyl inositol 4, 5-biphosphate into inositol 1, 4, 5-triphosphate (IP3). IP3 acts to open a calcium channel, which is part of the same molecule **(Saris et al., 2000)**.

Magnesium acts as non-competitive inhibitor of the IP3-gated calcium channel and of IP3 binding. Therefore, it may be considered as an intracellular calcium antagonist acting at IP, sensitive calcium release channels. It may also have a role as a calcium antagonist at other cell sites such as the ryanodine subgroup of calcium release channel receptors in the sarcoplasmic reticulum. In addition to interactions with calcium, magnesium has a marked effect on the regulation of transmembrane sodium and potassium movement **(Saris et al., 2000)**.

The importance of both intracellular magnesium ion ($Mg^{++}i$) and extracellular magnesium ion concentration ($Mg^{++}0$) is emphasized. ($Mg^{++}i$) blocks outward sodium and potassium currents whereas ($Mg^{++}0$) generally has an activating effect on ionic transport. Both ($Mg^{++}i$) and ($Mg^{++}0$) stimulate sodium-potassium ATPase at low concentrations and cause inhibition at high concentrations **(Saris et al., 2000).**

3.3 Magnesium and Diet

3.3.1 Daily Mg^{+2} Requirements: 250 - 300 mg/day

Dietary magnesium deficiency is more prevalent than generally suspected. The average diet is deficient in magnesium, especially in the young, in alcoholic persons, in those under stress, with diseases, or receiving certain drug therapies, and those who have increased magnesium needs.

It is widely assumed, that magnesium inadequacy is unlikely, however, the foods that are highest in magnesium as vegetables (especially legumes and dark green leafy vegetables), fish (including shellfish) and whole grains and nuts (Table 3.3), are not major constituents of the average diet. Nutrients that are high in diet, such as fat, sugar, salt, vitamin D, inorganic phosphate, proteins and more recently calcium supplementation and fibers all increase the dietary intake requirement of magnesium **(Konrad et al., 2004)**.

Table 3.3: High magnesium content foods (Konrad et al., 2004).

Type of foods	Magnesium content (mg%)
Cocoa and chocolate (bitter and sweet)	107-292
Nuts	132-411
Shellfish	34-414
Legumes	113-420
Grains and grain products	60-420
Dried fruit	59-92
Dark, leafy green vegetables	53-59

3.3.2 Recommended Dietary Allowance for Adults

The recommended dietary allowance is defined as, the amount of nutrient that maintains a balance of intake and output in healthy adult which is sufficient to assure health. The currently accepted nutritional

requirements for magnesium are summarized and listed by **Munro, 1980,** in (Table 3.4).

Analysis of worldwide metabolic balance studies showed that when (4 to < 5 mg/kg/day) of magnesium is taken, men tend to be in negative magnesium balance, whereas women remain in equilibrium but in areas where magnesium intake is higher (6 to > 8 mg/kg/day), both men and women were in positive magnesium balance during the studies. The decision that the recommended dietary allowance for magnesium in the stable adult should be 5-6 mg/kg/day was derived from the finding that maintenance of magnesium equilibrium was unreliable on lower intakes.

Table 3.4: Daily requirements for magnesium.

Period of life	Age-years	Daily need of Magnesium/day mg/day or (mEq/day)
Infant	0.0-0.5	50 (4.2)
	0.5-1	70 (5.8)
Children	1-3	150 (12.5)
	4-6	200 (16.6)
	7-10	150 (20.8)
Males	11-14	350 (29.2)
	15-18	400 (33.3)
	19-on	350 (29.2)
Females	11-14	300 (25.0)
	15-and on	300 (25.0)
	Pregnancy	450 (37.5)
	Lactation	450 (37.5)

3.3.3 Dietary Factors that Increase Magnesium Requirements

(1) Diets High In Saturated Fat:

Over consumption of saturated fat, which is accepted as a key factor in the high morbidity and mortality for cardiovascular disease, increases the need for magnesium. Magnesium deficiency alone has been shown to

cause cardiac and arterial pathologic changes in every species of animal in which it has been induced.

Fats form soaps with calcium and magnesium in the gut, thereby decreasing absorption of both fat and divalent cations. However, the protection afforded by high oral magnesium intake against both hyperlipidemia and cardiovascular lesions entails more than diminution of fat absorption. Magnesium supplementation decreases the enhanced thrombogenesis caused by high fat intake.

Magnesium is important in fat metabolism; the increase in magnesium intake exerts a favourable influence on adverse effects of diets too high in fat. **Rayssiguier et al., 1986,** found that the increase in low-density lipoproteins, very low-density lipoproteins and decreases in high-density lipoproteins are seen in magnesium deficient person. These changes were reversed with magnesium supplementation.

(2) Sugar:

Sugar loading causes magnesiuresis, possibly converting a marginal intake to a deficient one. Therefore, D.M. causes magnesium wasting **(Konrad et al., 2004)**.

(3) Calcemic Agents and Phosphates:

Among the other nutrients of which, the usual diet is likely to provide more than that is required, and excesses of which increase magnesium needs and are cardio-vasopathic, vitamin D is of interest as both a calcemic and hyperlipidemic sterol, and has been shown to be a steroid hormone. Vitamin D is often one of the components of experimental cardio-vasopathic diets against which magnesium is protective. Inorganic

phosphate, which is plentiful in the ordinary diet (through cola beverages and processed foods), is another component of cardio-vasopathic regimens.

Excess calcium is included in some of the cardio-vasopathic models and elevated myocardial calcium is characteristic of cardiac damage, the highest dietary Ca/Mg ratio, has the highest cardiovascular morbidity and mortality, and incidence of sudden death among young men.

(4) Alcohol:

Ethyl alcohol increases magnesium needs, even when taken in moderate quantities, through its enhancement of renal magnesium excretion. The efficacy of magnesium in treatment of the neuromuscular and cardiac disorder of alcoholism was early attributed to correction of the magnesium deficiency.

3.3.4 Physiological Factors Affecting Mg^{+2} Requirements

(1) Pregnancy, Growth and Development:

Studies show that magnesium intake in pregnant women has fallen, while their intakes of calcium, phosphate and vitamin D have risen. The lowest reported magnesium intake and reported negative magnesium balances during a long-term study during pregnancy were in Finland. Finland is the country with the lowest magnesium intake and the highest Ca/Mg ratio, as the highest cardiovascular morbidity and mortality rates in relatively young men **(Konrad et al., 2004)**.

Magnesium intake in pregnant American women of different economic status are about half (< 3 mg/kg/day) the recommended dietary

allowance, balance studies of white, middle-class, pregnant and American women have disclosed that low dietary magnesium results in negative magnesium balance during pregnancy. This is potentially a dangerous situation during a time when new tissue formation in mother and fetus mandates an adequate electrolyte supply.

Magnesium inadequacy during pregnancy may cause fetal arterial injury and is suggested by reports of coronary arterial lesions and generalized arteriosclerosis detected at autopsy in infancy and atherosclerosis and cardiac damage early in childhood **(Konrad et al., 2004)**.

(2) Aging:

The magnesium intake of the elderly tends to be low and the susceptibility to magnesium deficiency is intensified by diminish intestinal absorption and increased urinary output of magnesium. Elderly persons, who are subjected to disorders that impair absorption and renal function and who may be taking magnesium-wasting medications, are likely to be particularly vulnerable to magnesium deficiency.

Whereas long-standing magnesium deficiency affects the health of the aged and increases their susceptibility to adverse cardiac reactions to disease and drug that cause magnesium wasting deserves investigations. Transient ischemic cerebral attacks, to which the elderly are particularly prone, might be intensified by magnesium deficiency. Subjects who have added magnesium to their diets have been reported to be less likely to have transient ischemic events.

(3) Stress:

A variety of stresses, both psychological and physical, increase magnesium requirements and cause increased cellular magnesium loss. Stress and magnesium deficiency are mutually enhancing. Experimental magnesium deficiency has been shown to cause hypertrophy of juxtaglomerular index, which results in mineralocorticoid secretion, which in turn increases magnesium loss.

Vitro studies have shown that catecholamine secretion is increased by low Ca/Mg ratios and decreased by high Ca/Mg ratios in suspensions of catecholinergic cells of the adrenal cortex and ganglionic nerve endings. Subjects with personalities who have increase in urinary catecholamines and circulating free fatty acid levels, have been shown to have lower erythrocyte magnesium levels than do those with personalities who are less vulnerable to stress related cardiovascular disease **(Konrad et al., 2004)**.

3.4 Clinical Pharmacology

Magnesium sulphate is an organic salt (chemical compounded) containing magnesium, sulphur and oxygen, with the formula $MgSO_4$. Magnesium is an important cofactor for enzymatic reactions and plays an important role in neurochemical transmission and muscular excitability. As a nutritional adjunct in hyper alimentation, the precise mechanism of action for magnesium is uncertain. Early symptoms of hypomagnesemia (less than 1.5 mEq/L) may develop as early as three to four days or within weeks (**Peterson et al., 2006)**.

Predominant deficiency effects are neurological, e.g., muscle irritability, clonic twitching and tremors. Hypocalcaemia and hypokalemia often

follow low serum levels of magnesium. While there are large stores of magnesium present intracellular and in bones of adults, these stores often are not mobilized sufficiently to maintain plasma levels. Parenteral magnesium therapy repairs the plasma deficit and causes deficiency symptoms and signs to cease.

Magnesium prevents or controls convulsions by blocking neuromuscular transmission and decreasing the amount of Ach liberated at the end plate by the motor nerve impulse. Magnesium is said to have a depressant effect on the central nervous system (CNS), but it does not adversely affect the mother, fetus or neonate when used as directed in eclampsia or pre-eclampsia. Normal plasma magnesium levels range from 1.5 to 2.5 mEq/L.

As plasma magnesium rise above 4 mEq/L .the deep tendon reflexes are first decreased and then disappear as the plasma level approaches 10 mEq/L. At this level respiratory paralysis may occur. Heart block also may occur at this or lower plasma levels of magnesium. Serum magnesium concentrations in excess of 12 mEq/L may be fatal.

Magnesium acts peripherally to produce vasodilatation. With low doses only flushing and sweating occur, but larger doses cause lowering of blood pressure. The central and peripheral effects of magnesium poisoning are antagonized to extent by I.V administration of calcium (**Peterson et al., 2006)**.

3.4.1 Pharmacokinetics

With I.V administration, the onset of anticonvulsant action is immediate and lasts about 30 minutes. Following I.M administration, the onset of action occurs in about one hour and persists for three to four hours.

Effective anticonvulsant serum levels range 2.5 to 7.5 mEq/L. Magnesium is excreted solely by the kidneys at a rate proportional to the plasma concentration and glomular filtration **(Simhan and Caritis, 2007)**.

3.4.2 Medical Applications

Magnesium sulphate is a common pharmaceutical preparation of magnesium, commonly known as Epsom salts, used both externally and internally. Epsom salts are used as bath salts. The sulphate is supplied in a gel preparation for topical application in treating aches and pains. Oral magnesium sulphate is commonly used as a saline laxative or osmotic purgative. Magnesium sulphate is the main preparation of intravenous magnesium. Indications for internal use are **(Simhan and Caritis, 2007)**:

- Replacement therapy for hypomagnesaemia,
- Magnesium sulphate is the first-line antiarrhythmic agent for torsades de pointes in cardiac arrest under the 2005 ECG guide lines and for managing quinidine-induced arrhythmias,
- As bronchodilators after beta-agonist and anticholinergic agents has been tried, e.g in sever exacerbations of asthma. Studies conducted have revealed that magnesium sulphate can be nebulized to reduce the symptoms of acute asthma. It is commonly administered via the intravenous rout for the management of severe asthma attacks,
- Magnesium sulphate can be used to treat eclampsia in pregnant women,
- Magnesium sulphate can also delay labor (tocolysis) by inhibiting uterine muscle contraction in the case of premature labor, to delay preterm birth. However, meta-analyses have failed to support it as a tocolytic agent,

- Intavenous magnesium sulphate has been shown to prevent cerebral palsy in preterm babies. A recent systemic review suggests that antenatal intravenous magnesium sulphate can reduce the risk of cerebral palsy and gross motor dysfunction in preterm infants by on average 30%,
- Magnesium sulphate has been used as an experimental treatment of Irukandji syndrome caused by envenomation by certain species of Irukandji jellyfish, however the treatment remains unproven,
- Solutions of sulphate salts such as Epsom salt may be given as first aid for barium chloride poisoning.

3.4.3 Contraindications

Parenteral administration of the drug is contraindicated in patients with heart block or myocardial damage (**Peterson et al., 2006)**.

3.4.4 Precautions

In general, administer with caution if flushing and sweating occurs. When barbiturates, narcotics or other hypnotics (or systemic anesthetics) are to be given in conjugation with magnesium, their dosage should be adjusted with caution because of additive CNS depressant effects of magnesium.

Because magnesium is removed from the body solely by the kidneys, the drug should be used with caution in patients with renal impairment. Urine output should be maintained at a level of 100 ml or more during the four hours preceding each dose. Monitoring serum magnesium levels and the patient's clinical status is essential to avoid the consequences of overdose in toxemia.

Clinical indications of a safe dosage regimen include the presence of the patellar reflex (knee jerk) and absence of respiratory depression (approximately 16 breaths or more/min). When repeated doses of the drug are given parenterally, knee jerk reflexes should be tested before each dose and if they are absent, no additional magnesium should be given until they return.

Serum magnesium levels usually sufficient to control convulsions range from 3 to 6 mg/100ml (2.5 to 5 mEq/L). The strength of the deep tendon reflexes begins to diminish when magnesium levels exceed 4 mEq/L. Reflexes may be absent at 10 mEq magnesium/L, where respiratory paralysis is a potential hazard. An injectable calcium salt should be immediately available to counteract the potential hazards of magnesium intoxication in eclampsia.

Magnesium sulphate injection (50%) must be diluted to a concentration of 20% or less prior to I.V infusion. Rate of administration should be slow and cautious, to avoid producing hypermagnesemia. The 50% solution also should be diluted to 20% or less for I.M injection in infants and children **(Simhan and Caritis, 2007)**.

3.4.5 Laboratory Tests

Magnesium Sulphate injection should not be given unless hypomagnesmia has been confirmed and the serum concentration of magnesium is monitored. The normal level is 1.5 to 2.5 mEq/L.

3.4.6 Drug Interactions

CNS depressant (barbiturates, narcotics, other hypnotics or systemic anesthetics) when are given in conjugation with magnesium, their dosage

should be adjusted with caution because of additive CNS depressant effects of magnesium. CNS depressant and peripheral transmission defects produced by magnesium may be antagonized by calcium.

As regard neuromuscular blocking agents, excessive neuromuscular block has occurred in patients receiving parenteral Magnesium Sulphate and a neuromuscular blocking agent; these drugs should be administered concomitantly with caution. Also, with cardiac glycosides, magnesium sulphate should be administered with extreme caution in digitalized patients, because serious changes in cardiac conduction, which can result in heart block, may occur if administration of calcium is required to treat magnesium toxicity **(Simhan and Caritis, 2007)**.

3.4.7 Adverse Reactions

The adverse effects of parenterally administered magnesium usually are the result of magnesium intoxication. These include flushing, sweating, hypotension, depressed reflexes, flaccid paralysis, hypothermia, circulatory collapse, cardiac and CNS depression proceeding to respiratory paralysis. Hypocalcaemia with signs of tetany secondary to magnesium sulphate therapy for eclampsia has been reported (**Doyle et al., 2009b)**.

3.4.8 Over Dosage

Magnesium intoxication is manifested by a sharp drop in blood pressure and respiratory paralysis. Disappearance of the patellar reflex is a useful clinical sign to detect the onset of magnesium intoxication. In the event of over dosage, artificial ventilation must be provided until a calcium salt

can be injected I.V to antagonize the effects of magnesium **(Doyle et al., 2009b)**.

For treatment of overdose, artificial respiration is often required. Intravenous calcium, 10 to 20 ml of a 5% solution (diluted if desirable with isotonic sodium chloride for injection) is used to counteract effects of hypermagnesemia. Subcutaneous physostigmine, 0.5 to 1mg may be helpful. Hypermagnesemia in the newborn may require resuscitation and assisted ventilation via Endotracheal intubation or intermittent positive pressure ventilation as ventilation as well as I.V calcium **(Doyle et al., 2009b)**.

3.5 Recent Updates of Magnesium in Clinical Practice

(1) FAST-MAG Trial for Role of Magnesium in Stroke:

A large phase 3 clinical trial, the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) Trial studied 1,298 patients in June 2011 (International Standard Randomized Controlled serial Number NCT00059332) evaluated the benefit of field-initiated (within the first 2 h after onset of symptoms) magnesium in improving long-term functional outcome of patients with cerebral infarction and intracerebral haemorrhage.

The FAST-MAG Trial demonstrated that field initiation of magnesium sulphate in acute stroke is feasible, safe, and potentially efficacious. Based on these results, the large-scale, pivotal FAST-MAG Phase 3 trial of magnesium sulphate was planned with field initiation of study agent within 1-2h of onset, a time window not previously explored in neuroprotective studies, when the benefits of neuroprotective acute stroke therapies are likely to be greatest. By utilizing field delivery, the FAST-

MAG trial is the first neuroprotective study ever performed in the 0-2 hour window, when patients are most likely to benefit from neuroprotective interventions **(Saver et al., 2004)**.

(2) Role of Magnesium in Attenuation of Propofol Injection Pain

In comparative study of attenuation of the pain caused by propofol I.V injection, by granisetron, $MgSO_4$ and nitroglycerine, One hundred American Society of Anesthesiology (ASA) I and II adults, scheduled for various elective surgical procedures under general anesthesia (GA), were included in the study. They were randomly divided into four groups having 25 patients in each group.

Group A received pretreatment with I.V $MgSO_4$, group B received I.V granisetron, group C received I.V nitroglycerine and group D was the control group. One-fourth of the total calculated induction dose of propofol was administered over a period of 5 seconds. The patients were asked about the pain on injection. The intensity of pain was assessed using verbal response. A score of 0–3 which corresponds to no, mild, moderate and severe pain was recorded. All the three drugs reduced the incidence and intensity of pain on propofol injection. Granisetron was the most effective followed by nitroglycerine and $MgSO_4$ in attenuating pain on propofol I.V injection **(Singh et al., 2011)**.

(3) Role of Magnesium in Attenuation of Hemodynamic Stress Response to Pneumoperitoneum during Laparoscopic Chole-cystectomy

Both magnesium and clonidine are known to inhibit catecholamine and vasopressin release and attenuate hemodynamic response to Pneumoperitoneum. In a randomized, double blinded, placebo controlled

and comparative study designed to assess which agent attenuates hemodynamic stress response to Pneumoperitoneum better. 120 patients undergoing elective Laparoscopic Cholecystectomy (LCCE) were randomized into 4 groups of 30 each.

Group K patients received 50 ml normal saline over a period of 15 min after induction and before Pneumoperitoneum, group M patients received 50 mg/kg of magnesium sulphate in normal saline (total volume 50 ml) over same time duration. Similarly, group C_1 patients received 1 micg/kg clonidine and group C_2 1.5 micg/kg clonidine respectively in normal saline (total volume 50 ml). Blood pressure and heart rate were recorded before induction (baseline value), at the end of infusions and every 5 min after Pneumoperitoneum.

It was found that administration of $MgSO_4$ or clonidine attenuates hemodynamic response to Pneumoperitoneum. Although $MgSO_4$ 50 mg/kg produces hemodynamic stability comparable to clonidine 1 micg/kg, clonidine in doses of 1.5 micg/kg blunts the hemodynamic response to Pneumoperitoneum more effectively **(Nand et al., 2011)**.

(4) Effect of Magnesium Infusion on Thoracic Epidural Analgesia

In a recent study aimed to compare the efficacy of thoracic epidural block with (0.125%) bupivacaine, fentanyl combination and (0.125%) bupivacaine, fentanyl combination with adjunctive I.V magnesium infusion for the relief of postoperative pain in patients undergoing Lung Volume Reduction Surgery (LVRS).

Gupta et al. concluded that I.V magnesium could prolong Opioids-induced analgesia while minimizing nausea, pruritus, and somnolence. However, they could not state clearly whether this is the ideal dose or

higher doses might produce fewer side effects while prolonging analgesia. Furthermore, it might be suggested that magnesium may be considered as one of the ingredients of multimodal analgesic stratagems in reducing the severity of post-thoracotomy pain **(Gupta et al., 2011)**.

(5) I.V $MgSO_4$ versus Intrathecal Fentanyl, in Patients with Severe Preeclampsia, Scheduled for Caesarean Section, under Spinal Anesthesia

A double-blind (DB), prospective, randomized and controlled study of magnesium sulphate versus Intrathecal fentanyl, in patients with severe preeclampsia, scheduled for cesarean section, under spinal anesthesia. It was found that: I.V magnesium sulphate and Intrathecal fentanyl increased the duration of postoperative analgesia in severely preeclampsia patients undergoing cesarean section under spinal anesthesia; however, patients who received I.V $MgSO_4$ experienced lesser side effects than those who received intrathecal fentanyl **(Ahmed et al., 2011)**.

(6) Evaluation of Dose Effects of $MgSO_4$ on Rocuronium Injection Pain and Hemodynamic Changes by Laryngoscope and Endo-tracheal Intubation

Two hundred patients, ASA I and II, undergoing general anesthesia for elective surgery were randomly divided to 4 groups: group 1, 2, 3, 4 received saline 5 ml, magnesium 5, 10 and 20 mg/kg prior to 0.6 mg/kg of Rocuronium, respectively. Then, group 1 only was treated with esmolol (20 mg) before LTI. Pain intensity with Rocuronium injection was assessed using a four-point scale according to patient's movement.

Cardiovascular responses at baseline, after induction, 1 minute after LTI were determined. Compared to saline, 10 and 20 mg/kg of magnesium significantly reduced the incidence of overall movement after

Rocuronium injection (34% and 36% in group 3 and 4, respectively vs. 76% in the group 1). Generalized movement was seen in 4% of patients in groups 3 and 4, respectively.

Compared to baseline values, diastolic blood pressure immediately after LTI significantly increased within groups 1 and 2, but not within groups 3 and 4. Magnesium (10 and 20 mg/kg) prior to Rocuronium was effective in attenuating Rocuronium associated injection pain and cardiovascular changes by LTI **(Young et al., 2011)**.

(7) The Effects of Magnesium Sulphate Infiltration on Perioperative Opioids Consumption and Opioids-induced Hyperalgesia in Patients Undergoing Robot-Assisted Laparoscopic Prostat-ectomy with Remifentanil-based Anesthesia

Opioids not only exert an anti-nociceptive effect, but also modulate central NMDA receptors, resulting in hyperalgesia and acute Opioids tolerance. In this study, 75 patients scheduled for robot-assisted laparoscopic prostatectomy were randomly allocated into three groups of patients aimed to investigate the effect of the NMDA receptor antagonist, magnesium in preventing remifentanil-induced hyperalgesia. It was found that a relatively high dose and continuous infusion of remifentanil were associated with Opioids induced hyperalgesia. Wound infiltration with $MgSO_4$ decreased Opioids consumption and reduces Opioids induced hyperalgesia **(Cheol et al., 2011)**.

(8) Microcirculatory Changes during Open Label $MgSO_4$ Infusion in Patients with Severe Sepsis and Septic Shock

Fourteen patients (12 septic shocks, 2 severe sepsis) with a median APACHE II score of 20 were enrolled in a single-center open label study evaluated the effects of $MgSO_4$ infusion on the sublingual micro-

circulation perfusion in fluid resuscitated patients with severe sepsis and septic shock within the first 48 hours after ICU admission.

Directly prior to and after 1 hour of MgSO4 infusion (2 g) systemic hemodynamic variables, sublingual SDF images and standard laboratory tests, were obtained. No significant difference of the systemic hemodynamic variables was found between baseline and after $MgSO_4$ infusion. We did not observe any significant difference pre and post $MgSO_4$ infusion in the primary endpoint micro vascular flow index (MFI) of small vessels.

Other variables of microcirculatory perfusion were also unaltered. In the overall unchanged micro vascular perfusion, there was a non-significant trend to an inverse linear relationship between the changes of MFI and its baseline value. The correlation between baseline Mg concentrations and the change in MFI pre and post $MgSO_4$ infusion was non-significant **(Pranskunas et al., 2011)**.

(9) The Effects of Postoperative Brachial Plexus Block Using $MgSO_4$ on the Postoperative Pain after Upper Extremity Surgery

This study aimed to evaluate brachial plexus block using $MgSO_4$ on postoperative analgesia. 38 patients who were scheduled to undergo upper extremity surgery were randomly allocated into two groups: patients receiving axillary brachial plexus block with 0.2% Ropivacaine 20 ml and normal saline 2 ml (group S) or 0.2% Ropivacaine 20 ml and $MgSO_4$ 200 mg (group M).

Before extubation, the blocks were done and PCA was started, and then, the patients were transported to a post anesthetic care unit. The postoperative VAS, opioids consumption, and side effects were recorded.

The two groups were similar regarding the demographic variables and the duration of the surgery. No differences in VAS scores were observed between the two groups. There was no statistically significant difference in Opioids consumption between the two groups. Nausea was observed in three patients for each group. Axillary brachial plexus block using $MgSO_4$ did not reduce the level of postoperative pain and Opioids consumption **(In Gyu Choi et al., 2011)**.

(10) Evaluation of a Single-Dose of Intravenous $MgSO_4$ for Prevention of Postoperative Pain after Inguinal Surgery

This study was undertaken to study efficacy of single dose of I.V $MgSO_4$ to reduce post-operative pain in patients undergoing inguinal surgery. 100 patients undergoing inguinal surgery were divided randomly in two groups of 50 each. For the patients of $MgSO_4$ group, the radial artery was punctured with a 20-gauge catheter and used for monitoring continuous arterial pressure and blood sampling **(Kang et al., 2011)**.

After anesthesia induction, 4 g of magnesium was mixed with 100 ml normal saline and infused for 5 minutes. Magnesium, calcium, activated clotting time (ACT) and thromboelastographic parameters were checked before and 60 minutes after the magnesium infusion. The ECG changes after magnesium infusion were also checked before commencing Cardiopulmonary Bypass (CPB).

After magnesium infusion, the serum level of magnesium increased significantly but serum calcium did not change significantly. ACT did not change significantly before or after magnesium infusion. The thromboelastographic parameters showed no significant changes before or after magnesium infusion. None of the patients converted to sinus rhythm from AF after the magnesium infusion. Magnesium infusion did

not influence the course of AF and coagulation in patients during pre bypass period with AF undergoing mitral valve annuloplasty **(Kang et al., 2011)**.

(11) Effect of Magnesium Pre-treatment on Reperfusion Injury during Living Donor Liver Transplantation

Ischemia reperfusion (IR) injury is a complex phenomenon that leads to organ dysfunction and causes primary liver failure following liver transplantation. **Kim et al., 2011,** investigated whether an I.V administration of magnesium before reperfusion can prevent or reduce IR injury. Fifty-nine living donor liver transplant recipients were randomly assigned to an MG group (n = 31) or an NS group (n = 28).

Each group was also divided in two groups based on the preoperative magnesium levels (normal: $\geq$ 0.70 mmol/L, low: $<$ 0.70 mmol/L). The MG groups received 25 mg/kg of $MgSO_4$ mixed in 100 ml normal saline intravenously before reperfusion and the NS groups received an equal volume of normal saline. The levels of lactate, pH, arterial oxygen tension, and base excess were measured to assess reperfusion injury at five specific times, which were 10 min after the beginning of a hepatic phase, and 10, 30, 60 and 120 min after reperfusion **(Kim et al., 2011)**.

To evaluate postoperative organ function, the serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin and creatinine levels were measured at preoperative day 1, postoperative day 1 and 5. The blood lactate levels were significantly lower at 10, 30, 60 and 120 min after reperfusion in the MG groups compared to the NS groups **(Kim et al., 2011)**.

In addition, significantly higher blood lactate levels were observed in the NS group with preoperative hypomagnesaemia than in MG groups. Magnesium administration before reperfusion of liver transplantation significantly reduces blood lactate levels. These findings suggest that magnesium treatment may have protective effects on IR injury during living donor liver transplantation **(Kim et al., 2011).**

CHAPTER 4

ANESTHETIC IMPLICATIONS OF MAGNESIUM

4.1 Magnesium and Anesthesia

At the beginning of the last century, magnesium was proposed to induce anesthesia effectively. Although later studies could not support this hypothesis and seriously questioned sufficient blood–brain barrier penetration of intravenous magnesium (and thus a true central nervous system effect of the drug itself), magnesium has been suggested for reducing anesthetic requirements, attenuating cardiovascular effects from laryngoscopy and intubation, and exerting muscle-relaxing effects **(Sasaki et al., 2002)**.

4.1.1 Mechanisms of Action

Details of the mechanisms underlying the anesthesia-enhancing effects of magnesium remain unknown **(Sasaki et al., 2002)**.

1. A competitive antagonism on hippocampal presynaptic calcium channels that regulate neurotransmitter release in the central nervous system has been suggested. Volatile anesthetics, such as isoflurane, are thought to partially induce anesthesia by inhibition of these channels.
2. Attenuation of catecholamine release from the adrenal medulla and calcium antagonistic effects on vascular smooth muscle cells also may contribute to the anesthetic effects of magnesium.
3. In terms of neuromuscular blockade, the inhibition of calcium-mediated release of Ach from the presynaptic nerve terminal at the neuromuscular junction plays an important role. A decrease of postsynaptic sensitivity to Ach and direct effects on the membrane potential of myocytes also may contribute.

4.1.2 Magnesium and Hypnotics

There are greater differences in the results of clinical trials on anesthetic actions of magnesium. Two double blind, randomized, and controlled trials demonstrated a reduction of propofol requirements guided by Bispectral Index monitoring after administration of I.V $MgSO_4$ (bolus of 30 mg/kg, followed by continuous infusion of 10 mg/kg/h until end of surgery) in patients undergoing spinal surgery.

However, in one study magnesium also significantly delayed postoperative recovery for patients receiving magnesium and control patients, respectively **(Gupta et al., 2006)**.

In a study performed over 60 elective surgery patients, who neither were premedicated nor received any other drugs for induction of anesthesia, **Durmus, et al.** observed an increased Minimal Alveolar Concentration (MAC) of sevoflurane at the time of skin incision when magnesium was administered before anesthesia induction. Agitation and flushing, side effects observed only in magnesium-treated patients may have counteracted potential anesthetic effects.

Pretreatment with 2.48 mmol I.V $MgSO_4$ was found to reduce the incidence and intensity of etomidate-induced myoclonic movements during induction of anesthesia. Moreover, catecholamine release and cardiovascular effects in response to tracheal intubation were found to be attenuated by I.V magnesium in most clinical trials (**Durmus et al., 2006)**.

4.1.3 Magnesium and Analgesia

Several animal and human studies report antinociceptive effects of magnesium when administered intravenously or intrathecally.

4.1.3.1 Mechanisms of Action

1. Inhibition of calcium influx (calcium channel blockers augment morphine-induced analgesia and decrease total opioid consumption).
2. Antagonism of NMDA receptors and the prevention of enhanced ligand-induced NMDA signaling in a state of hypomagnesemia.
3. In addition, magnesium seems to attenuate or even prevent central sensitization after peripheral tissue injury or inflammation because of inhibition of dorsal horn NMDA receptor **(Czarnetzki et al, 2010)**.

Since the early 1990's, the effects of magnesium on postoperative pain and Opioids consumption have been studied intensively. However, study results are varied. Whereas most studies describe decreased intra- and postoperative analgesic requirements after Mg^{+2} supplementation, a few report no or insignificant beneficial effects **(Tramer and Glynn 2007)**.

A symptomatic review in 2007 that included 14 randomized trials failed to provide convincing evidence. Differences in dose and onset of magnesium administration; type of magnesium salt and pain scores used, as well as choice of patient population; standard baseline pain medication; and anesthesia may contribute to these inconsistencies in the literature.

For instance, $MgSO_4$ was most recently shown to significantly decrease visual analog scale scores as well as total patient-controlled analgesia drug (morphine and ketorolac) consumption in patients undergoing total hip arthroplasty at 4-48 h after surgery. I.V $MgSO_4$ was given as a bolus (50 mg/kg) 15 min before induction of spinal anesthesia, followed by a continuous infusion (15 mg/kg/h) until the end of surgery **(Tramer and Glynn 2007)**.

However, in a comparative study with oral Nifedipine, intravenous Nimodipine, and Magnesium Sulphate in Postoperative Analgesia **Zarauza, et al.,** found no beneficial effects of $MgSO_4$ on postoperative pain, as assessed by visual analog scale and morphine consumption, when given as an adjunct to general anesthesia in colorectal surgery patients. An initial bolus of 30 mg/kg given 20 min after induction of anesthesia was followed by a continuous $MgSO_4$ drip 2 g/h for 20 h. Intraoperative anesthesia was maintained using continuous infusion of fentanyl, whereas postoperative analgesia was provided by a morphine patient-controlled analgesia device **(Zarauza et al., 2000)**.

In conclusion, the use of oral nifedipine, I.V nimodipine, or magnesium sulphate at normal clinical doses failed to decrease postoperative morphine requirements in patients undergoing colorectal surgery. Therefore, their clinical use specifically for postoperative pain management may not be justified. It is possible that the use of L-CCBs or magnesium sulphate by other routes of the administration (intrathecal/epidural), with or without opioids, may offer clinical advantages **(Zarauza et al., 2000)**.

4.1.3.2 Magnesium and Pre-emptive Analgesia

The concept of pre-emptive analgesia was introduced in by **Woolf and Thompson**. They demonstrated through experimental studies that post injury pain hypersensitivity results via a central mechanism. Pre-emptive analgesia has been defined as an antinociceptive treatment that prevents the establishment of altered central processing of afferent input from injuries (**Woolf and Thompson, 1991)**.

Therapies that have been tested in pre-emptive trials include NSAIDS, intravenous opioids, intravenous ketamine, peripheral local anesthetics, caudal and epidural analgesia, dextromethorphan and gabapentin. One intravenous adjuvant medication that has shown potential in pre-emptive analgesia is magnesium **(Kissin, 2000)**.

Table 4.1: Important clinical trials of $MgSO_4$ as analgesic with respect to study design and outcome (Herroeder et al., 2011).

Reference & Study Type	Study-Population	Anesthesia & Analgesia	Study Drug	Results	Favours $MgSo_4$
Bilir et al., 2007, PRCT, db n=50	Hip replacemnt	CSE (hyperbaric bupi)	PCEA (fenta 25 micg ± $MgSo_4$ 50 mg bolus & cont. inf 100 mg/24 h)	Sign smaller doses & total consumption of epidural fenta ($MgSo_4$)	+
Kaya et al., 2009, PRCT, db n=40	Abd. HE	Thiopental, Cisatracurium, Remifentanil, Sevoflurane, morphine-PCA (postop.)	30 mg/kg $MgSO_4$ 15 min before induction, con. inf. 500 mg/h	Sign of decreased total morphine consumption (MgSo4)	+
O'Flaherty et al., 2003, PRCT, db n=80 (3-12y/0)	TE	Sevoflurane, N_2O, fent (periop.) paracetamol, codeine (postop.)	30 mg/kg $MgSO_4$ bolus preop.	No effect on postop. Pain or analgesic consumption	-
Tramer et al., 1996, PRCT, db n=200	Ambulatory ilioinguinal hernia repair or varicosis surgery	Propofol, fenta, isoflurane/N_2O diclo (ilio-inguinal-ilio-hypogastric nerve block)	4 g $MgSO_4$ after induction	No difference in time to first rescue analgesic or pain intensities	-
Mentes et al., 2008, PRCT, db n=83	LCCE	Fenta, propofol, cisatracurium, sevoflurane/N2O tramadol-PCA (postop.)	50 mg/kg $MgSO_4$ intraop.	Sign lower pain Scores no difference in total tramadol	+/-
Ozcan et al., 2007, PRCT, db n=24	Thoracotomy	Propofol, fenta, vecuronium, morphine-PCA (postop.)	$MgSO_4$ 30 mg/kg cont. inf. 10 mg/kg/h (postop.)	Significant decreased morphine consumption, no difference in pain scores	+/-

abd. = abdominal; bupi = bupivacaine; cont. = continuous; CSE = combined spinal epidural; diclo = diclofenac; fenta = fentanyl; HE = hysterectomy; inf. = infusion; intraop. = intraoperative; $MgSO_4$ = magnesium sulphate; N_20 = nitrous oxide; PCA = patient controlled analgesia; PCEA = patient controlled epidural analgesia; periop. = perioperative; postop. = postoperative; PRCT = prospective randomized placebo-controlled trial; sign. = significant.

4.1.4 Magnesium and Muscle Relaxants

It has been shown that magnesium produces dose-related inhibition of neuromuscular transmission by competition with calcium for membrane channels on the presynaptic terminals, leading to a decrease in Ach release. Thus, the potential exists for possible interaction between magnesium and muscle relaxants used during anesthesia **(Ozcan et al., 2007)**.

(a) Magnesium and Depolarizing Neuromuscular Blocking Agents:

The clinical effects of $MgSO_4$ on depolarizing muscle relaxants seem to be rather small. $MgSO_4$ does not interfere with onset and duration of succinylcholine-induced neuromuscular block but seems to prevent associated muscle fasciculations and may attenuate potential succinylcholine-induced increases of serum potassium.

(b) Magnesium and Non-depolarizing Neuromuscular Blocking Agents:

Magnesium has been shown to potentiate non-depolarizing neuromuscular blocking agents. After a dose of magnesium sulphate 40 mg/kg, the ED_{50} of vecuronium was reduced by 25%, the onset time was nearly halved and recovery nearly doubled **(Ozcan et al., 2007)**.

The reduction in onset time of non-depolarizing blockers has been used clinically to produce intubation conditions more rapidly. The concept of priming to produce a more rapid onset of block involves sequential administration of 20-30% of ED_{95} of a non-depolarizing agent followed 4-6 minutes later by ED_{95}. Magnesium sulphate has been shown to produce rapid onset of block when used as priming agent with pancuronium **(Ozcan et al., 2007)**.

In patients undergoing cardiac surgery, administration of magnesium sulphate, resulting in ionized levels of 1.3 mmol/L, results in a 30–35 min prolongation of the neuromuscular blockade induced with intubating and maintenance doses of cisatracurium and does not alter hemodynamic stability. Magnesium sulphate given 15 min before propofol anesthesia reduces the onset time of Rocuronium by about 35% and prolongs the total recovery time by about 25% **(Ozcan et al., 2007)**.

4.2 Magnesium and Obstetrics

Magnesium sulphate was first used to prevent eclamptic seizures in 1906 by Horn in Germany, who injected it Intrathecal. An intramuscular regimen was used in 1926 to prevent recurrent seizures in women with eclampsia and the drug was given intravenously in 1933 to women with preeclampsia and eclampsia **(Idama and Lindow, 1998)**.

4.2.1 Preeclampsia

Preeclampsia is a multisystem disorder of unknown origin. It complicates 3–10% of pregnancies and is a major cause of maternal and fetal morbidity and mortality **(Mac et al., 2001)**.

Preeclampsia is defined as new-onset hypertension and proteinuria developing after the 20^{th} week of gestation up to several weeks after delivery, and it may be aggravated by seizures or coma (eclampsia). Underlying mechanisms include an abnormal vascular response to placentation with increased systemic vascular resistance, enhanced platelet aggregation, stimulation of inflammation and coagulation, and endothelial dysfunction **(Mac et al., 2001)**.

- ***Action of Magnesium Sulphate in Pregnancy Induced Hypertension:***

1. Magnesium seems to improve clinical symptoms of Pre-eclampsia and eclampsia primarily by systemic, cerebral, and uterine vasodilation **(Sibai et al, 2005)**.
2. In addition to having a direct effect on the vessels, magnesium was shown to increase concentrations of the two endogenous potent vasodilators endothelium-derived relaxing factor and calcitonin gene-related peptide and attenuate circulating concentrations of endothelin-1, an endogenous vasoconstrictor **(Halhali et al., 2001)**.

It was found that magnesium attenuated peroxide-induced vasoconstriction in isolated human placental cotyledons by inhibition of thromboxane synthesis and calcium channel antagonism. Evaluation of potential risks and benefits of magnesium in Preeclampsia and eclampsia requires differentiation of its administration in mild to severe forms of Preeclampsia, in the prevention of eclampsia or its progression, and in treatment of eclamptic convulsions **(Halhali et al., 2001)**.

- ***Mild Preeclampsia:***

A total of 357 patients with well-defined mild Preeclampsia were randomized during labor or the postpartum period in two different double-blind and placebo-controlled trials. No difference in rate of seizures (none in both groups) or in the progression to severe Preeclampsia between women receiving placebo or magnesium (12.5 and 13.8%, respectively) could be observed. One study reported higher rates of postpartum hemorrhage and adverse effects in two cases after magnesium treatment. However, other studies reported a beneficial effect of magnesium in this particular stage of disease **(Halhali et al., 2001)**.

A decision analysis of whether magnesium should be used for seizure prophylaxis in patients with mild Preeclampsia indicated that both (magnesium & no-magnesium) clinical strategies are acceptable and should be selected based on values and preferences of the patient and clinician. Both strategies were considered essentially equivalent with regard to outcome because the no-magnesium strategy was associated with a reduction of neonatal mortality and maternal side effects but also an increased risk of maternal death and neurologically compromised neonates **(Halhali et al., 2001)**.

In a prospective observational study, **Alexander, et al.** compared the effects of magnesium prophylaxis for all women with gestational hypertension or Preeclampsia to administration of $MgSO_4$, only if mild Preeclampsia progressed to severe disease. They observed a 50% overall increase in the prevalence of eclampsia and a subsequent increase in maternal and neonatal morbidity when $MgSO_4$ was applied only to women with disease progression **(Alexander et al., 2006)**.

- ***Severe Preeclampsia:***

In addition to several case reports and smaller studies, four large trials evaluated the effects of I.V magnesium on the prevention of eclamptic convulsions in 12,673 patients with severe Preeclampsia. The main study was conducted at 175 hospitals in 33 countries that included 10,110 women (42.5% defined as having severe or imminent Preeclampsia in each group). Although a significant risk reduction was found for seizures in women assigned to magnesium administration, results were criticized because of heterogeneous clinical characteristics and poorly defined aspects of patient care. However, as demonstrated in an extensive review by **Sibai**, the overall results of these trials indicate a significantly smaller incidence of eclampsia **(Sibai, 2004)**.

Moreover, no adverse effects on maternal or fetal/neonatal morbidity were observed, although respiratory depression was significantly higher after magnesium prophylaxis in severely pre-eclamptic women.

A Cochrane review including nine trials evaluating the effects of magnesium in the progression of Preeclampsia to eclampsia found a more than 50% risk reduction compared with placebo. No difference in neonatal and maternal mortality was observed. Approximately 25% of magnesium-treated women experienced side effects, mainly flushing **(Belfort et al., 2003)**.

4.2.2 Eclampsia

Eclampsia is believed to complicate 1 in 100 to 1 in 1700 pregnancies in developing countries and 1 in 2000 pregnancies in Europe and the developed world. Magnesium sulphate has been the first-choice drug in The USA since the 1930's for controlling the first fit and for preventing further fits yet only 2% UK obstetricians admit to having used it.

The Collaborative Eclampsia Trial including 1,687 patients, showed a clear benefit of magnesium on seizure recurrence (52% and 67% lower risk for additional convulsions compared with diazepam and phenytoin, respectively), but found no differences in maternal morbidity and mortality. Cochrane systematic reviews confirmed that $MgSO_4$ is more effective than diazepam, phenytoin, or a "lytic cocktail" (usually a mixture of chlorpromazine, promethazine, and pethidine) for treatment of eclampsia **(Duley, 2009)**.

- ***Action of Magnesium Sulphate in Eclampsia:***

The precise site of action of magnesium sulphate in eclampsia is not known.

1. Experimentally, magnesium has been shown to block the NMDA subtype of glutamate channel, which during cerebral ischemia leads to lowering of the trans-membrane potential allowing calcium ion influx across the membrane and from the endoplasmic reticulum and mitochondria. This leads to further calcium influx as membrane phospholipids are hydrolysed by activated enzymes. Magnesium blocks calcium at intracellular sites in addition to the outer lipid membrane. This could make it superior to conventional calcium antagonists that act only on the outer membrane **(Duley et al., 2003)**.
2. Experimentally, magnesium has been shown to protect hippocampal cell cultures from anoxia and glutamate and has been shown to prolong the ischemic time before irreversible cell damage in the spinal cord.
3. Direct neuromuscular block has also been suggested as a mechanism of action in eclampsia, but this seems unlikely as serum concentrations well below those needed to suppress neuromuscular transmission exert anti-eclamptic effects.
4. Calcium and magnesium act as antagonists of each other in blood vessel tone regulation. Increases in calcium ion concentration cause vasospasm which is reversed by magnesium and worsened by lowering magnesium concentrations.

4.2.3 Magnesium and Tracheal Intubation in Obstetrics

Tracheal intubation of patients with hypertensive disorders in pregnancy causes marked increases in systemic arterial, pulmonary arterial and pulmonary capillary wedge pressures leading to increased risk of intracerebral hypertensions and hemorrhage.

Conventional strategies for obtunding the hypertensive response to intrubation, such as (β blocker, topical local anesthesia, opioids and vasodilators appear to be less effective in Preeclampsia.

Magnesium sulphate has been shown to obtund the hypertensive response to intubation in patients with Preeclampsia. **Allen et al.** showed no increase in systolic arterial pressure for 5 min after intubation in women pretreated with magnesium sulphate 40 mg/kg or alfentanil 10 micg/kg, but a significant increase in women pretreated with lidocaine 1.5 mg/kg. Both magnesium sulphate and alfentanil had side effects at these doses, with magnesium causing tachycardia and alfentanil causing neonatal depression. The mechanism of action appears to be the inhibition of catecholamine release from the adrenal medulla with epinephrine concentrations unchanged from, baseline and a significant decrease in the increase in norepinephrine concentrations compared with controls **(Allen et al., 1991)**.

4.2.4 Magnesium Sulphate as Tocolytic

Preterm birth is defined as birth before 37 weeks of gestation and is associated with a significant risk of neurologic morbidity and early neo-natal mortality. Its exact pathophysiology remains unknown, but different maternal and fetal factors, such as poly- or oligohydramnios, intrauterine infection, or uterine over distension resulting in premature ruptures of membranes, fetal endocrine activation, etc. Magnesium seemed to play a significant role in preterm labor and birth and it is widely used as a tocolytic agent in different parts of the world and has been shown to attenuate uterine contractility in vitro and in vivo.

Underlying mechanisms include a decrease in intracellular calcium concentration and a subsequent inhibition of myosin light-chain kinase.

However, results of clinical trials have not been convincing. Large clinical trials have not shown any benefit of magnesium over placebo or nifedipine in the delay of delivery **(Simhan and Caritis, 2007)**.

A recent randomized controlled trial in Kyushu Island (Japan) revealed that adjuvant magnesium with ritodrine significantly reduced uterine contractions than magnesium alone, when uterine contractions are intractable with ritodrine infusion. In addition, when used in the prior treatment of Preeclampsia, magnesium did not affect duration of labour, although a higher dose of oxytocin is necessitated **(Simhan and Caritis, 2007)**.

4.2.5 Magnesium and Placental Blood Flow

The utero-placental unit may also be affected favourably by magnesium sulphate. Gravid ewes receiving magnesium sulphate towards the end of gestation showed a decrease in mean arterial pressure but an increase in uterine blood flow and fetal PaO_2 **(Simhan and Caritis, 2007)**.

4.2.6 Magnesium and Fetal Heart Rate

In humans, fetal heart rate variability in utero showed no significant changes during infusion of magnesium sulphate, but only a small increase after a bolus dose was given to preeclamptic patients **(Simhan and Caritis, 2007)**.

4.2.7 Magnesium and Fetal Neuroprotection

The multicenter, placebo-controlled and double-blind Beneficial Effects of Antenatal Magnesium Sulphate (BEAM) Trial showed no beneficial effect of antenatal $MgSO_4$ on the combined risk of moderate or severe

cerebral palsy or death when given to women at immolinent risk for delivery at 24 through 31 weeks of gestation. However, $MgSO_4$ significantly decreased the risk of moderate or severe cerebral palsy among surviving children.

This finding was recently confirmed by a Cochrane database review evaluating five trials with a total of 6,145 neonates. Antenatal magnesium given to women at risk of preterm birth substantially reduced the risk of cerebral palsy, there was a significant reduction in the rate of substantial gross motor dysfunction, but pediatric mortality or other neurologic impairments were not affected **(Doyle et al., 2009a)**.

4.2.8 Treatment Regimens and Monitoring of $MgSO_4$ in Obstetric

Although there have been many different treatment regimens over the past 70 years for the use of magnesium sulphate in pregnancy, it is now being suggested that the regimens used in the Eclampsia Trial Collaborative Groups study should be used as standard, as they have been proved to produce a beneficial effect without risk of side effects **(Doyle et al., 2009a)**.

Monitoring of serum magnesium has been used to assess therapeutic concentrations and adverse effects. Target serum concentrations have been suggested to range from 2 to 4 mmol/L, with side effects such as loss of reflexes and respiratory depression occurring at concentrations of more than 5 and 7 mmol/L respectively. However, serum monitoring was not undertaken in the Eclampsia Trial Collaborative Groups study, but data on similar regimens suggest that serum concentrations of magnesium would have been less than 2 mmol/L. Monitoring of patellar reflexes and ventilatory frequency may be of equal benefit to monitoring serum concentrations, as loss

of the patellar reflexes occurs well before respiratory depression and arrest **(Rouse et al., 2008)**.

4.3 Magnesium and CVS

4.3.1 Magnesium and Myocardial Infarction

Acute myocardial infarction (AMI) and related arrhythmias are still one of the major causes of death in the United States and most western countries **(Bederson et al., 2009)**.

Mechanisms of action of magnesium in AMI **(Bederson et al., 2009)**:

1. Magnesium was found to induce coronary and systemic vasodilation to improve metabolism of cardiomyocytes, and to attenuate ischemia–reperfusion injury.
2. Magnesium was shown to inhibit platelet aggregation and to prevent thrombosis in micro vascular surgery. A possible anti-atherosclerotic effect was demonstrated in patients with IHD with increase in high to very-low-density lipoprotein ratio.
3. Reduction of myocardial oxygen consumption (MVO_2) secondary to direct depression of contractility reduced systemic overload, and attenuation of catecholamine-induced elevated oxygen demand.
4. Additional systemic anti-catecholamine effects, including suppression of noxious stimulation-induced noradrenaline release and associated hemodynamic effect.
5. It is supposed that during AMI magnesium may reduce cytoplasmic calcium overload and protect mitochondria against calcium influx, which is the leading cause of myocardial cell death.

6. Magnesium acted as a cofactor of enzymes, Na^+/K^+ adenosine 5-triphosphatase and Ca adenosine 5-triphosphatase, which are important regulators of myocardial membrane stability.
7. Intravenous application of magnesium is supposed to prevent cellular depletion of magnesium. Magnesium is supposed to lower potassium loss through obstructing effect upon potassium channels.
8. Magnesium prolongs the absolute refractory period and shortens the relative refractory period, thereby reducing the incidence of infarction related arrhythmias.
9. Hypomagnesemia is associated with a higher incidence of lethal arrhythmias after AMI, whereas intravenous administration of magnesium reduced early mortality.

Dosage of $MgSO_4$: 50 mmol (12.5 g) for the first 24 h and 12 mmol (3 g) for the second 24 h) decreased 30-day mortality to 6.7% (17% for control patients when given within 3h after hospital admission. Infarct size could also be limited when magnesium was administered within 15–45 min after reperfusion of the coronaries **(Ying et al., 2007)**.

4.3.2 Major Clinical Trials on the Role of Magnesium on Ischemia

Major clinical studies on the role of magnesium on ischemia–reperfusion injury have been conducted because reperfusion injury after myocardial ischemia was shown to crucially affect patients'outcome. However, inconsistent data were obtained.

- ***Leicester Intravenous Magnesium Intervention Trial, 1992:***

In the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2), 2,316 patients with assumed myocardial infarction were

included and they received either 8 mmol (2 g) $MgSO_4$ for 5 min, followed by 65 mmol (16.25 g) for 24 h, or placebo. All cause mortality at 28 days in the treatment group was significantly less than that of control patients.

- ***Fourth International Study of Infarct Survival, 1995:***

In the fourth International Study of Infarct Survival (ISIS-4), 58,050 patients with suspected myocardial infarction were included and randomized to either $MgSO_4$ treatment (8 mmol (2 g) for 15 min, followed by 72 mmol (18 g) over 24 h) or standard care. Thrombolytic therapy was administered in both groups as indicated. 35 days after hospital admission, an insignificant increase in mortality (6%) as well as a significantly higher rate of bradycardia, heart failure, and death caused by cardiogenic shock after magnesium treatment were observed. These effects were suggested to result from significant induced hypotension after magnesium administration **(Ying et al., 2007)**.

The most probable explanations for the controversial results of LIMIT-2 and ISIS-4 relate to the differences in timing of magnesium administration, dosing, and a low control group mortality rate in ISIS-4. Cardio-protective effects of magnesium were shown to require high serum concentrations at the time of reperfusion.

In LIMIT-2, the median time from onset of chest pain to randomization was 3 h compared with 8 h in the ISIS-4 Trial. According to the protocol, patients in LIMIT-2 began receiving magnesium when thrombolytic therapy was initiated, whereas patients in ISIS-4 received magnesium after, rather than before, or with thrombolytic therapy. In 30% of patients who did not undergo thrombolysis, the median time to randomization was

12 h, so a relevant number of patients might have already achieved spontaneous reperfusion **(Santoro et al., 2000)**.

The dose of magnesium administered could also have played an important role because other trials using less than 75 mmol (18.75 g) showed a significantly reduced early mortality. In previous trials, the benefit of magnesium correlated well with control group mortality. Control group mortality in ISIS-4 was only 7.2%, suggesting that most patients were at low risk and thus unlikely to benefit from magnesium therapy **(Santoro et al., 2000)**.

- ***Magnesium in Coronaries Trial (MAGIC):***

The Magnesium in Coronaries (MAGIC) Trial, a multicenter, DB, placebo-controlled trial, was designed to resolve these controversies by evaluating whether administration of intravenous magnesium to high-risk patients, patients older than 65 yr, or those not eligible for reperfusion therapy in the course of myocardial infarction would result in better survival.

A total of 6,213 patients, receiving either $MgSO_4$ (2 g bolus over 15 min, followed by 17 g [~68 mmol] over 24 h) or placebo were included, and the study drug was started within 6 h after onset of clinical symptoms (median time of 3.8 h) and before angioplasty or fibrinolysis. All patients received standard treatment. Magnesium treatment had no beneficial effects on the primary (30-day mortality) or the secondary outcome measures (incidence of heart failure).

Several reasons for the lack of effect of magnesium administration were discussed. Publication bias and small sample sizes in previous trials may have overestimated magnesium's potential benefit. The cardio protective

effects of magnesium may have been covered by current therapies for myocardial infarction not being used in previous trials, the doses of $MgSO_4$ being used were too high, or magnesium simply being ineffective **(Santoro et al., 2000)**.

- ***Minor Clinical Trials on Role of Magnesium in Ischemia:***

Gyamlani, et al. enrolled 100 patients with diagnosed AMI, who received 15 g $MgSO_4$ over 48 h starting within 2 h of admission. When thrombolytic agents were applied, $MgSO_4$ was given within the following 30 min of treatment. Development of arrhythmias (8% vs. 34%), cardiac failure (4% vs. 14%), and mortality (4% vs. 20%) were significantly reduced by magnesium **(Gyamlani et al., 2000)**.

In 150 patients undergoing angioplasty with low or intermediate risk of AMI, $MgSO_4$ infusion (7 g over 5 h) significantly decreased aortic systolic pressure before intervention. However, primary (30-day infarct size) and secondary end points (ventricular arrhythmias, death, and others) were not affected **(Santoro et al., 2000)**.

- ***Magnesium and Cardiac Arrest:***

Magnesium was reported to have a beneficial effect on the incidence of cardiac arrest after refractory ventricular fibrillation. In a small prospective and controlled study, normomagnesemia was directly correlated to successful resuscitation after cardiac arrest after ventricular fibrillation or tachycardia **(Hassan et al., 2002)**.

Evaluating the effects of 2 g $MgSO_4$ during resuscitation after cardiopulmonary arrest, **Hassan, et al.** included 105 patients with refractory or recurrent ventricular fibrillation not responding to initial

defibrillation. Magnesium did not improve return of spontaneous circulation or discharge from hospital alive. Similarly, magnesium did not improve the rate of successful resuscitation, survival for 24 h, or survival until hospital discharge in a randomized, placebo-controlled trial studying 156 patients with cardiac arrest regardless of their initial rhythm **(Hassan et al., 2002)**.

- ***Magnesium and Cardiac Arrhythmias:***

Although magnesium is not considered a classic anti-arrhythmic drug, it may convert some types of malignant arrhythmias. Accordingly, low mg^{+2} serum concentrations were shown to be potentially pro-arrhythmogenic **(Touyz, 2004)**.

- ***Anti-arrhythmic Mechanisms of Magnesium:***

Being an endogenous calcium antagonist, magnesium slows electrical activity of the S-A node, prolongs A-V conductance, and finally increases the refractory period of the A-V node.

Decrease in the level of extracellular magnesium shortens the effective refractory period, but lengthen the relative refractory period, thereby increasing the vulnerability of the ventricles to fibrillation. The anti-arrhythmic properties of magnesium depend heavily on the concentration of other ions, particularly of potassium and are mediated either by a direct effect of magnesium on myocardium, or by its calcium antagonistic effect and interaction with potassium **(Touyz, 2004)**.

Postulated anti-arrhythmic mechanisms for magnesium **(Iseri, 1990)**:

- Decreases cellular ischemia-reperfusion injury,
- Prevents early ischemia-induced prolongation of action potential,
- Suppresses early after depolarization and associated torsade de points,

- Suppresses delayed after depolarization in the setting of digitalis, catecholamine, or ischemia-reperfusion-induced calcium overload.
- Suppresses noradrenaline release in the ischemic-reperfused,
- Prevents secondary intracellular calcium overload caused by ischemia-induced,
- Similar to extracellular calcium, magnesium attenuates hyperkalemia-induced myocyte depolarization and prolonged QRS duration,
- Attenuates digitalis-induced myocyte potassium loss,
- Attenuates reperfusion-induced myocyte sodium overload and potassium loss,
- Attenuates ischemia-induced myocyte depolarization

4.3.3 Magnesium in Acute Atrial Fibrillation

Atrial Fibrillation (A.F) is one of the most common of all cardiac arrhythmia's; it may occur in a paroxysmal or a sustained form and is characterized by a very rapid (greater than 300 beats per minute), irregular, and disorganized depolarization of the atria, including an irregular and often rapid ventricular response. The onset of new A.F during the preoperative period is less common. There are many precipitating factors, although volatile agents themselves may have an anti-fibrillatory action. Alternatively, A.F fibrillation may occur for the first time during anesthesia and surgery **(Coleman et al., 2009)**.

Many trials of drug therapy for acute A.F are uncontrolled and as up to 50% of cases of recent-onset A.F revert spontaneously to sinus rhythm, direct current cardio-version remains the best method for managing acute onset A.F. Being an important cofactor in the myocardial Na^+-K^+ ATPase enzyme, which regulates electrical activity in the heart, treatment with magnesium may correct rhythm disturbances in patients with both low and normal magnesium

concentrations. Its efficacy in ventricular arrhythmias has been well documented **(Coleman et al., 2009)**.

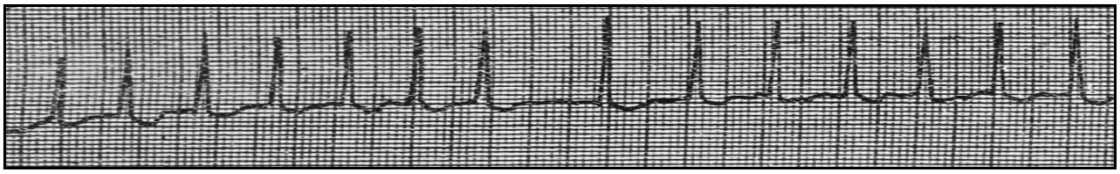

Figure 4.1: Atrial fibrillation (Coleman et al., 2009).

Dosage: 2 g magnesium sulphate over 5-15 minutes. Then infuse 6 g magnesium sulphate in 500 ml saline over 6 hours (1 g/h). Also**,** I.V magnesium has proven to be safe and effective for rate control in A.F and for prophylaxis of postoperative A.F **(Coleman et al., 2009)**.

- ***Magnesium and Post Cardiac-Surgery A.F:***

Arrhythmias, especially A.F, are frequently complications after cardiac surgery, with a typical time frame of 24–96 h after surgery and a peak incidence on postoperative day 2. Patients treated with β-blockers before surgery, and those undergoing valvular surgery, are at highest risk.

The underlying mechanisms are multifactorial **(Toraman et al., 2001)**:

1. Hypomagnesemia, caused by CPB,
2. High-dose diuretic therapy,
3. Surgical stress,
4. Exogenous catecholamines, is one known risk factor for the postoperative development of A.F.

Clinical trials studying the effects of perioperative magnesium prophylaxis gave conflicting results. In 200 patients undergoing Coronary Artery Bypass Graft (CABG), **Toraman, et al.** reported that preoperative, intraoperative, and early postoperative administration of 6 mmol $MgSO_4$ significantly reduced postop. A.F (2% vs. 21% in the control group) **(Toraman et al., 2001)**.

In a meta-analysis on the prophylactic use of magnesium during surgery, **Alghamdi, et al.,** described a significant risk reduction of A.F after magnesium administration. Eight studies with a total of 1,033 patients were included. $MgSO_4$ doses ranged from 7.5 to 25 g, administered between 2 and 5 days after surgery **(Alghamdi, et al., 2005)**.

Reviewing 15 randomized controlled trials, **Shepherd, et al.,** found A.F to be less likely the longer prophylaxis lasted and the earlier it was initiated. However, one has to be careful in interpreting these data because a statistically significant heterogeneity was present **(Shepherd et al., 2008)**.

In recent large clinical trials in which magnesium was used concomitantly with β-blockers as standard therapy, magnesium showed little or no effect. A dose of 5 g intravenous $MgSO_4$ given in addition to an established oral β-blocker protocol until postoperative day 4 did not reduce the incidence of atrial arrhythmias in 927 non-emergent cardiac surgery patients (**Cook, et al., 2009**).

4.3.4 Supraventricular Arrhythmias

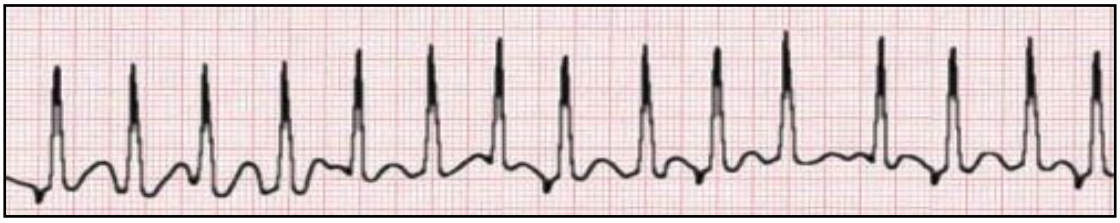

Figure 4.2: Supraventricular Tachycardia (SVT) (Cook et al., 2009).

In a small prospective study, **Moran et al.,** reported $MgSO_4$ to be superior to amiodarone in conversion of acute atrial tachyarrhythmias in critically ill patients (**Moran, et al., 1995)**.

Primarily studying the effects of milrinone in 1,068 patients with moderate to severe congestive heart failure (New York Heart Association III/IV), this large clinical trial also evaluated the prognostic significance of alterations in serum magnesium. There was no evidence that low serum magnesium is an independent risk factor for sudden death or all cause death. Magnesium is a relative safe drug, provided that patients are observed for signs of toxicity and the serum concentration is monitored. In cardiac surgery, the administration of two grams of magnesium sulphate in adults, regardless of the magnesium level, has been shown to reduce the incidence of post pump SVT **(Cook et al., 2009)**.

4.3.5 Ventricular Arrhythmia

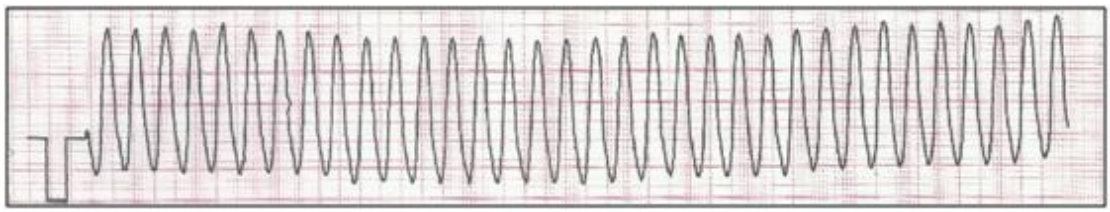

Figure 4.3: Ventricular Tachycardia (VT) (Ceremuzynski et al., 2000).

Magnesium has been used successfully in the treatment of ventricular arrythmias associated with AMI, Long QT syndromes and digoxin toxicity. The mechanism of magnesium in treatment of ventricular arrhythmias is increasing the threshold stimulus required to provoke either Ventricular Tachycardia (VT) or Ventricular Fibrillation (VF). Current treatment options consist of cardioversion, amiodarone, and normalization of serum electrolytes, including magnesium. Two small studies demonstrated reduced and even suppressed episodes of nonsustained monomorphic ventricular tachycardia after magnesium administration. However, to date there is no solid clinical evidence

recommending magnesium in the treatment or prophylaxis of monomorphic ventricular tachycardia **(Ceremuzynski et al., 2000)**.

In the acute management of ventricular tachycardia, intravenous magnesium infusion is recommended if the QT interval was prolonged (> 0.44 second), except in the presence of renal failure. Magnesium is not only effective in suppressing ventricular arrhythmias, but can be effective in ventricular tachycardia refractory to lidocaine as well. For **Dosage,** polymorphic ventricular tachycardia can be terminated with 2-4 g intravenous bolus magnesium sulphate **(Ceremuzynski et al., 2000)**.

4.3.6 Torsades de Pointes

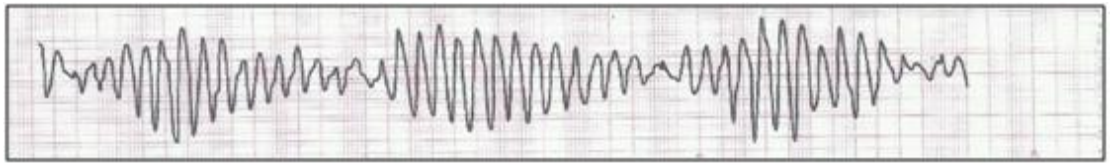

Figure 4.4: Torsades de Pointes (Ceremuzynski et al., 2000).

Torsade de pointes is referred to twisting around the points, the ECG features of the torsade de pointes include labile QT intervals, prominent U waves, and a pause-dependant onset of arrhythmia. Torsades de pointes tachycardias certainly benefit from the administeration of magnesium. Malfunction of potassium channels results in delayed ventricular repolarization and inactivation of calcium channels. The late calcium influx combined with the prolonged repolarization causes early after depolarizations, leading to torsades de pointes and associated long QT intervals. Magnesium attenuates these pathologic changes by inhibiting calcium currents, as shown by a variety of experimental and clinical data **(American Heart Association, 2005)**.

As an urgent measure, 2 g $MgSO_4$ (25–50 mg/kg in children) should be the drug of choice, followed by electrolyte stabilization and efforts to accelerate the basic heart rate **(American Heart Association, 2005)**.

4.4 Digoxin-induced Arrhythmias

Magnesium is well established in the management of digoxin-induced tachyarrhythmias. Digoxin antibodies are the basic treatment, but in hypomagnesemic patients, especially those susceptible to digoxin-induced arrhythmias, I.V administration of magnesium should be part of the immediate standard therapy until Fab antibodies are available **(Fuster et al., 2006)**.

4.5 Multifocal Atrial Tachycardia (MAT)

MAT is characterized by multiple P wave morphologies and a variable P-R interval, the ventricular rate is irregular, it is easily confused with A.F, it is most often seen in patients with chronic lung disease and it has been linked to theophylline therapy, other predisposing conditions include hypokalemia, magnesium deficiency, acute pulmonary embolism, AMI, and congestive heart failure **(Zipes et al., 2006)**.

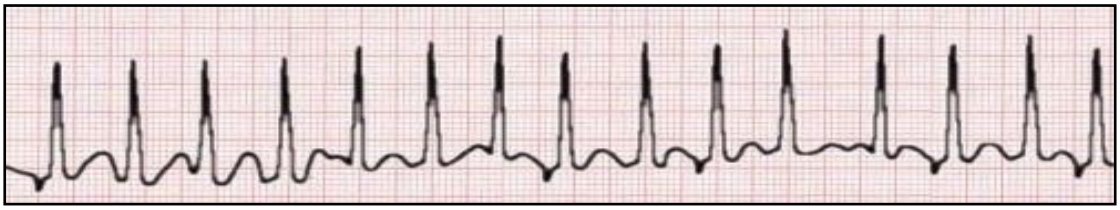

Figure 4.5: Multifocal atrial tachycardia (Zipes et al., 2006).

Acute multifocal atrial tachycadia may be difficult to manage, in patients with severe lung disease, aggravating conditions, such as hypoxemia, should be corrected then to proceed in treatment. I.V magnesium sulphate is used in

the same regimen as in A.F, in addition to the anti-arrhythmic actions, magnesium also dilates pulmonary arteries, and in the presence of hypokalemia, I.V magnesium is given first (2 g magnesium sulphate in 50 ml saline over 15 minutes), then infuse 40 mg potassium over 1 hour. The magnesium pre-treatment is often necessary for correcting hypokalemia **(Zipes et al., 2006)**.

4.6 Magnesium and Cardiac Surgery

Global myocardial ischemia induced by aortic cross clamping causes heterogeneous injury, in that left ventricular subendocardium is more vulnerable to irreversible injury than epicardial layer. Stunning is the term used to define transient left ventricular dysfunction due to subendocardial injury without transmural necrosis and it can be resolved by the passage of time with mild inotropic support, but significant left ventricular dysfunction usually occurs in patients with pre-existing areas of old myocardial infarction and scar. With the onset of ischemia, deterioration in the contractile function of the heart with changes in the cardiac rhythm, depletion of the ATP stores loss of cellular energy generation mechanisms **(Fuster et al., 2006)**.

Studies in the 1970's showed that myocardial ischemia followed by reperfusion results in cytoplasmic calcium overload. There is now general agreement that during and after periods of ischemia, transmembrane calcium influx occurs by several routes, and that cytoprotective agents, including magnesium, attenuate the increase in intracellular calcium by multiple mechanisms **(Fuster et al., 2006)**.

4.6.1 Magnesium and Cardioplegia

Cardioplegia is considered, as a measure of myocardial protection strategy, principles of cardioplegia are **(Fuster et al., 2006)**:

- Immediate arrest,
- Maintaining appropriate PH,
- Hypothermia (normothermic cardioplegic induction, reperfusion, continuous warm cardioplegic infusion have promising results in specific clinical setting),
- Providing substrate (glucose, FFA, ATP, creating phosphate precursors),
- Avoiding cellular reperfusion damage (reducing calcium content in the cardioplegic solution, reducing oxygen radical damage by including inhibitors of the enzymes that generate oxygen radicals or the enzymes that enhance their catabolism, or substances that bind oxygen radicles),
- Avoiding of edema (raising the osmolality of the solutions with manitol, glucose, or albumin)

Although experimental evidence supports the use of magnesium in cardioplegia solutions, clinical studies have reported that patients undergoing CABG who received magnesium containing cardioplegia and higher concentration of magnesium in serum, fewer ischemic changes in their electrocardiograms, and fewer postoperative ventricular arrhythmias occur.

Perioperative use of magnesium was beneficial in decreasing incidence of postoperative hypertension, decreased concentration of myocardial creatine kinase, decreased incidence of elevated S-T segment, and increased cardiac output, also perioperative administration of magnesium

include improved left ventricular diastolic function, reduced post-operative pain and reduced requirement of analgesic agents **(Fuster et al., 2006)**.

4.6.2 Administration of Magnesium Sulphate in Cardioplegia

The dose is 4 g magnesium sulphate given over 20 minutes just before CPB then single bolus dose 2 gram just before removal of aortic cross-clamping **(Zipes et al., 2006)**.

Postoperative, supplementation with magnesium should be continued despite normal concentration of total magnesium in serum because ionized or ultrafilterable hypomagnesemia may occur, magnesium sulphate should be given at dose of 12 g for 24 hours, followed by 3 g each day for 3 days (unless renal insufficiency is present; serum creatinine > 2 mg/dL). Concentration of total magnesium in serum should be measured daily **(Bilir et al., 2007)**.

Although the important pharmacologic actions of magnesium are primarily extracellular, free cytosolic magnesium modulates the intracellular environment through its influence on ion channels and transport mechanisms. The most two important points are **(Zipes et al., 2006)**:

- **First**, magnesium modulates calcium flux in pathophysiologic and physiologic states. Increasing concentrations of magnesium (cytosolic) Mg^{+2} during early ischemia or hypoxia has beneficial effects on calcium channels during stress; i.e., calcium flux is inhibited.

- **Second**, depletion of magnesium, as occurs after prolonged ischemia and reperfusion, contributes to progressive calcium overload and subsequent cell damage. In addition, loss of magnesium may promote

calcium overload from intracellular sources, elevated concentrations of magnesium inhibit efflux of calcium from sarcoplasmic reticulum.

Two recent mechanisms are believed to be involved in inhibition of calcium current by extracelluar magnesium:

(1) Effects mediated by canonic screening of fixed negative external surface charges.
(2) Competition with Ca^{+2} ions for a site within the channel itself. Elevated extracellular divalent cation concentrations stabilize excitable membranes and raise the excitation threshold in voltage dependent channels. Divalent cations such as magnesium effectively neutralize fixed negative charges on the outside of the cell membrane either by binding or, more likely, by electrostatic screening, causing alterations of transmembrane potential in the vicinity of the channel, divalent cations also effectively decreases the local permeant cation (Ca^{+2}) concentration, thereby reducing current flow. Magnesium affects both L-type and T-type calcium channels.

Circumstantial evidence suggests that magnesium reduces endothelial injury **(Zipes et al., 2006)**.

- **First**, deficiency of magnesium potentiates oxygen free radical-induced postischemic injury in working isolated rat hearts.

- **Second**, agents that attenuate the intial ischemic injury, namely calcium antagonist administrated before re-perfusion, also reduce the severity of no re-flow and preserve endothelial function.

Finally, experimental areas of no re-flow are decreased, and vascular endothelial and smooth muscle function are preserved after

administration of magnesium cardioplegia (16 mmol = 4g) (**Landymore et al., 1994)**.

4.6.3 CPB-Related Hypomagnesemia

Concentration of total magnesium in serum decreases significantly during CPB and these concentrations persist into the post-CPB period, during which they are associated with increased morbidity. Several factors have been implicated in CPB-related hypomagnesaemia (**Landymore et al., 1994)**.

- **First**, measurable preoperative hypomagnesaemia is common in patients undergoing cardiac surgery.
- **Second**, after induction of anesthesia and before CPB, hemodilution with magnesium free fluids. Increasing concentrations of catecholamines also may have contributed to the decrease.
- **Third,** during CPB, additional hemodilution, binding to albumin in the pump prime, and redistribution secondary to catecholamine–induced increases in concentrations of FFA. Although urinary excretion of magnesium may increase slightly during CPB.

Intraoperative administration of magnesium-containing cardioplegia solutions (or the equivalent I.V bolus dose of magnesium) prevents the decrease in concentrations of total magnesium seen during and after CPB, but the concentrations of ionized magnesium may still be decreased.

In a study where the influence of the addition of magnesium on myocardial protection with intermittent antegrade warm blood hyperkalemic cardioplegia in patients undergoing CABG was

investigated and compared with intermittent antegrade warm blood hyperkalemic cardioplegia only.

Twenty-three patients undergoing primary elective coronary revascularization were randomized to one or two different techniques of myocardial protection. In the first group, myocardial protection was induced using intermittent antegrade warm blood hyperkalemic cardioplegia. In the second group, the same technique was used except that magnesium was added to the cadioplegia.

It was found that intermittent antegrade warm blood hyperkalemic cardioplegia supplemented with magnesium prevents substrate (ATP and amino acid) derangement early after reperfusion (**Landymore, et al., 1994)**.

4.7 Magnesium and Major Vascular Surgery

Magnesium is a Vasodilator produces VD by directly acting on the blood vessels and by interfering with wide range of VC substances. In addition to its direct effects on the vessel wall, raised serum magnesium levels may also reduce peripheral vascular tone by a number of other mechanisms, including:

1. Sympathetic blockade,
2. Inhibition of catecholamine release. Magnesium vasodilates by inhibiting calcium influx at the vascular smooth muscle membrane and possibly by interfering with release of calcium from intracellular sites **(Standley et al., 1997)**

Infusion of magnesium increases the endothelial release of prostacyclin, not only in cultured human endothelial cells but also in healthy non pregnant volunteers and preeclamptic patients. These results suggest that vascular

actions of magnesium in healthy individuals and preeclamptic patients are mediated, at least in part, by the release of prostacyclin antagonizes pathologic platelet adhesion, aggregation, and resulting microvascular occlusion secondary to endothelial dysfunction in this order.

Also at the level of the vascular smooth muscle cell membrane, extracellular calcium appears to be essential for endothelium-dependant vascular smooth muscle relaxation; an increase in endothelial cell intracellular calcium accompanies basal production or release of nitric oxide (NO) and the release of NO in response to a wide variety of endothelium-dependent dilators **(Standley et al., 1997)**.

Entry of calcium in endothelial cells, however, is not voltage-gated; i.e., these cells are non excitable. Rather, calcium entry is capacitative; it is activated by the depletion of intracellular calcium stores. Although the effect of magnesium on capacitative entry of calcium in endothelial cells has not been addressed specifically, elevated extracellular magnesium has been shown to inhibit capacititive calcium entry in other cells. Experimental studies have shown that **(Euser and Cipolla, 2009):**

1. Removal of extracellular magnesium causes a potent endothelium-dependent VD response.
2. Removal of magnesium in arteries with disrupted endothelium leads to VC.
3. Both responses are reversible with re-addition of magnesium. When concentrations of magnesium or calcium are increased to higher than the physiologic range (>1.2 mmol/L and > 1.5 mmol/L, respectively), the direct endothelium-independent effects dominate.

When the concentration of Ca^{+2} is > 1.5 mmol/L in the presence of a normal concentration of magnesium, endothelium intact rings contract; when the concentration of Mg^{+2} is > 1.2 mmol/L, endothelium-intact ring relax. Because Ca^{+2} is obligatory for smooth muscle contraction and basal NO formation or release, and because Mg^{+2} opposes the action of Ca^{+2} at both sites, those studies suggest that the responsiveness of vascular smooth muscle to changes in concentration of Mg^{+2} and Ca^{+2} reflects the sum of responses at the endothelial and smooth muscle cells. Studies of the effects of Mg^{+2} on agonist-induced, NO-mediated relaxation of arteries have produced contradictory results **(Euser and Cipolla, 2009)**.

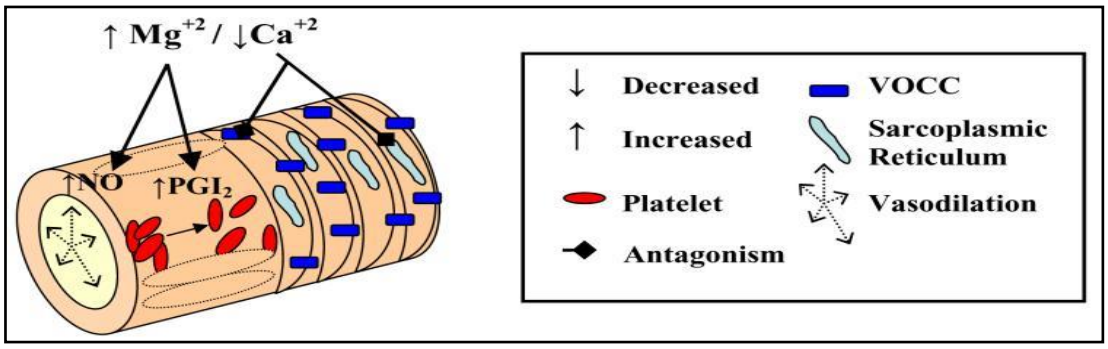

Figure 4.6: Vascular Effects of Magnesium Sulphate (Euser and Cipolla, 2009).

Magnesium is a potent vasodilator of uterine and mesenteric arteries, and aorta, but has minimal effect on cerebral arteries. In vascular smooth muscle, magnesium competes with calcium for binding sites, in this case for voltage-operated calcium channels (VOCC). Decreased calcium channel activity lowers intracellular calcium, causing relaxation and vasodilatation. In endothelium, magnesium has been shown to increase production of prostaglandin I_2 (through unknown mechanisms), which in turn decreases platelet aggregation. Magnesium also increases NO production causing vasodilatation **(Euser and Cipolla, 2009)**.

These vasodilator effects and the anti-arrhythmic effects of magnesium suggest that it may be used during aortic cross clamping for major vascular surgery. An additional possibility studied recently involves the role of magnesium as an NMDA antagonist. NMDA receptors mediate some of the pathological events after ischemia in the neural tissue and magnesium may offer some protection to the spinal cord during the surgical repair of supra renal aortic aneurysms **(Euser and Cipolla, 2009)**.

Patients candidate for major vascular surgery, i.e. (abdominal aorta and peripheral vasculature), often have significant cardiac, pulmonary, renal and/or endocrine disease. Hypertension is common in patients who have peripheral vascular disease and if uncontrolled, those patients often experienced the highest blood pressure during laryngoscopy and intubation, were likely to require vasodilator therapy and were likely to develop periods of myocardial ischemia. Coronary artery diseases and history of previous myocardial infarction may be present **(Mack et al., 2009)**.

- ***Dose of Magnesium in Major Vascular Surgery:***
  - Intravenous infusion of magnesium: 2 g (8 mmol) in 10 ml dextrose 5% over 10 minutes followed by 5 g (20 mmol) in 500 ml dextrose 5% over 3-12 hours.
  - Intrathecal 3 mg/kg intrathecal magnesium sulphate before thoracic aortic cross-clamping **(Mack et al., 2009)**.

- ***Magnesium and CVS Drug Interactions:***

Numerous studies have pointed out a relevant role for magnesium deficiency in the development of many CVS diseases. Some

pharmacological treatments may interfere with magnesium turnover, and magnesium deficiency may alter the pharmacokinetics and pharmacodynamics of some CVS drugs. Loop and thiazide-like diuretics increase magnesiuresis, and total body magnesium deficiency may appear during prolonged treatment with diuretically active doses of these drugs. The potassium retaining agents, such as amiloride, triamterene and spironolactone, tend to retain magnesium but they are not magnesium-retaining substances to the extent to which they are potassium-retaining diuretics. The interaction between magnesium and digitalis is complex. Magnesium, acting as an indirect antagonist of digoxin at the sarcolemma Na^+-K^+ATPase pump, reduces cardiac arrhythmias due to digoxin poisoning **(Mack et al., 2009)**.

Recent controlled studies have shown that treatment with magnesium significantly reduces the frequency and complexity of ventricular arrhythmias in digoxin-treated patients with congestive heart failure without digoxin toxicity. Magnesium improves the efficacy of digoxin in slowing the ventricular response in atrial fibrillation. Digoxin reduces tubular magnesium reabsorption, and in patients with congestive heart failure. This interaction may be cumulative with other causes of magnesium deficiency (diurectics, diet, poor intestinal absorption). The complex and potentially life-threatening interactions between magnesium and some cardiovascular drugs suggest that magnesium status should be carefully monitored in patients receiving drugs. Therapy with correction of magnesium is rapidly acting, has a safe toxic-therapeutic ratio, is easy to administer and titrate. Therefore, the correction of magnesium deficit should always be considered for patients with cardiomyopathy **(Mack et al., 2009)**.

4.8 Magnesium and Pheochromocytoma

Pheochromocytoma is a catecholamine-producing and secreting neoplasm arising primarily from the adrenal medulla with an estimated incidence of 500–1,100 cases in the United States each year. The care of patients during surgical removal of pheochromocytoma poses a significant anesthetic challenge because of the well-described hemodynamic disturbances occurring when a tumor is manipulated and finally resected. Standard preoperative treatment includes pharmacologic stabilization by α- and β-adrenergic antagonists. Several case reports have described the successful use of magnesium during pheochromocytoma crisis **(Fawcett and Edkins, 2001)**.

- ***Mechanisms of Magnesium Action in Pheochromocytoma:***

Magnesium may stabilize hemodynamics by inhibition of catecholamine release from the adrenal medulla and peripheral adrenergic nerve endings, direct blockade of catecholamine receptors and vasodilatation, and anti-arrhythmic properties related to L-type calcium channel antagonism. Magnesium has potent anti-arrhythmic and α-adrenergic effects in baboons treated with continuous adrenaline infusion, leading to an increase of cardiac output and stroke volume. It appears to dilate arterial, rather than venous, vessels but did not depress myocardial function **(Fawcett and Edkins, 2001)**.

Magnesium may be an effective drug in adults and children for providing hemodynamic stability during pheochromocytoma surgery in addition to standard therapy. To achieve maximal effect, serum concentrations of 2–4 mmol/L should be maintained. In Adults, several concepts for the anesthetic care of patients undergoing surgical removal of pheochromocytoma have been described. However, because of the

tumors low incidence, large prospective clinical trials are missing, and conclusions have to be drawn from a few small studies and case reports **(Fawcett and Edkins, 2001)**.

In Children where 20% of all pheochromocytomas occur, magnesium may be a treatment option. In a 5-year-old boy undergoing laparoscopic tumor resection, intraoperative hemodynamic stability was successfully achieved with a loading dose of 40 mg/kg, followed by continuous infusion of 15–30 mg/kg/h $MgSO_4$. Additional administration of nicardipine was required only twice, during Pneumoperitoneum and tumor manipulation **(Minami et al., 2002)**.

- ***Pheochromocytoma Crisis:***

Hypertensive crisis caused by pheochromocytoma may be an additional indication for magnesium. Magnesium was shown to improve severe hypertension and hypertensive encephalopathy in three patients with pheochromocytoma. Based on magnesium's arteriolar-dilating properties, its use might be advantageous to that of sodium nitroprusside, which dilates both arterioles and venules and may thus worsen hemodynamics, especially in hypovolemic patients.

Because magnesium was shown to inhibit catecholamine receptors, it may be superior to other competitive adrenergic antagonists, such as phentolamine and doxazosin, because excessive catecholamine concentrations may be present **(James and Cronje, 2004)**.

4.9 Magnesium and Respiratory System

- ***Bronchial Asthma:***

Bronchial Asthma is a common disorder affecting more than 12 million people in the United States, with an estimated 1.8 million visits to emergency departments for acute asthma each year**.** For mechanisms of magnesium action in bronchial asthma, there is a variety of experimental data suggests that magnesium-induced bronchodilatation may be mediated by several pathways **(Mannino et al., 2002)**:

1. Attenuation of calcium-induced muscle contractions.
2. Inhibition of cholinergic neuromuscular transmission.
3. Anti-inflammatory activity.
4. Potentiation of β-agonists on adenyl cyclase.
5. Reversal of magnesium depletion after β-adrenergic treatment.
6. Evidence also exists that prostaglandin-mediated vascular smooth muscle relaxation may be magnesium-dependent.
7. Magnesium possesses mild sedative effects that are valuable to achieving anxiolysis and relaxation in acute bronchoconstriction.

- ***Intravenous Magnesium:***

In 2000, a Cochrane systematic review evaluated seven trials (five adult, two pediatric) with a total of 665 patients for the efficacy of I.V magnesium as an adjunct to standard therapy (β-agonists and systemic corticosteroids) in the treatment of severe asthma. The pooled results failed to show a significant benefit for magnesium with respect to pulmonary function and hospital admission **(Rowe et al., 2000)**.

However, subgroup analysis of patients with acute severe asthma showed an improvement of peak expiratory flow rate by 52.3 L/min and forced

expiratory volume in 1 s by a mean of 9.8% of the predicted value, as well as a marked decrease in hospital admissions when treated with a single dose of $MgSO_4$ (2 g in adults and 25–100 mg/kg in children given over 20–35 min). The authors concluded that there is no evidence for the routine use of I.V magnesium in all asthmatic patients but that it appears beneficial in patients presenting with acute severe asthma **(Rowe et al., 2000)**.

These data are supported by a recently published review combining new evidence of six trials (three adult, three pediatric) with the original Cochrane article now including a total of 965 patients. Magnesium seems less beneficial in chronic stable asthma. A daily dose of 450 mg magnesium chelate did not benefit chronic asthmatic adults. Despite the lack of effect in chronic asthma, magnesium may be advantageous in patients with bronchial hyperactivity **(Rowe and Camargo, 2008)**.

A randomized, controlled, and double-blind study demonstrated a significant improvement in methacholine-provoked bronchial hyper-reactivity in 30 patients after I.V $MgSO_4$ (0.3 mmol/kg/h). Several case reports support these findings, one of which describes continuous magnesium infusion to facilitate rapid extubation and recovery in a ventilated patient not responding to standard bronchodilating therapy. In pediatric patients, Subgroup analysis of the Cochrane review evaluating the effects of I.V magnesium on patients with acute asthma revealed a benefit for magnesium **(Rowe and Camargo, 2008)**.

A recent meta-analysis recommended the use of magnesium in children with moderate to severe acute asthma. Five randomized, placebo-controlled trials including 182 children were evaluated. I.V magnesium was associated with a significant absolute risk reduction for

hospitalization (number needed to treat = 4), a significantly smaller risk for persistent bronchoconstriction and a significant improvement of the asthma symptom score. Because different dose regimens were used (25 mg/kg, 40 mg/kg, 75 mg/kg), and the dose-response relation differed among studies, future research should focus on the optimal dose regimen for children (**Cheuk et al., 2005)**.

In this regard, **Glover, et al.,** showed that a loading dose of 29.6 mg/kg $MgSO_4$ followed by a continuous infusion dose of 18 mg/kg/h for the treatment of refractory wheezing in children in an ICU was a safe mode of drug application **(Glover et al., 2002)**.

- ***Inhaled Magnesium:***

A Cochrane review including six trials (three adult, two pediatric, one mixed) and a total of 296 patients failed to provide convincing evidence that the addition of nebulized $MgSO_4$ (95–385 mg or 250–280 mmol) to standard bronchodilator therapy (inhaled β-agonists) improves the outcome of patients presenting with acute asthma. Compared with β-agonist treatment alone, pulmonary function was improved, and those with severe asthma had a significant difference when analyzed separately; the total $MgSO_4$ dose applied varied, dependent on the number of nebulizations and co-interventions, such as additional administration of corticosteroids, which further impairs comparisons between studies. Inhaled $MgSO_4$ alone did not have any benefit on pulmonary function compared with β-agonists and did not influence the rate of hospital admission **(Blitz et al., 2005)**.

Aggarwal, et al., studied the effects of nebulized $MgSO_4$ and salbutamol compared with salbutamol alone in 100 patients with acute asthma

classified as severe or life threatening. Despite nebulization three times at intervals of 20 min and increasing doses, there was no difference in spirometric or laboratory values or hospital admission between the two groups **(Aggarwal et al., 2006)**.

- ***Chronic Obstructive Pulmonary Disease:***

Only a small number of studies addressed the effects of magnesium on COPD. In a randomized, placebo-controlled, double-blind clinical trial, **Skorodin, et al.,** studied the effects of I.V $MgSO_4$ (1.2 g) after nebulized albuterol treatment in 72 patients presenting with acute exacerbation of COPD. After 30–40 min, the PEFR was significantly improved in the magnesium group, although there was no difference with regard to Dyspnea. Administration of I.V $MgSO_4$ (2 g) in 22 patients with stable COPD was associated with a reduction of lung hyperinflation and improved muscle strength **(Skorodin, et al., 1995)**.

- ***Magnesium and Neonatal Pulmonary Hypertension:***

Magnesium sulphate has been studied extensively with a beneficial effect in the treatment of neonatal pulmonary hypertension. Experimentally, randomized studies with induced pulmonary arterial hypertension suggest that systemic vasodilator effects of magnesium may be pronounced at doses required to cause pulmonary artery vasodilatation, and therefore selective pulmonary artery dilators such as nitric oxide may be safer. The mechanism of action of magnesium on the pulmonary artery appears to be via c_AMP and c_GMP-mediated relaxation **(Wu et al., 1995)**.

- ***Magnesium and Respiratory Failure:***

Magnesium deficiency has also been shown to be important as a cause of respiratory muscle failure. Patients with low muscle magnesium concentrations but normal serum levels are common in pulmonary intensive care units (47% of patients). These patients have longer stays than patients with normal muscle magnesium concentration. Magnesium replacement therapy has been shown to increase respiratory muscle power in patients with hypomagnesaemia but routine magnesium replacement therapy in mechanically ventilated patients has not been proved to be of benefit **(Do Amaral et al., 2008)**.

4.10 Magnesium and CNS

- ***Magnesium and Neuroprotection:***

Because of its diverse roles in various cellular functions, magnesium has been suggested to have beneficial effects in several neurologic disorders. For mechanisms of action, recent brain research proposes that, during ischemia, released excitatory amino acid neurotransmitters accumulate at toxic concentrations with neuronal death. Their action is mediated by the receptor subtype N-methyl-D-aspartate (NMDA). The protective effect of NMDA receptor blockade with Intrathecal magnesium sulphate was investigated during spinal cord ischemia induced by aortic occlusion for 12 minutes **(McKee et al., 2005)**.

In addition to NMDA antagonism, magnesium was shown to protect neurons and glial cells by numerous other modes of action **(Mami et al., 2006)**:

1. Magnesium exerted anti-excitotoxic properties in different animal models by inhibiting ischemia-induced glutamate release and calcium-dependent enzymes and prevented cellular apoptosis in hippocampal slices of newborn piglets.
2. In a rat model of cerebral ischemia, cortical spreading depression and anoxic depolarization were shown to be attenuated.
3. In subarachnoid hemorrhage, magnesium is a cerebral vasodilator, shown to increase cerebral blood flow in rat brain.

- ***Magnesium and Epilepsy:***

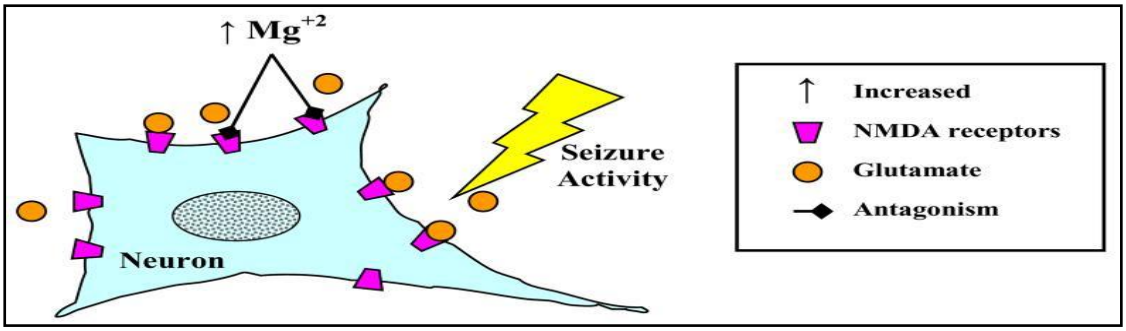

Figure 4.7: Anticonvulsant activity of magnesium sulphate (Euser and Cipolla, 2009).

Seizures consist of an excessive release of excitotoxic neurotransmitters including glutamate. Excessive glutamate can activate NMDA receptor, leading to massive depolarization of neuronal networks and bursts of action potentials. Magnesium may act to increase the seizure threshold by inhibiting NMDA receptors, thereby limiting the effect of glutamate. It has been argued that the mechanism of action of magnesium in treating seizures is by neuromuscular block, but this seems unlikely given that the serum concentrations used are well below those produce neuromuscular block **(Euser and Cipolla, 2009)**.

- ***Effect of $MgSO_4$ on Cerebral Edema and the Blood-brain Barrier:***

The calcium antagonistic effects of magnesium can also affect the cerebral endothelium that forms the blood-brain barrier. Decreased cell calcium inhibits endothelial contraction and opening of tight junctions that are linked to the actin cytoskeleton. Decreased tight junction permeability limits paracellular transport of vascular contents, ions and proteins, which can promote vasogenic edema and seizures. It is also possible that magnesium sulphate diminishes transcellular transport by limiting pinocytosis that is known to occur rapidly during acute hypertension **(Euser and Cipolla, 2009)**.

Magnesium may also down regulate aquaporin 4 (AQP4), water channel protein localized to astrocytic endfeet, and possibly cerebral endothelium, that is associated with cerebral edema formation (through unknown mechanisms) as shown in Figure 4.8 **(Euser and Cipolla, 2009)**.

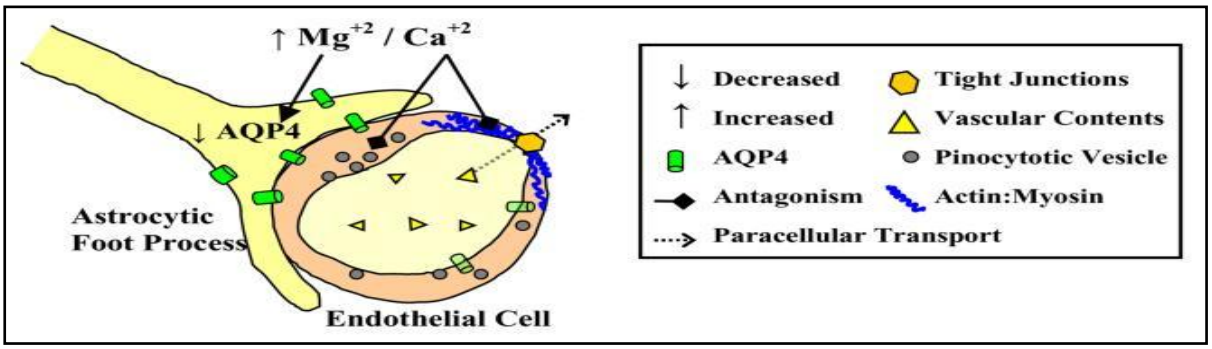

Figure 4.8: Effect of $MgSO_4$ on cerebral edema and the blood-brain barrier (Euser and Cipolla, 2009).

- ***Magnesium and Stroke:***

The large multicenter Intravenous Magnesium Efficacy in Stroke (IMAGES) Trial evaluated the benefit of magnesium in the treatment of acute stroke. A total of 2,589 patients were randomized to receive either I.V $MgSO_4$ 16 mmol (4 g) over 15 min, then 65 mmol (16.25 g) over 24 h

or placebo after acute stroke. No difference in mortality or (permanent) disability could be observed after 90 days **(Muir et al., 2004)**.

A non randomized trial in 2004 demonstrated dramatic early recovery in 42% of patients and good 90-day global functional outcome in 75% of patients treated with I.V $MgSO_4$ (4 g loading dose followed by 16 g as a maintenance dose) within 2 h after stroke onset. Although there is little evidence for a time frame facilitating maximal neuroprotective efficacy of magnesium in stroke, the most promising window is assumed to cover the first 3 h after onset of ischemia. Thus, the lack of effect seen in the IMAGES Trial may result in part from a delay in treatment because only 3% of patients received I.V magnesium within the first 3 h after onset of symptoms, whereas the initiation of magnesium administration averaged 12 h **(Saver et al., 2004)**.

Additional limitations include the lack of a reliable measure of initial stroke severity as an important predictor of outcome and verification of sufficient magnesium concentrations in ischemic tissue. An increase of blood pressure is known to improve recovery after stroke. However, magnesium did induce mild hypotension. Thus, it remains open to debate whether the net effect observed results from a mixture of neuroprotection and injury caused by decreased perfusion of ischemic tissue. Subgroup analysis revealed a potential benefit of magnesium in patients with subcortical stroke lacunar syndromes, although post hoc analyses need to be interpreted carefully **(Saver et al., 2004)**.

Current guidelines of the American Stroke Association do not recommend magnesium as a neuroprotective agent in the early management of ischemic stroke (Class III, Level of Evidence A, and American Heart Association) **(Adams et al., 2007)**.

- ***Magnesium and Carotid Surgery:***

Patients undergoing carotid endarterectomy are at particular risk for postoperative cognitive deficits caused by cortical ischemia after intraoperative hypotension or embolic events. A single randomized, double blind, placebo-controlled trial analyzed data of 92 patients with asymptomatic or symptomatic carotid artery stenosis with > 60% scheduled for carotid endarterectomy. $MgSO_4$ given as a 2 g loading dose over 25 min and a maintenance dose of either 8 g or 16 g over 24 h significantly improved neurocognitive function on postoperative day 1 compared with placebo or higher-dose $MgSO_4$ (4 g loading dose, 16 g as maintenance dose) **(Mack et al., 2009)**.

The same group showed that the dose of $MgSO_4$ did not influence the requirement, duration, or amount of postoperative pressor support. However, a truly neuroprotective effect of magnesium during carotid endarterectomy is difficult to claim because potential confounders such as residual effects of anesthetics cannot be completely ruled out considering an observation period of only 24 h after surgery in that study **(Chiu et al., 2006)**.

- ***Magnesium and Subarachnoid Hemorrhage (SAH):***

Delayed cerebral ischemia is one of the main causes of death and disability after SAH and usually occurs 4-10 days after the initial bleeding event. The placebo-controlled Magnesium Sulphate in Aneurysmal Subarachnoid Hemorrhage (MASH) Trial suggested that I.V $MgSO_4$ as an adjuvant to nimodipine may reduce delayed cerebral ischemia by 34% and subsequent poor outcome, defined as **Rankin score** more than 4 after 3 months, by 23%. Administration of 64 mmol/day

$MgSO_4$ was started within 4 days after subarachnoid hemorrhage until 2 weeks after aneurysm occlusion **(Dorhout et al., 2007)**.

Likewise, a systematic review analyzed three trials that compared $MgSO_4$ with placebo in addition to nimodipine, and reported borderline statistical significance for the RR of poor outcome after subarachnoid hemorrhage (RR 0.75; 95% CI, 0.57–1.00). However, the most recently published I.V Magnesium Sulphate for Aneurysmal Subarachnoid Hemorrhage [iMASH]-Trial could not demonstrate any benefit of I.V magnesium, given within the first 48 hours after the initial bleeding event for up to 14 days, over placebo with respect to neurological outcome (Extended Glasgow Outcome Scale 5 to 8) at 6 months in 327 patients with aneurysmal subarachnoid hemorrhage **(Wong et al., 2010)**.

- ***Magnesium and Traumatic Brain Injury:***

Traumatic brain injury is a major cause of death and disability worldwide. Its pathophysiology involves a primary event, characterized by neuronal cell death, ischemia, brain edema, and others, followed by secondary insults of multifactorial nature, which are believed to exacerbate the neurologic damage **(Sen and Gulati, 2010)**.

Despite considerable experimental evidence regarding the neuro-protective effects of magnesium in traumatic brain injury, clinical trials provide conflicting results. **Temkin, et al.** randomized 499 patients with moderate or severe traumatic head injury to either placebo or $MgSO_4$ within 8 h after injury continuing for 5 days and targeting serum concentrations of 1.0-1.85 mmol/L or 1.25–2.5 mmol/L. Magnesium did not have any benefit on the primary outcome measure based on mortality, seizures, functional measures, or neuropsychologic tests when assessed 6

months after injury. Patient outcome seemed to be affected rather negatively **(Temkin et al., 2007)**.

In contrast, **Dhandapani, et al.,** reported a favorable outcome in 30 patients with closed traumatic brain injury randomized to $MgSO_4$ within 12 h after injury. Outcome was evaluated using the Glasgow Coma Scale 3 months after injury. Patients received 4 g I.V $MgSO_4$ and 10 g Intra Mascular (IM) $MgSO_4$ as a loading dose, followed by I.M maintenance dose of 5 g every 4 h for 24 h. No significant side effects were observed. Because the number of patients included in that study is rather small, data should be interpreted carefully. Larger trials for definite evaluation of magnesium's effect in traumatic brain injury are certainly required **(Dhandapani et al., 2008)**.

- ***Magnesium and Spinal Cord Injury or Ischemia:***

Paraplegia is a known complication after surgery on the descending thoracic aorta. Thoracic aortic-cross clamping causes an increase in proximal aortic and Cerebral Spinal Fluid (CSF) pressures. Ischemic injury to spinal cord after cross clamping of the descending aorta can occur independently of aortic disease, a precipitous uniform of spinal surface oxygen tension downstream to the clamping site irrespective of level, in addition, hemodynamic changes occur, after aortic cross clamping, blood tends to drain away from the spinal cord rather than supplying it longitudinally **(Simpson et al., 1994)**.

Sodium nitroprusside, although effectively decreasing proximal aortic pressure, has been implicated in worsening the incidence of paraplegia by further increasing CSF pressure and decreasing distal blood pressure, thereby reducing spinal cord perfusion pressure. Magnesium activates alkaline phosphates and pyrophosphates, is an NMDA channel blocker, affects calcium uptake, affects adenyl cyclase generation of cyclic AMP,

and affects membrane sodium-potassium ATPase in addition to producing vasodilatation and producing a familiar curariform activity at the neuromuscular junction **(Simpson et al., 1994)**.

Once primary injury to the spinal cord has occurred, reduction of secondary injury and ischemia by stabilizing hemodynamics and spinal perfusion pressure is most important. Magnesium has proven its neuroprotective potential in experimental spinal cord injury. Whether these effects translate to the clinical setting remains to be evaluated in large clinical trials **(McKee et al., 2005)**.

4.11 Magnesium and Migraine

Peikert et al., 1996, evaluated the prophylactic effect of daily 600 mg (24 mmol) of oral magnesium for 12 weeks in multi-centre, placebo-controlled trial. They found that magnesium group had less frequency of migraine attacks and the number of days with migraine but with more diarrhea and gastric irritation than placebo group. However, **Pfaffenrath, et al., 1996,** did not find any significant difference between magnesium group given 250 mg (10 mmol) daily for 12 weeks and placebo group in their study.

The importance of magnesium in the pathogenesis of migraine headache is clearly established by a large number of clinical studies. Magnesium concentration has an effect on serotonin receptors, nitric oxide synthesis and release, NMDA receptors, and a variety of other migraine related receptors and neurotransmitters. The available evidence suggests that up to 50% of patients during an acute migraine attack have lower levels of ionized magnesium. Infusion of magnesium results in a rapid and

sustained relief of an acute migraine in such patient **(Mauskop and Altura, 1998)**.

Thomas et al., 2000, found a significantly lower concentration of total magnesium in erythrocyte and ionized magnesium in lymphocyte in migraine patients in comparison to controls.

CHAPTER 5

PATIENTS AND METHODS

- **Ethics Committee:**

  The study was approved by the Ethics Committee of Benha Faculty of Medicine and written informed consent was obtained from each patient.

- **Type of Study:**

  Prospective, comparative, double blind and randomized study.

- **Inclusion Criteria:**

  - Ninety patients of either gender were randomly allocated into three equal groups.
  - ASA physical status classes I or II.
  - Age ranged between 20 - 50 years.
  - Type of operations: Elective lower abdominal surgery.
  - Methods of randomization: Closed envelope.
  - These patients were randomly allocated into three equal groups:
    - **Group F (Fentanyl Group):** Were received Fentanyl 2 micg/kg by I.V infusion (on 100 cc saline 0.9%) over 20 min. preoperatively 30 minutes before induction.
    - **Group M (Magnesium Group):** received $MgSO_4$ 50 mg/kg by I.V infusion (on 100 cc saline 0.9%) over 20 min. half an hour preoperatively.
    - **Group FM:** received fentanyl 2 micg/kg + $MgSO_4$ 50 mg/kg by I.V infusion (on 100 cc saline 0.9%) over 20 min. half an hour preoperatively.

- **Exclusion Criteria**
  - Hepatic,
  - Renal,
  - Diabetic,
  - Hypertensive,
  - Cardiovascular dysfunction,
  - Atrioventricular block,
  - Bronchiolar asthma,
  - Chronic obstructive pulmonary disease,
  - Hematological disorders,
  - Pregnancy,
  - Known allergy to magnesium sulphate,
  - Obesity,
  - Prior treatment with Ca channel blocker, opioids, and anticoagulants.

- **Anesthetic Management:**
  - **Before the induction of anesthesia**:
    - Routine monitoring in the form of (ECG, pulse oximetry, NIBP, capnography.) was started.
    - Wide bore I.V line was inserted.
  - **All patients received the same general anesthetic technique:**
    - In the form of I.V induction by propofol 2 mg/kg and intubation was facilitated by atracurium 0.5 mg/kg. Anesthesia

maintained by isofloran 1.5 MAC and incremental doses of atracurium 0.15 mg/kg every 20 min.

- At the end of surgery, neuromuscular blocker reversed by neostigmine 40 micg/kg + atropine 20 micg/kg I.V.

Then the patients extubated when fulfill **criteria of extubation**, which are*:*

1. Ability to cough or swallow,
2. Sustained eye opening for at least 5 seconds (without diplopia),
3. Sustained head or leg lifts for at least 5 seconds (without support),
4. Sustained protrusion of the tongue (without fad),
5. Sustained forceful hand grip (without fad),
6. Ability to resist removal of a tongue blade from clenched teeth (the most recent and the most sensitive clinical test)

While, tests assessed in **unconscious patients** are **(Lake et al., 2001)**:

- Inspiratory force to produce 25 cm H_2O (airway pressure),
- Vital capacity,
- Tidal volume.

- **The Following Parameters Were Recorded:**
  - Mean Arterial Blood Pressure,
  - Heart Rate,
  - Blood Sugar,
  - Cortisol Level.
  - **At The Following Intervals:**

- Preoperatively just before induction and after application of test medications,
- After skin incision,
- Just before skin closure.

- **Post operatively** the patients were transferred to the post anesthetic care unit (PACU) for 24 h.

- **Visual analog score (VAS) and shivering scale** were recorded when the patient arrived into the PACU then every 2 hours for 24 hours.

  VAS: there is 10 cm horizontal line labelled "no pain" at one end and "worst pain imaginable" on the other end. The patients were asked to mark on this line where the intensity of the pain lies. The distance from "no pain" to the patient mark numerically indicates the severity of the pain **(Morgan et al., 2006)**.

  Shivering scale: there are 5 grades from 0-4 **(Morgan et al., 2006)**.

  0 ≡ No shivering
  1 ≡ Piloerection, peripheral vasoconstriction or peripheral cyanosis without other cause
  2 ≡ Visible muscular activity confined to one muscle group
  3 ≡ Visible muscular activity confined to > one muscle group
  4 ≡ Gross muscular activity involving the entire body

- **The time to the 1st analgesic dose required** was recorded, which is the time started from the patient recovery to the time of requesting analgesia.

- **The total analgesic requirement** was recorded.

- **The postoperative hospital stay** started from patient arrival to PACU and ended by patient discharge) was recorded.

  - **Criteria For Discharge (Home Readiness) (Barash et al., 2006):**

    1- Orientation to time, place, and person.
    2- Stable vital signs for 30-60 minutes (and no respiratory distress).
    3- Ability to ambulate unassisted e.g., walk in straight line.
    4- Ability to tolerate oral fluids (not mandatory in all patients as it induce vomiting).
    5- Ability to void (not mandatory in all patients as some surgical manipulation can inhibit the micturation reflex).
    6- Absence of significant pain, bleeding, nausea, or vomiting.

Table 5.1: Post-Anesthesia discharge scoring system (Barash et al., 2006).

Parameter	Description	Score
Pain	• Acceptable to the patient and treated with oral medications • Continuous after repeated treatment	2 1
Vital signs (BP& pulse)	• Within 20% of preoperative baseline. • 20-40% of preoperative baseline. • > 40% of preoperative baseline.	2 1 0
Surgical bleeding	• Minimal, no surgical drapes changes required. • Moderate, up to 2 drapes changes required. • sever, >2 drapes change required	2 1 0
Motor activity	• Steady gait, no dizziness or meet preanesthetic level. • Requires assistance. • Unable to ambulate.	2 1 0
Nausea & Vomiting	• None to minimal treated with oral medications. • Moderate, treated with oral medications. • Continuous after repeated treatment.	2 1 0
Results:	10 = total score ≥ 9 = required for post-anesthesia discharge	

- **Data Management And Statistical Analysis:**
  - Analysis of data was done by using SPSS version 16.
  - Quantitative data was presented as mean ± Standard deviation.
  - Qualitative data was presented as numbers and percentages.
  - Quantitative data was analyzed by using Analysis Of Variance (ANOVA) test.
  - Qualitative data was analyzed by using Chi-square test.
  - P – Value < 0.05 was considered statistically significant.
  - P – Value < 0.01 was considered statistically highly significant.

CHAPTER 6

RESULTS

This study was conducted on 90 Patients scheduled for elective lower abdominal surgery. Patients were divided into three equal groups:

- **Group F (fentanyl group) (30 patients):** was given general anesthesia + fentanyl 1-2 micg/kg (added to 100 cc 0.9% saline) I.V infusion over 30 min. before induction.

- **Group M (magnesium group) (30 patients):** was given general anesthesia + $MgSO_4$ 3 g (added to 100 cc 0.9% saline) I.V infusion over 30 min. before induction.

- **Group FM (fentanyl+magnesium group) (30 patients):** was given general anesthesia + fentanyl 1-2 micg/kg + $MgSO_4$ 3 g (added to 100 cc 0.9% saline) I.V infusion over 30 min. before induction.

Table 6.1 shows the demographic characteristics of patients.

As regard Age, the average age of group F was (29.7 year), group M was (26.7 year), and group FM was (27.8 year). ANOVA test was used to analyze the difference and showed that F= 0.68 and P-value = 0.5 which is statistically non-significant.

As regard sex, there was 13(M) and 17(F) in group F ,16(M) and 14(F) in group M ,18(M) and 12(F) in group FM. Chi-Square test = 1.7 and P-value = 0.43 which is statistically non-significant.

As regard weight, the average weight of group F was (67.4), group M was (68.7), and group FM was (68.5). F-test = 0.25 and P-value = 0.43 which is statistically non-significant.

As regard ASA classification of patients, there was 25 (ASA I) and 5 (ASA II) in group F, 27 (ASA I) and 3 (ASA II) in group M, 28 (ASA I)

and 2 (ASA II) in group FM .Chi-Square test = 0.77 which is statistically non-significant.

Table 6.1: Demographic characteristics of patients (mean ±SD).

		Group F	Group M	Group FM	Test of Significance	P- Value
AGE (year)		29.7 ± 12.5	26.7 ± 8.1	27.8 ± 8.8	0.68	0.5
SEX	**M**	13 (43.3%)	16 (53.3%)	18 (60%)	$X^2 = 1.7$	0.43
	F	17 (56.7%)	14 (46.7%)	12 (40%)		
Weight (kg)		67.4 ± 5.5	68.7 ± 9.7	68.5 ± 6	0.25	0.77
ASA	**I**	25 (83.3%)	27 (90%)	28 (93.3%)	$X^2 = 1.57$	0.45
	II	5 (16.7%)	3 (10%)	2 (6.7%)		

As regard types of operations, there was no significant difference among groups (Table 6.2).

Table 6.2: Types of operations included in the study.

	Group F	Group M	Group FM	X^2	P- Value
Appendectomy	10 (33.3%)	11 (36.7%)	12 (40%)	1.9	0.9
Hernia repair	6 (20%)	8 (26.7%)	7 (23.3%)		
Hysterectomy	4 (13.3%)	3 (10%)	5 (16.7%)		
Varicocele	10 (33.4%)	8 (26.6%)	6 (20%)		

As regard the statistical changes in the Mean Arterial Pressure (MAP) preoperatively, after skin incision and before skin closure in the three groups by using ANOVA test as follows:

- MAP in the preoperative period was (99.5 ± 13.4) in group F, (91.9 ± 9.1) in group M, and (98.5±12.4) in group FM. F-test = 3.7 and P-value = 0.02 which is statistically significant (Table 6.3, Figure 6.1).

- MAP after skin incision show (91.4 ± 16.6) in group F, (95.7 ± 8.07) in group M, and (94.7 ± 8.07) in group FM. F-test = 0.59 and P-value = 0.54 which is statistically non significant (Table 6.3, Figure 6.1).

- MAP before skin closure show (91.06 ± 01.5) in group F, (91.4 ± 9.4) in group M, (96.7 ± 13.4) in group FM. F-test = 2.3 and P-value = 0.1 which is statistically non significant (Table 6.3, Figure 6.1).

Table 6.3: Comparison among groups as regard MAP (mean ± SD).

MAP (mmHg)	Group F	Group M	Group FM	F- Test	P- Value
Preoperative	99.5 ± 13.4	91.9 ± 9.1	98.5 ± 12.4	3.7	0.02
After s. incision	91.4 ± 16.6	95.7 ± 8.07	94.7 ± 8.07	0.59	0.54
Before s. closure	91.06 ± 10.5	91.4 ± 9.7	96.7 ± 13.4	2.3	0.1

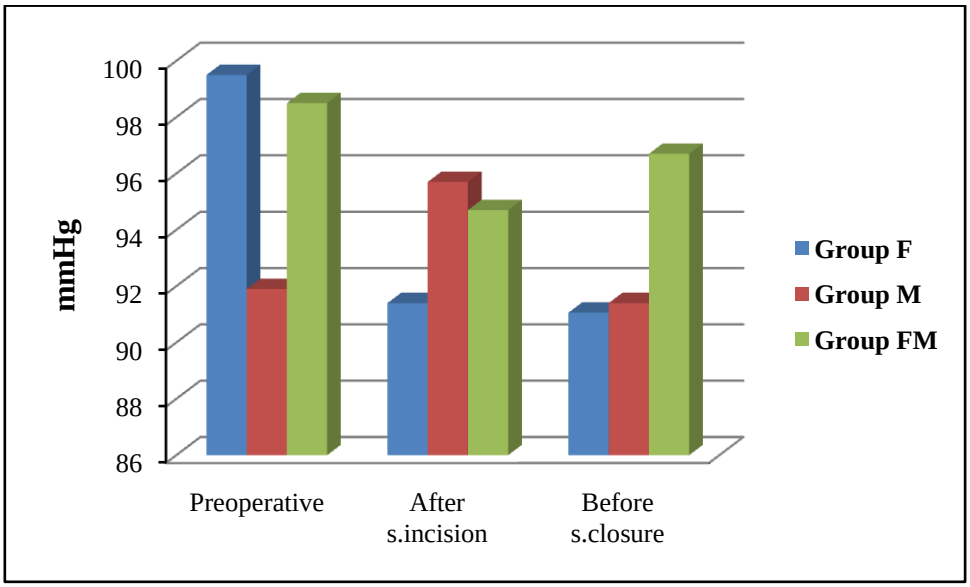

Figure 6.1: Comparison among groups as regard MAP.

As regard statistical changes in the HR, which occurred preoperatively, after skin incision, and before skin closure in the three groups by using ANOVA test as follow:

- HR in the preoperative period show (93 ± 11.2) in group F, (87.7 ± 18.09) in group M, and (90.3 ± 18.6) in group FM.F-test = 0.75 and P-value = 0.47 which is statistically non significant (Table 6.4, Figure 6.2).

- HR after skin incision show (86.9 ± 17.4) in group F, (93.2 ± 15.3) in group M, (79.4 ± 9.7) in group FM. F-test = 6.7 and P-value = 0.0018 which is statistically significant (Table 6.4, Figure 6.2).

- HR before skin closure show (84.2 ± 17.9) in group F, (82.2 ± 15.1) in group M, (80.3 ± 13.1) in group FM. F-test = 0.46 and P-value = 0.63 which is statistically non significant (Table 6.4, Figure 6.2).

Table 6.4: Comparison among groups as regard heart rate (mean ±SD).

HR(b/min)	Group F	Group M	Group FM	F- Test	P- Value
Preoperative	93 ± 11.2	87.7 ± 18.09	90.3 ± 18.6	0.75	0.47
After skin incision	86.9 ± 17.4	93.2 ± 15.3	79.4 ± 9.7	6.7	0.0018
Before skin closure	84.2 ± 17.9	82.2 ± 15.1	80.3 ±13.1	0.46	0.63

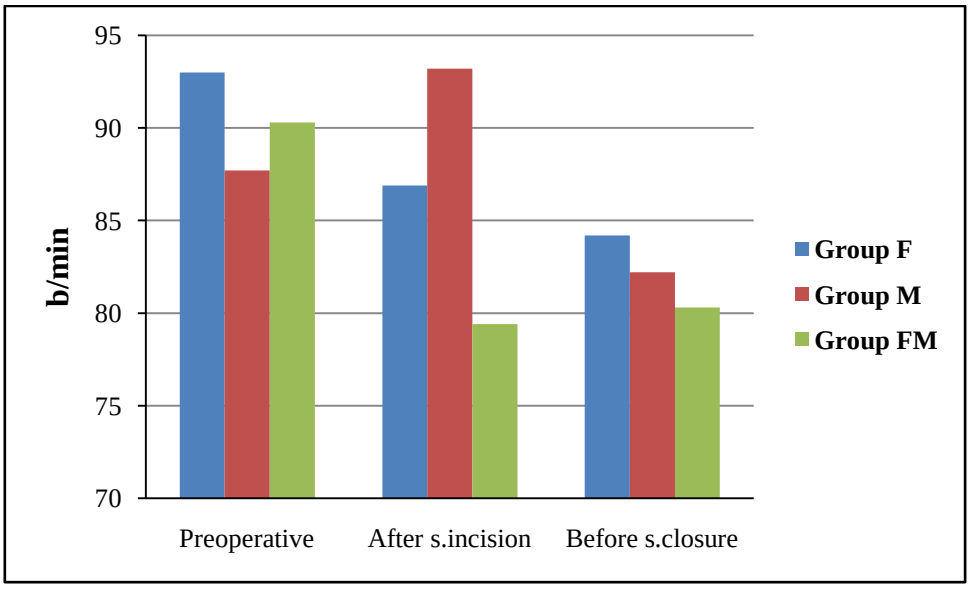

Figure 6.2: Comparison among groups as regard HR.

As regard the statistical changes in the blood sugar, which occurred in preoperatively, after skin incision, and before skin closure in the three groups by ANOVA test as follow:

- Blood sugar in the preoperative period show (87.2 ± 20.5) in group F, (97.5 ± 24.9) in group M, (98.6 ± 17.6) in group FM. F-test = 2.6 and P-value = 0.078 which is statistically non significant (Table 6.5, Figure 6.3).

- Blood sugar after skin incision show (82.1 ± 15.9) in group F, (99.3 ± 13.09) in group M, (97 ± 26.11) in group FM. F-test = 6.2 and P-value = 0 .003 which is statistically significant (Table 6.5, Figure 6.3).

- Blood sugar before skin closure show (99.2 ± 12.5) in group F, (111.9 ± 28.8) in group M, (121.9 ± 28.9) in group FM. F-test = 6.4 and P-value = 0.002 which is statistically significant (Table 6.5, Figure 6.3).

Table 6.5: Comparison among groups as regard blood sugar (mean ±SD).

B. sugar (mg/dL)	Group F	Group M	Group FM	F- Test	P- Value
Preoperative	87.2 ± 20.5	97.5 ± 24.9	98.6 ± 17.6	2.6	0.078
After s. incision	82.1 ± 15.9	99.3 ± 13.09	97 ± 26.11	6.2	0.003
Before s. closure	99.2 ± 12.5	111.9 ± 28.8	121.9 ± 28.9	6.4	0.002

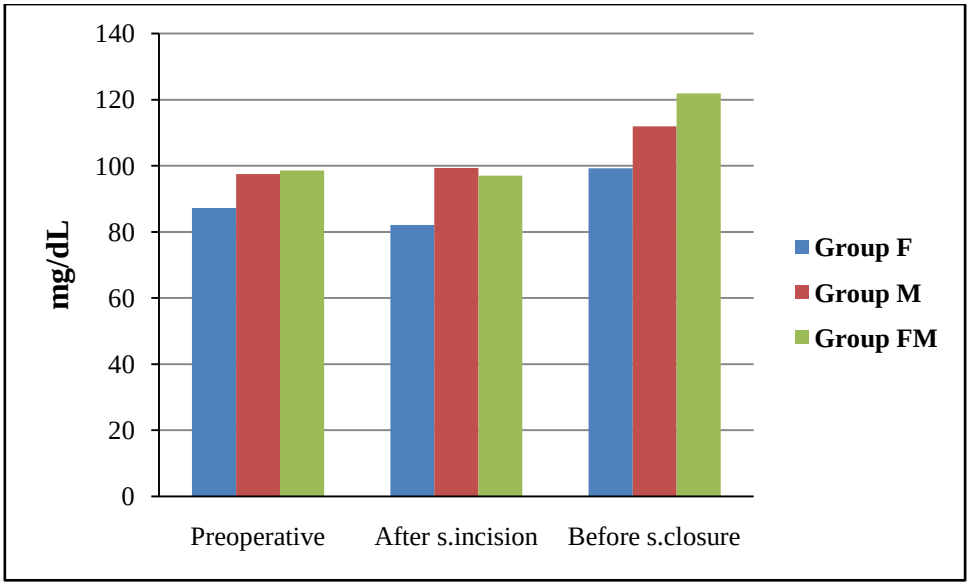

Figure 6.3: Comparison among groups as regard blood sugar.

As regard statistical changes in the serum cortisol level, which occurred preoperatively, after skin incision, and before skin closure in the three groups by ANOVA test as follow:

- Serum cortisol level in the preoperative period show (21.1 ± 3.5) in group F, (20.3 ± 3.07) in group M, (12.2 ± 1.6) in group FM.F-test = 1.09 and P-value = 0.3 which is statistically non significant (Table 6.6, Figure 6.4).

- Serum cortisol level after skin incision show (27.6 ± 2.9) in group F, (26.6±3.4) in group M, (16.3±2.08) in group FM. F-test = 140.1 and P-value = <0.01 which is statistically significant. (Table 6.6, Figure 6.4).

- Serum cortisol level before skin closure show (28.4 ± 4.3) in group F, (27.6 ± 1.6) in group M, (24.9 ± 2.5) in group FM.F-test = 10.6 and P-value = < 0.01 which is statistically significant (Table 6.6, Figure 6.4).

Table 6.6: Comparison among groups as regard serum cortisol level (mean ±SD).

S.cortisol(micg/dL)	Group F	Group M	Group FM	F- Test	P- Value
Preoperative	21.1 ± 3.5	20.2 ± 3.07	21.2 ± 1.6	1.09	0.3
After s.incision	27.6 ± 2.9	26.6 ± 3.4	16.3 ± 2.08	140.1	< 0.01
Before s.closure	28.4 ± 4.3	27.6 ± 1.6	24.9 ± 2.5	10.6	< 0.01

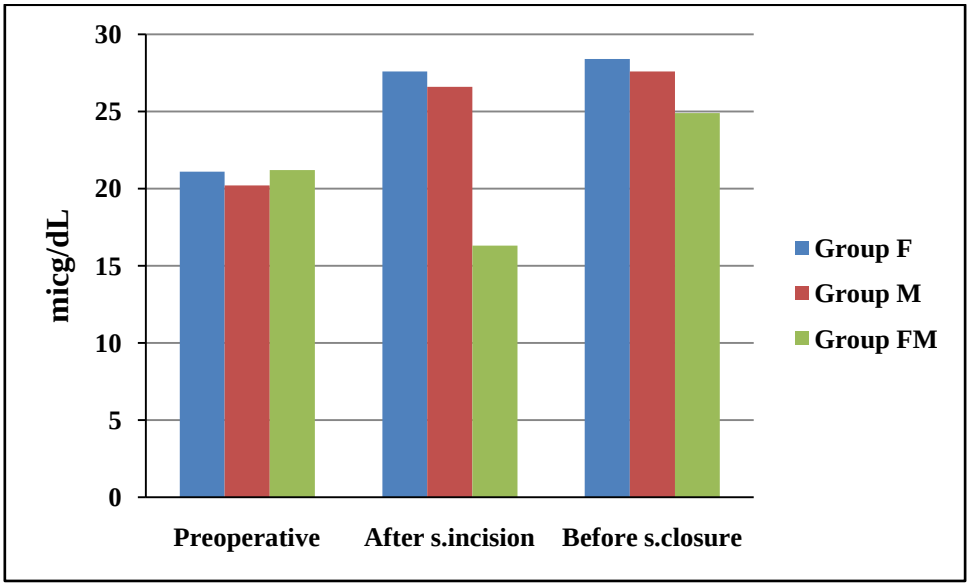

Figure 6.4: Comparison among groups as regard serum cortisol level.

As regard statistical changes in the 1st analgesic dose required postoperatively between the three groups as follow:

The 1st analgesic dose required (min) in group F was (41.8 ± 20.6), in group M was (57 ± 29.2), and in group FM was (138 ± 34.2) .F-test = 97.9 and P-value = 0.001 which is statistically significant (Table 6.7, Figure 6.5).

Table 6.7: Comparison among groups as regard time to 1st analgesic dose required postoperatively.

1st analgesic request (min.)	Group F	Group M	Group FM	F- Test	P- Value
	41.8 ± 20.6	57 ± 29.2	138 ± 34.2	97.9	0.001

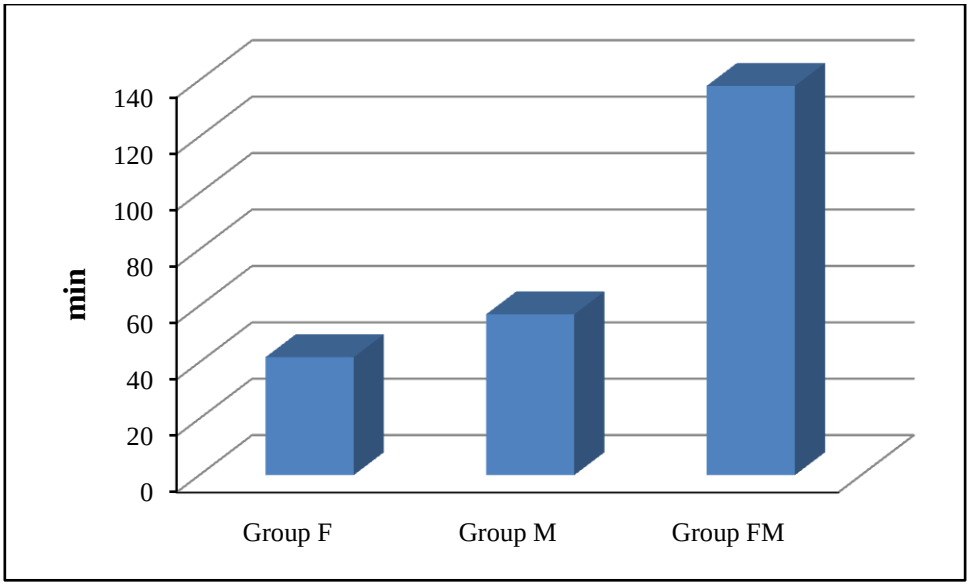

Figure 6.5: Comparison among groups as regard 1st analgesic dose required postoperatively.

As regard statistical changes in the post operative shivering between groups as follow:

The postoperative shivering was occurred in 14 cases in F group, 9 cases in group M, and 2 cases in FM group .Chi-square test show 12.07, and P-value was 0.002 which is statistically significant (Table 6.8, Figure 6.6).

Table 6.8: Comparison among groups as regard postoperative shivering.

Postoperative shivering	Group F	Group M	Group FM	X^2	P- Value
YES	14 (46.7%)	9 (30%)	2 (6.7%)	12.07	0.002
NO	16 (53.3%)	21 (70%)	28 (93.3%)		

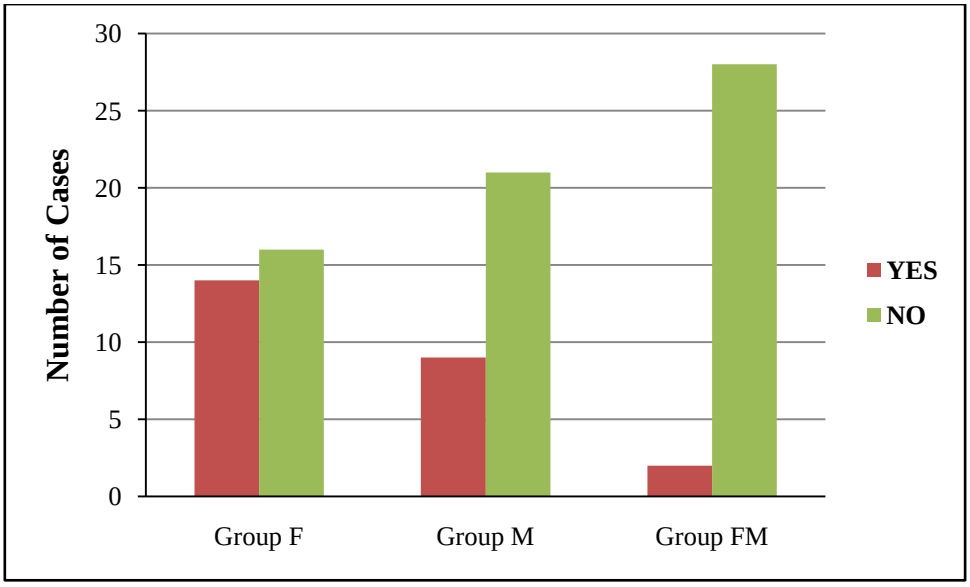

Figure 6.6: Comparison among groups as regard postoperative shivering.

As regard statistical changes in the postoperative VAS between the three groups by ANOVA test as follow:

VAS at baseline was, in Group F (1.7 ± 0.75), Group M (1.8 ± 0.77), and Group FM (1.7 ± 0.65), F-value was 0.52 and P-value was 0.6 which is statistically non-significant. VAS at 2 hrs postoperatively was, in Group F (2.4 ± 0.72), Group M (2.7 ± 0.65), Group FM (2.3 ± 0.59), F-value was 2.8 and P-value was 0.06 which is statistically non significant. VAS at 4 hrs postoperatively was, in Group F (5.5 ± 0.5), Group M (5.6±0.49), Group FM (2.6 ± 0.56), F-value was 325.8 and P-value was < 0.001, which is statistically significant.

VAS at 6 hrs postoperatively was, in Group F (5.6 ± 0.49), Group M (5.5 ± 0.57), Group FM (2.7 ± 0.52), F-value was 284.7 and P-value was < 0.001 which is statistically significant. VAS at 9 hrs postoperatively was, in Group F (6.4 ± 0.56), Group M (6 ± 0.55), Group FM (3.6 ± 0.6), F-value was 199.2 and P-value was < 0.001, which is statistically significant. VAS at 12 hrs postoperatively was, in Group F (7.63 ± 0.49), Group M (7.4 ± 0.67), Group FM 7.46 ± 0.73 (), F-value was 1.05 and P-

value 0.34 was which is statistically non significant (Table 6.9, Figure 6.7).

Table 6.9: Comparison among groups as regard postoperative VAS.

VAS	Group F	Group M	Group FM	F- Value	P- Value
Baseline	1.7 ± 0.75	1.8 ± 0.77	1.7 ± 0.65	0.52	0.6
2 hrs	2.4 ± 0.72	2.7 ± 0.65	2.3 ± 0.59	2.8	0.06
4 hrs	5.5 ± 0.5	5.6 ± 0.49	2.6 ± 0.56	325.8	< 0.001
6 hrs	5.6 ± 0.49	5.5 ± 0.57	2.7 ± 0.52	284.7	< 0.001
9 hrs	6.4 ± 0.56	6 ± 0.55	3.6 ± 0.6	199.2	< 0.001
12 hrs	7.63 ± 0.49	7.4 ± 0.67	7.46 ± 0.73	1.05	< 0.34

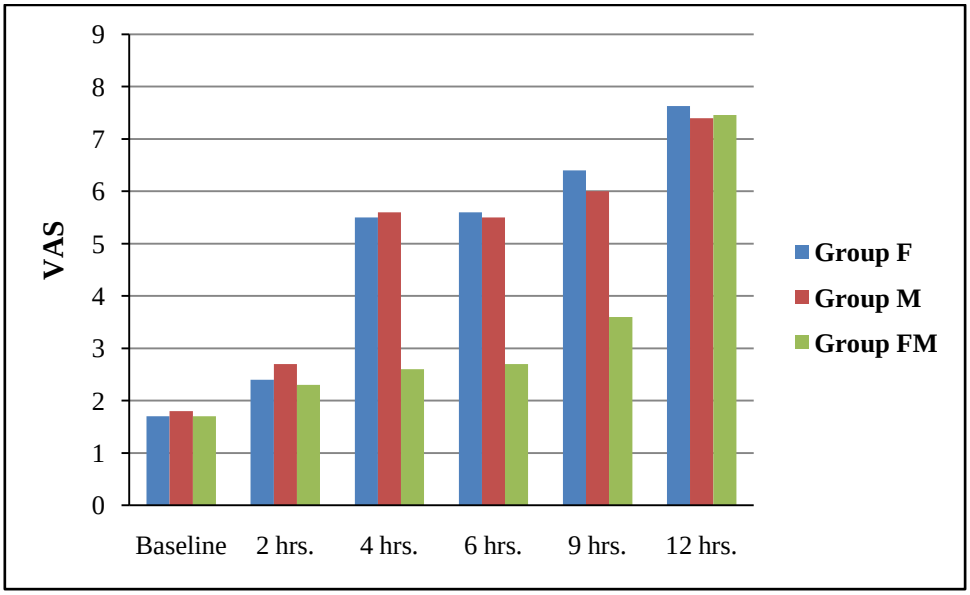

Figure 6.7: Comparison among groups as regard postoperative VAS.

As regard, the statistical changes in the postoperative hospital stay between groups by ANOVA test as follow:

The postoperative hospital stay (hour) in group F was (31.2 ± 14.6), in group M was (30 ± 15.6), in group FM was (9.2 ± 5.3). F-test = 28.1 and P-value = < 0.001 which is statistically significant (Table 6.10, Figure 6.8).

Table 6.10: Comparison among groups as regard postoperative hospital stay.

Hospital Stay Time (hrs)	Group F	Group M	Group FM	F- Test	P- Value
	31.2 ± 14.6	30 ± 15.6	9.2 ± 5.3	28.1	< 0.001

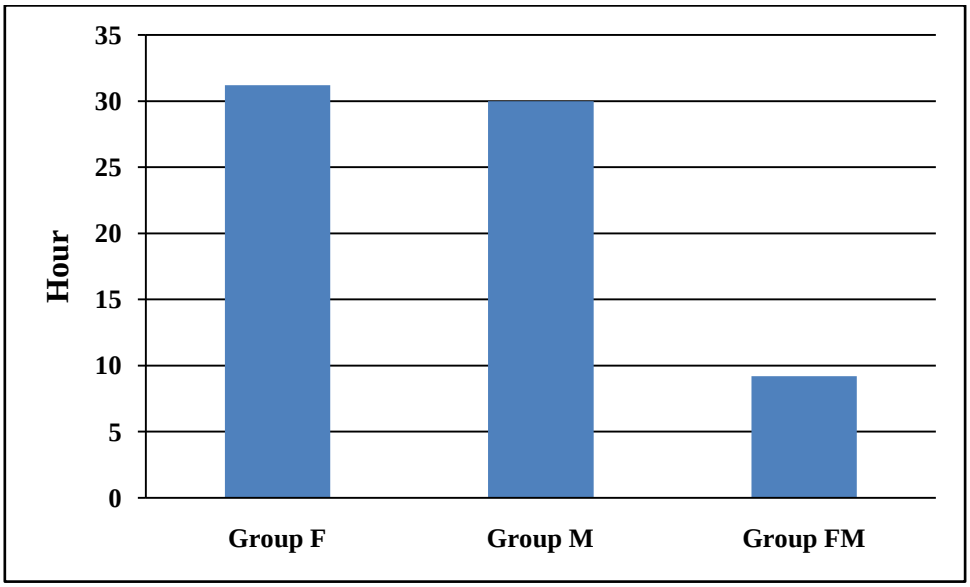

Figure 6.8: Comparison among groups as regard postoperative hospital stay.

CHAPTER 7

DISCUSSION

Uncontrolled post-operative pain is associated with a number of adverse sequels that can lead to post-operative morbidity. Greater understanding of these phenomena would help to motivate staff provide better analgesia. A long line of publications continue to highlight an ongoing inadequacy in modern acute pain management with up to 30% of patients still suffering moderate to severe pain following surgery **(Ko et al., 2001)**.

Magnesium inhibits calcium entry into the cell via a noncompetitive blockade of the N-methyl-D-aspartate (NMDA) receptor. Magnesium and the NMDA receptor are thought to be involved in the modulation of pain. Magnesium is also a physiological calcium antagonist at different voltage-gated channels, which may be important in the mechanisms of antinociception **(Begon et al., 2001)**.

In our work, we studied the effect of magnesium sulphate on postoperative pain relief after lower abdominal surgery and so reducing postoperative analgesic requirement.

Ninety patients were included in the study and classified into three equal groups, Magnesium group receive 3 gm $MgSO_4$ (50 mg/kg) adjusted according to **Maheshwari et al.** who gave $MgSO_4$ (50 mg/kg) I.V bolus after the induction of spinal anesthesia **(Maheshwari et al., 2009)** and **Jee et al.** who gave $MgSO_4$ (50 mg/kg) I.V preoperatively in LCCE **(Jee et al., 2009).**

In our study, we started by 50 mg/kg (3 g) of $MgSO_4$ plus 100 cc saline 0.9% intravenous infusion 30 minutes preoperatively. Fentanyl group received 2 micg/kg fentanyl and the last group (FM group) receive both 3 gm $MgSO_4$ and 2 micg/kg Fentanyl by the same technique as before. We monitor MAP, HR, blood glucose level and serum cortisol preoperatively, after skin incision and just before skin closure. Then postoperatively we

monitored the time to the first analgesic request, VAS, shivering scale, and the postoperative hospital stay.

As regard MAP, we have shown that the administration of magnesium sulphate has a significant effect (P value = 0.02) on MAP in the preoperative period, but there was no significant changes (P value > 0.1) in MAP intraoperatively.

Our result goes with **Hwang et al.** who studied the effect of I.V infusion of magnesium sulphate during spinal anaesthesia on improving postoperative analgesia in forty ASA I or II patients (20 in magnesium group, and 20 in saline group) undergoing total hip replacement under spinal anaesthesia. They found that MAP changes were similar in the two groups **(Hwang et al., 2010).**

Also our result goes with **Telci et al.** who studied the effect of magnesium sulphate on reducing Intraoperative anesthetic requirements in Eighty-one ASA I or II patients (36 women, 45 men) undergoing elective spinal surgery which divided into two groups, The magnesium group and control group. They found that there are no significant changes in MAP between the two groups **(Telci et al., 2002).**

But our result not goes with **Lee and Kwon** whose studied the beneficial effects of Magnesium sulphate as an adjuvant during general anaesthesia, in Seventy-two patients undergoing Caesarean section were randomly assigned to receive i.v. saline (control group) or magnesium sulphate 30 mg/kg bolus +10 mg/kg/h continuous infusion (Mg 30 group) or 45 mg/kg bolus +15 mg/kg/h continuous infusion (Mg 45 group) after induction.

They founded that the MAP remained at a significantly lower level in magnesium sulphate-treated subjects than in Controls; this probably indicates that the analgesic properties of magnesium sulphate reduce sympathetic stimulation (**Lee and Kwon, 2009)**. This different result is mostly due to the physiological changes of pregnancy (as the sedating effect of progesterone), and also due to giving magnesium as a bolus then infusion which may increasing the magnesium level in the blood, so giving more effect on MAP.

In addition, our result not goes with **Seyhan et al.** who studied the effect of three different dose regimens of magnesium on propofol requirements, hemodynamic variables and postoperative pain relief in gynecological surgery in eighty women, ASA I or II, were allocated to four equal groups. The control group received normal saline infusion 15 min before induction; magnesium group received 40 mg/kg of magnesium in 100 cc normal saline 15 min before induction of anesthesia, followed by 4 h infusion of normal saline after intubation.

In the other two-magnesium groups 15 min infusion of 40 mg/kg magnesium sulphate in total 100 cc normal saline was given before induction of anesthesia, followed by 4h infusion of either 10 or 20 mg/kg/h magnesium sulphate after intubation. They found that all magnesium groups demonstrated lower MAP values than control group and conclude that increasing magnesium dosage did not offer any advantages, but induced hemodynamic consequences **(Seyhan et al., 2006).** This may be due to using different dose regimens of magnesium sulphate.

Additionally, our result as regard MAP not goes with **Christopher et al.** who did a systemic review of a fourteen randomized trials on magnesium

as an adjuvant to postoperative analgesia (778 patients, 404 received magnesium). They used magnesium sulphate (I.V bolus + infusion) and (I.V bolus only), magnesium gluconate (I.V bolus + infusion), magnesium laevulinate (I.V bolus + infusion), using a different techniques as they give magnesium pre- or intraoperative with or without postoperative, I.V or I.M. They found that there was increased incidence of hypotension in the magnesium group than in the control group **(Christopher et al., 2007).** This difference in results is mostly propably due to using different types of magnesium, given in different times and by different techniques.

Also our study not goes with **Jee et al.** who studied the effect of magnesium suphate on attenuation of arterial blood pressure increase during LCCE in Thirty-two patients undergoing LCCE were randomly assigned to two groups; a control group was given saline, and a magnesium group received magnesium sulphate 50 mg/kg immediately before pneumoperitoneum. They found that adminstraion of magnesium sulphate has a significant effect in attenuation of arterial blood pressure during LCCE **(Jee et al., 2009)**. This difference in results may be due to using a different surgical technique (laparoscopy) not open surgical technique as used in our study.

As regard HR in our study, we found that administration of magnesium suphate has no significant changes ($P > 0.4$) in HR among the different groups in the preoperative period and before skin closure, but has a significant changes ($P = 0.0018$) after skin incision.

Our result goes with **Hwang et al.** who studied the effect of magnesium sulphate during spinal anesthesia on improving postoperative analgesia in forty patients divided into two equal groups, magnesium group (received

$MgSO_4$) and saline group (received normal saline) .They found that there was no significant difference in HR was observed between the two groups during the Perioperative period **(Hwang et al., 2010).**

Also, our result goes with **Telci et al.** who studid the effect of magnesium sulphate on reducing intraoperative anesthetic requirements in eighty-one patients undergoing elective spinal surgery, divided into two parallel groups, magnesium group which received $MgSO_4$ (30 mg/kg) and control group, which received the same volume of isotonic solution. They found that there no significant changes in HR between the two groups **(Telci et al., 2002).**

In addition, our result goes with **Jee et al.** who studied the effect of magnesium sulphate on attenuation of arterial blood pressure and heart rate during LCCE in thirty-two patients undergoing LCCE were randomly assigned to two groups; a control group was given saline, and a magnesium group received magnesium sulphate 50 mg/kg immediately before pneumoperitoneum. They found that adminstraion of magnesium sulphate has no significant effect on HR during LCCE **(Jee et al., 2009)**

But, our result not goes with **Seyhan et al.** who studied the effect of three different dose regimens of magnesium on propofol requirements, hemodynamic variables and postoperative pain relief in gynecological surgery in eighty women which were allocated to four equal groups. The control group received normal saline infusion 15 min before induction; magnesium group received 40 mg/kg of magnesium in 100 cc normal saline 15 min before induction of anesthesia, followed by 4h infusion of normal saline after intubation, In the other two magnesium groups 15 min infusion of 40 mg/kg magnesium sulphate in total 100 cc normal saline was given before induction of anesthesia, followed by 4h infusion of

either 10 or 20 mg/kg /h magnesium sulphate after intubation. They found that all magnesium groups demonstrated lower HR values than the control group in almost all measurements (**Seyhan et al., 2006).** These different results are almost due to using different dose regimens of magnesium.

In addition, our result as regard HR not goes with **Christopher et al.** who did a systemic review of a fourteen randomized trials on magnesium as an adjuvant to postoperative analgesia (778 patients, 404 received magnesium). They used Mg sulphate (I.V bolus + infusion) and (I.V bolus only), Mg gluconate (I.V bolus + infusion), Mg laevulinate (I.V bolus + infusion), using a different techniques as they give magnesium pre- or intraoperative with or without postoperative, I.V or I.M. They found that there was increased incidence of bradycardia in the magnesium group than in the control group **(Christopher et al., 2007).** This difference in results is due to using different types of magnesium, given in different times and by different techniques.

As regard the blood glucose level, in our study we found that there was no significant difference ($P = 0.078$) in blood glucose level among the groups in the preoperative period, but there was a significant ($P < 0.05$) increase in blood glucose level in the magnesium groups during the Intraoperative period.

Our result goes with **Sales et al.** who studied the role of magnesium on blood sugar control. In their study, researchers evaluated the relationship between magnesium status and blood sugar control in subjects with elevated blood sugar levels. The subjects were assessed for dietary magnesium intake and magnesium levels in urine, plasma, and red blood cells. The subjects were also evaluated for fasting blood sugar, 2-hour

post-prandial (after eating) blood sugar, and hemoglobin A1C, which is a measurement of blood sugar control over the previous 3 months. Kidney function was also assessed due to the fact that magnesium is excreted from the body via the kidneys. Thus microalbuminuria, which is the amount of the protein albumin in the urine; proteinuria, the amount in protein in the urine; and serum and urine creatinine, a measurement of kidney function, were also evaluated.

The results of the study showed that magnesium intake and levels of urine, plasma, and red blood cell magnesium were low in this population. In fact, 77 percent of the subjects had at least one value below the cut-off point of low magnesium status. The subjects also demonstrated poor blood sugar control with elevated blood sugar levels and 2-hour post-prandial glucose levels. The researchers found that the parameters that influenced fasting blood sugar were urine and plasma magnesium levels and dietary magnesium intake. In addition, they showed that plasma magnesium was influenced by creatinine clearance, a calculated value that represents overall kidney function.The researchers concluded that magnesium levels were affected by kidney function and are altered in subjects with elevated blood sugar levels. They also concluded that magnesium plays an important role in healthy blood sugar levels. (**Sales et al., 2011)**

But, our result not goes with **Keith et al.** who studied the Dose Optimization of Intravenous Magnesium Sulphate after Acute Stroke. In their study, within 24 hours of the onset of clinically diagnosed stroke, patients were randomized to receive placebo or one of three intravenous $MgSO_4$ infusions: a loading infusion of 8, 12, or 16 mmol, followed by 65 mmol over 24 hours. Serum magnesium concentrations and blood glucose concentrations were determined. Outcome at 30 and 90 days was

recorded. They found that there was no effects of magnesium on blood glucose were evident **(Keith et al., 1998)**. These different resuts due to using magnesium in different doses, applying the study on patient with stoke not healthy individuals and there was no effect of surgical operation or general anesthesia on the results.

In addition, our result not goes with **Hruby et al.** who founded that the higher magnesium intake is associated with lower fasting glucose and insulin, with no evidence of interaction with select genetic loci, in a meta-analysis of 15 CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology). In their study, favorable associations between magnesium intake and glycemic traits, such as fasting glucose and insulin, were observed in observational and clinical studies, but whether genetic variation affects these associations were largely unknowns. They hypothesized that single nucleotide polymorphisms (SNPs) associated with either glycemic traits or magnesium metabolism, affects the association between magnesium intake and fasting glucose and insulin **(Hruby et al., 2013)**.

Fifteen studies from the CHARG Consortium provided data from up to 52,684 participants of European descent without known diabetes. After adjustment for age, sex, energy intake, BMI, and behavioral risk factors, magnesium was inversely associated with fasting glucose. No magnesium-related SNP or interaction between any SNP and magnesium reached significance after correction for multiple testing. They concluded that a higher magnesium intake was associated with lower fasting glucose and insulin. This difference with our result is mostly due to giving magnesium as a dietary supplementation (oral rout not I.V), which affects on the metabolism of magnesium.

As regard the cortisol level in our study, there was no significant changes (P-value = 0.3) in the cortisol levels between the three groups in the preoperative period, but there was a significant ($P < 0.01$) decrease in the cortisol level during the Intraoperative period in the magnesium groups.

Our result not goes with **Jee et al.** who studied the effect of magnesium suphate on attenuation of arterial blood pressure increase during LCCE in thirty-two patients undergoing LCCE were randomly assigned to two groups; a control group was given saline, and a magnesium group received magnesium sulphate 50 mg/kg immediately before Pneumoperitoneum. They found that the Baseline cortisol levels were similar in the two groups, but in the control group, cortisol levels were elevated at 5 ($P < 0.05$) and 10 min ($P < 0.01$) post-Pneumoperitoneum and after surgery ($P < 0.01$) vs. baseline, and in the magnesium group, cortisol levels were elevated at 5 ($P < 0.05$) and 10 min ($P < 0.05$) post-Pneumoperitoneum and after surgery ($P < 0.01$). Therefore, there was no significant difference between the groups **(Jee et al., 2009)**.

This difference in the study mostly because of using different methods in the study and different surgical technique (which founded that the hypothalamic–pituitary–adrenal axis is still stimulated during Pneumoperitoneum under general anesthesia.

In addition, our result as regard cortisol level not goes with **Vedat et al.** who studied the effect of magnesium supplementation with or without exercise on cortisol level. In their study, the hormone levels were compared before and after administration of 10 mg/kg magnesium sulphate. They found that the cortisol levels increased only as a result of combined exhaustion and magnesium supplements, and not affected by magnesium administration only **(Vedat et al., 2008).** These different

results are almost due to using a low dose of magnesium sulphate administration plus there no effect of both general anesthesia and surgical stress.

As regard the time to the 1st analgesic dose required postoperatively in the current study, we found that there was a significant (P = 0.001) increase in time to the 1st analgesic dose required postoperatively in the groups received magnesium. Therefore, there was a significant decrease in the postoperative analgesic consumption in the patients received magnesium.

Our result goes with **Hwang et al.** who studied the effect of I.V infusion of magnesium sulphate during spinal anesthesia on improving postoperative analgesia in forty ASA I or II patients (20 in magnesium group, and 20 in saline group) undergoing total hip replacement under spinal anesthesia .after surgery, apatient-controlled analgesia (PCA) device containing morphine and ketorolac was provided for the patients. They founded that cumulative postoperative PCA consumptions were significantly lower in magnesium group **(Hwang et al., 2010).**

In addition, our result goes with **Christopher et al.** who did a systematic review of randomized trials on the effect of magnesium as an adjuvant to postoperative analgesia. They performed a comprehensive search (electronic databases, bibliographies, all languages) for randomized comparisons of magnesium and placebo in the surgical setting. Information on postoperative pain intensity and analgesic requirement was extracted from the trials and compared qualitatively. They found that eight trials (57% of all) reported on a significant decrease in postoperative analgesic requirements in patients received magnesium compared with placebo **(Christopher et al., 2007)**.

Also our result goes with **Seyhan et al**. who studied the effect of three different dose regimens of magnesium on propofol requirements, hemodynamic variables and postoperative pain relief in the gynecological surgery in eighty women, which were allocated to four equal groups. The control group received normal saline infusion 15 min before induction; magnesium group received 40 mg/kg of magnesium in 100 cc normal saline 15 min before induction of anesthesia, followed by 4 h infusion of normal saline after intubation.

In the other two magnesium groups 15 min infusion of 40 mg/kg magnesium sulphate in total 100 cc, normal saline was given before induction of anesthesia, followed by 4 h infusion of either 10 or 20 mg/kg/h magnesium sulphate after intubation. They found that the patients received magnesium supplementation consumed about 40% less morphine in the postoperative period compared with control patients **(Seyhan et al., 2006)**.

Also our result goes with **Levaux et al.** who studied the effect of Intraoperative magnesium sulphate on pain relief and patient comfort after major lumbar orthopedic surgery in 24 patients randomly allocated to receive either an infusion of 50 mg/kg magnesium sulphate or an equivalent volume of saline at induction of anesthesia. They found that postoperative opioids consumption was lower in the magnesium group, and they recommended the support of magnesium sulphate as a useful adjuvant for postoperative analgesia after major lumber surgery **(Levaux et al., 2003)**.

Additionally, our result goes with **Herbert et al.** who studied the effect of magnesium sulphate in reducing intra- and postoperative analgesic requirements in a randomized, double-blind study with two parallel

groups. They assessed the analgesic effect of Perioperative magnesium sulphate administration in 46 ASA physical Status I or II patient undergoing arthroscopic knee surgery with total I.V anesthesia. The patients received either magnesium sulphate 50 mg/kg preoperatively and 8 mg/kg/h intraoperatively or the same volume of isotonic sodium chloride solution I.V. Anesthesia was performed with propofol (2 mg/kg for induction, 6-8 mg/kg/h for maintenance), fentanyl (3 micg/kg for induction), and vecuronium (0.1 mg/kg for intubaion).

During the Intraoperative and postoperative periods, patients in the magnesiumgroup required significantly less fentanyl than those in the control group (control group 0.089 ± 0.02 micg/kg/min versus magnesium group 0.058 ± 0.01 micg/ Kg/min; $P < 0.05$ and control group 0.021 ± 0.013 micg/kg/min and magnesium group 0.0031 ± 0.0018 micg/kg/min; $P < 0.01$ for Intraoperative and Postoperative periods, respectively). They concluded that, in a clinical setting with almost identical levels of surgical stimulation, I.V magnesium sulphate administration reduces intraoperative and postoperative analgesic requirements compared with isotonic sodium chloride solution administration.these results demonstrated that magnesium could be an adjuvant to Perioperative analgesic management (**Herbert et al., 1998).**

Also our study goes with **Tramer et al.** who studied the role of magnesium sulphate in the postoperative analgesia in a randomized double-blind study, 42 patients undergoing elective abdominal hysterectomy with general anesthesia received 20% magnesium suphate or saline (control) 15 ml intravenously before start of surgery and 2.5 ml/h for the next 20 h. Postoperative morphine requirement was assessed for 48 h using patient-controlled analgesia. By comparing to the control group, they founded that magnesium treated patients consumed less

morphine during the first 48 h postoperatively, and they recommended that magnesium could be of interest as an adjuvant to postoperative analgesia **(Tramer et al., 1996)**.

But our result not goes with **Zarauza et al.** who did a comparative study with oral nifedipine, intravenous nimodipine, and magnesium sulphate in postoperative analgesia, in 92 patients undergoing elective colorectal surgery. In randomized double-blind study, patients were assigned to one of four groups. The control group received placebo. The nifedipine group received 60 mg of oral nifedipine. The magnesium group received an initial dose of 30 mg/kg followed by 10 mg/kg/h of magnesium sulphate over 20 h. The nimodipine group received 30 micg/kg/h of nimodipine over 20 h. Postoperative morphine consumption was assessed for 48 h. They founded that the Perioperative application of I.V magnesium failed to decrease postoperative morphine requirements after colorectal surgery **(Zarauza et al., 2000)**. This difference in result is almost because of using a low dose of magnesium.

As regard the postoperative shivering in our study, we found that there was a significant (P = 0.002) decrease in shivering occurance among the magnesium groups.

Our result goes with **Christopher et al.** who did a systematic review of randomized trials on the effect of magnesium as an adjuvant to postoperative analgesia. They performed a comprehensive search (electronic databases, bibliographies, all languages) for randomized comparisons of magnesium and placebo in the surgical setting. They founded that shivering occurance was less often with magnesium and the difference was statistically significant **(Christopher et al., 2007)**.

But our result not goes with **Levaux et al.** who studied the effect of Intraoperative magnesium sulphate on pain relief and patient comfort after major lumbar orthopedic surgery in 24 patients randomly allocated to receive either an infusion of 50 mg/kg magnesium sulphate (group Mg) or an equivalent volume of saline (group C) at induction of anesthesia. They found that shivering at emergence was observed in three patients from each group and there was no significant difference between the groups as regard shivering occurance (**Levaux et al., 2003).** This different result may be due external effect of ambient temperature of operating room.

As regard VAS in our study, there was a significant difference in VAS in the magnesium groups.

Our result goes with **Hwang et al.** who studied the effect of magnesium sulphate during spinal anesthesia on improving postoperative analgesia in forty patients divided into two equal groups, magnesium group (received $MgSO_4$) and saline group (received normal saline) .They found that the postoperative VAS scores was markedly lower in the magnesium group **(Hwang et al., 2010)**

Also our result goes with **Levaux et al.** who studied the effect of Intraoperative magnesium sulphate on pain relief and patient comfort after major lumbar orthopedic surgery in 24 patients randomly allocated to receive either an infusion of 50 mg/kg magnesium sulphate (group Mg) or an equivalent volume of saline (group C) at induction of anesthesia. They founded that the VAS pain scores were significant lower in group Mg than in group C **(Levaux et al., 2003)**.

In addition, our result goes with **Grace et al**. who studied the Analgesic Efficacy of Intravenous Magnesium Infusion. They revealed that IV

magnesium was associated with a decrease in visual analog pain scores at 4-6, 12 and 24 hours after surgery **(Grace et al., 2011)**.

But our result not goes with **Herbert et al.** who studied the effect of magnesium sulphate in reducing intra- and postoperative analgesic requirements in a randomized, double-blind study with two parallel groups, they assessed the analgesic effect of Perioperative magnesium sulphate administration in 46 ASA physical Status I or II patient undergoing arthroscopic knee surgery with total I.V anesthesia. The patients received either magnesium sulphate 50 mg/kg preoperatively and 8 mg/kg/h intraoperatively or the same volume of isotonic sodium chloride solution I.V.

Anesthesia was performed with propofol (2 mg/kg for induction, 6-8 mg/kg/h for maintenance), fentanyl (3 micg/kg for induction), and vecuronium (0.1 mg/kg for intubaion). They founded that the postoperative VAS scores were not significantly different between the control group and magnesium group. This suggested that the quality of analgesia was equivalent in both groups (**Herbert et al., 1998).** This difference in result may be due to absence effect of inhalational anesthesia on pain.

CHAPTER 8

SUMMARY

Effective treatment of peri- and post-operative pain represents an important component of postoperative recovery as it serves to blunt autonomic, somatic and endocrine reflexes with a resultant potential decrease in perioperative morbidity. It has become common practice to employ a polypharmacological approach to the treatment of postoperative pain, because no agent has yet been identified that specifically inhibits nociception without associated side effects.

Magnesium is the fourth most plentiful cation in the body. It has antinociceptive effects in animal and human models of pain. These effects are primarily based on the regulation of calcium influx into the cell and that is the natural physiological antagonism of the N-methyl-D-aspartate (NMDA) receptor. These effects have prompted the investigation of magnesium as an adjuvant for postoperative analgesia**.**

Ninety patients, ASA I or II status, aged from 20 to 50 years, undergoing lower abdominal surgery, and received general anesthesia by the same anesthetic technique. Classified into three equal groups, the Fentanyl group (F group) received 2 micg/kg Fentanyl, the magnesium group received 3 g (50 mg/kg) magnesium sulphate, the third group received both Fentanyl 2 micg/kg plus magnesium sulphate 3 g (50 mg/kg), Magnesium sulphate or Fentanyl added to 100 cc 0.9% saline and gave to patients I.V infusion 30 minutes before induction of anesthesia.

The following parameters were recorded, MAP, HR, Serum cortisol level and blood sugar level. At the following intervals: before induction of anesthesia, after skin incision, and before skin closure. Then postoperatively the following parameters were recorded, the time to the 1^{st} analgesic dose required, VAS, shivering scale, and postoperative hospital stay.

As regard the demographic characteristics of patients, there was no significant difference among groups as regard age, sex, weight, ASA and type of operations. As regard MAP in the preoperative period there was statistically significant (P-value = 0.02) difference between groups. But MAP after skin incision and before skin closure showed statistically non significant (P-value > 0.05) difference between groups.

As regard HR in the preoperative period and before skin closure, there was no statistically significant (P-value >0.05) difference between groups. But HR after skin incision showed statistically significant (P-value > 0.05) difference between groups.

As regard Blood sugar in the preoperative period, there was statistically non-significant (P-value = 0.078) difference between groups. But Blood sugar after skin incision and before skin closure showed statistically significant (P-value = 0.002) difference between groups.

As regard serum cortisol level in the preoperative period, there was no statistically significant (P-value = 0.3) difference between groups. But the serum cortisol level after skin incision and before skin closure showed statistically significant (P-value <0.01) difference between groups.

As regard the time to 1st analgesic dose required postoperatively between the three groups, there was statistically significant (P-value = 0.001) difference between groups.

As regard the postoperative shivering, there was a significant difference (P-value was 0.002) between groups.

As regard statistical changes in the postoperative VAS between the three groups, there was a significant difference in VAS at 4 hrs, 6 hrs,

and 9 hrs postoperatively. But there was no significant difference in VAS at baseline (just arrival at PACU), 2 hrs, and 12 hrs postoperatively.

As regard the postoperative hospital stay, there was a statistically significant (P-value = < 0.001) difference between groups.

Conclusion

The administration of magnesium is effective in controlling blood glucose and serum cortisol level intraoperatively, also effective in pain relief after lower abdominal surgery between 4 and 9 hours postoperatively. In addition, it is effective in decreasing postoperative shivering scale, analgesic consumption and hospital stay.

REFERENCES

(1) Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, Grubb RL, Higashida RT, Jauch EC, Kidwell C, Lyden PD, Morgenstern LB, Qureshi AI, Rosenwasser RH, Scott PA, and Wijdicks EF (2007):
Guidelines for the Early Management of Adults With Ischemic Stroke: A guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke; 38: 1655–711.

(2) Aggarwal P, Sharad S, Handa R, Dwiwedi S N, and Irshad M (2006):
Comparison of Nebulized Magnesium Sulphate and Salbutamol Combined with Salbutamol Alone in The Treatment of Acute Bronchial Asthma: A randomized study. Emerg Med J; 23: 358–62.

(3) Ahmed Said Elgebaly, Ahmed Ali Eldabaa, Ahmed Ali, Abd ELhafez and Manal Mostafa Abdalla (2011):
Comparison of Intravenous Magnesium Sulfate Versus Intrathecal Fentanyl, In Patients with Severe Preeclampsia, Scheduled for Cesarean Section, Under Spinal Anesthesia**.** Journal of Obstetric Anesthesia and Critical Care; 1 (I): 21–25.

(4) Alday ME, Redondo-Calvo FJ, and Criado JA (2005):
Magnesium in Anesthesia and Postoperative Recovery Care. Rev. ESP. Anesthesiol; 52 (4): 222-234.

(5) Alexander JM, McIntire DD, Leveno KJ, and Cunningham FG (2006):
Selective Magnesium Sulfate Prophylaxis for the Prevention of Eclampsia in Women with Gestational Hypertension. Obstet Gynecol; 108: 826–32.

(6) Alghamdi AA, Al-Radi OO, and Latter DA (2005):
Intravenous Magnesium for Prevention of Atrial Fibrillation after Coronary Artery Bypasses Surgery: A systematic review and meta-analysis. J Card Surg; 20: 293–9.

(7) Ali BS, Khazaeli P, Ghasemi F (2007):
Ionized and Total Magnesium Concentration in Patients with Severe Preeclampsia-Eclampsia Undergoing Magnesium Sulfate Therapy. J Obstet Gynaecol Res.; 33: 138-143.

(8) [Allen RW, James MFM, and Uys PC (1991):
Attenuation of the Pressor Response to Tracheal Intubation in Hypertensive Proteinuric Pregnant Patients by Lignocaine, Alfentanil and Magnesium Sulphate. Br J Anesthesia; 66: 216–23.

(9) Altan A, Turgut N, Yildiz F, Turkmen A, and Ustun H (2005):
Effects of Magnesium Sulphate and Clonidine on Propofol Consumption, Haemodynamics and Postoperative Recovery. British Journal of Anaesthesia 94 (4): 438–441.

(10) Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, and Smith D (2002):
Do Women With Pre-Eclampsia, And Their Babies, Benefit From Magnesium Sulphate? The Magpie Trial: A randomized placebo-controlled trial. Lancet; 359: 1877–90.

(11) Altmann D, Eggmann U, and Ammann P (2008):
Drug Induced QT Prolongation. Wien Klin Wochenschr; 120(5-6):128-35.

(12) American Heart Association Guidelines for Cardiopul-monary Resuscitation and Emergency Cardiovascular Care (2005):
Part 7.2: Management of Cardiac Arrest. Circulation; 112: IV–58.

(13) Anagnostou TL, Savvas I, Kazakos GM, Raptopoulos D, Ververidis H, and Roubies N (2008):
Thiopental and Halothane Dose-Sparing Effects of Magnesium Sulphate in Dogs. Veterinary Anesthesia and Analgesia; 35: 93–99.

(14) Apfel CC, Kranke P, Eberhart LH, Roos A, and Roewer N:
Comparison of Predictive Medals for Postoperative Nausea and Vomiting. Br J Anaesth; 234-240.

(15) Barakat AJ, Rennet OM (2001):
Gitelman's Syndrome (Familial Hypo- Kalemic Hypomagnesemia). J Nephrol; 14(1): 430–7.

(16) Barash PG, CullenBF, Stoelting RK (2009):
Clinical Anesthesia, 5th ed. Philadelpia: Ippincott Williams & Wilkins; 1242:1243.

(17) Bederson JB, Connolly ES Jr, Batjer HH, Dacey RG, Dion JE, Diringer MN, Duldner JE Jr, Harbaugh RE, Patel AB, and Rosenwasser RH (2009):
Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage: A Statement for Healthcare Professionals from a Special Writing Group of the Stroke Council, American Heart Association. Stroke; 40: 994–1025.

(18) Begon S, Pickering G, Eschalier A, Dubray C. (2002):
Magnesium Increases Morphine Analgesic Effect in Different Experimental Models of Pain. Anesthesiology; 96:627-32.

(19) Begon S, Pickering G, Eschalier A, Mazur A, Rayssiguier Y, and Dubray C (2001):
Role of Spinal NMDA Receptors, Protein Kinase C and Nitric Oxide Synthase in the Hyperalgesia Induced By Magnesium Deficiency in Rats. Br J Pharmacol; 134:1227-36.

(20) Belfort MA, Anthony J, Saade GR, and Allen JC Jr (2003):
A Comparison of Magnesium Sulfate and Nimodipine for the Prevention of Eclampsia. N Engl J Med; 348: 304–11.

(21) Bhatia A, Kashyap L, pawar DK, and Trikha A (2004):
Effect of Magnesium Infusion on Perioperative Analgesia in Open Cholecystectomy.J Clin Anesth., 16:262-5.

(22) Bigal ME, Bordini CA, Tepper SJ, Speciali JG (2002):
Intravenous Magnesium Sulphate in the Acute Treatment of Migraine without Aura and Migraine with Aura. Arandomized, Double-blind, placebo-controlled study. Cephalalgia; 22:345-53.

(23) Bilir A, Gulec S, Erkan A and Ozcelik A (2007):
Epidural Magnesium Reduces Postoperative Analgesic Requirements. British Journal of Anesthesia; 98: 519–523.

(24) Blitz M, Blitz S, Beasely R, Diner BM, Hughes R, Knopp JA, and Rowe BH (2005):
Inhaled Magnesium Sulfate in the Treatment of Acute Asthma. Cochrane Database Syst Rev; CD003898.

(25) Booth JV, Phillips-Bute B, McCants CB, Podgoreanu MV, Smith PK, Mathew JP, and Newman MF (2003):
Low Serum Magnesium Level Predicts Major Adverse Cardiac Events after Coronary Artery Bypass Graft Surgery. Am Heart J; 145: 1108–13.

(26) Brill S, Sedgwick PM, Hamann W, and Di Vadi PP (2002):
Efficacy of Intravenous Magnesium in Neuropathic Pain. Br J Anesth; 89:711-14.

(27) Burgess DC, Kilborn MJ and Keech AC (2006):
Interventions for Prevention of Post-Operative Atrial Fibrillation and Its Complications after Cardiac Surgery: A meta-analysis. Eur Heart J; 27: 2846–57.

(28) Cahill AG, Macones GA, Odibo AO and Stamilio DM (2007):
Magnesium for Seizure Prophylaxis in Patients with Mild Preeclampsia. Obstet Gynecol; 110: 601–7.

(29) Ceremuzynski L, Gebalska J, Wolk R, and Makowska E (2000):
Hypomagnesemia in Heart Failure with Ventricular Arrhythmias. Beneficial effects of magnesium supplementation. J Intern Med; 247: 78–86.

(30) Cete Y, Dora B, Ertan C, Ozdemir C, and Oktay C (2005):
A Randomized Prospective Placebo-Controlled Study of Intravenous Magnesium Sulphate versus Metoclopramide in the Management of Acute Migraine Attacks in the Emergency Department.Cephalalgia; 25:199-204.

(31) Chandran S, Haqeb ME, Wickramsinghe HT and Wint Z (2004):
The Use of Mg in Severe Persistant Pulmonary Hypertension of the Newborn; Journal of tropical pediatric; Aug; 50: 219-23.

(32) Charron J, Rainville P, and Marchand S (2006):
Direct Comparison of Placebo Effects on Clinical and Experimental Pain.Clin J pain.22:204-211.

(33) Cheol Lee, Yoon-Kang Song, Hyun-Myun Jeong, and Seong-Nam Park (2011):
The Effects of Magnesium Sulfate Infiltration on Perioperative Opioid Consumption and Opioid-Induced Hyperalgesia in Patients Undergoing Robot-Assisted Laparoscopic Prostatectomy with Remifentanil-Based Anesthesia. Korean J Anesthesiol.; 61: 244–250.

(34) Cheuk DK, Chau TC, and Lee SL (2005):
A meta-Analysis on Intravenous Magnesium Sulphate for Treating Acute Asthma. Arch Dis Child; 90: 74–7.

(35) Chiu C, Heyer EJ, Rampersad AD, Zurica J, Ornstein E, Sahlein DH, Sciacca RR, and Connolly ES Jr (2006):
High dose magnesium infusions are not associated with increased pressor requirements after carotid endarterectomy. Neurosurgery; 58: 71–7.

(36) Choi JC, Yoon KB, Um DJ, Kim C, Kim JS, and Lee SG (2002):
Intravenous Magnesium Sulphat Administration Reduces Propofol Infusion Requirements during Maintenance of Propofol-N_2O Anesthesia, Part 1: Comparing Propofol Requirements According To Hemodynamic Responses. Part 2: Comparing Bispectral Index in Control and Magnesium Groups. Anesthesiology; 97:1137-41.

(37) Chong MS and Bajwa ZH (2003):
Diagnosis and Treatment of Neuropathic Pain. J Pain Symptom Manage. 25 (5 suppl):S4-S11.

(38) Christopher Lysakowski, Lionel Dumont, Christoph Czarnetzki, and Martin R. Tramer (2007):
Magnesium as an Adjuvant to Postoperative Analgesia: A systemic Review of Randomized trials. Anesth Analg; 104:1532-9.

(39) Coleman CI, Sood N, Chawla D, Talati R, Ghatak A, and Kluger J (2009):
Intravenous Magnesium Sulfate Enhances The Ability Of Dofetilide To Successfully Cardiovert Atrial Fibrillation Or Flutter: Results of the Dofetilide and Intravenous Magnesium Evaluation. Europace; 11: 892–5.

(40) Cook RC, Humphries KH, Gin K, Janusz MT, Slavik RS, Bernstein V, Tholin M, and Lee MK (2009):
Prophylactic Intravenous Magnesium Sulphate In Addition To Oral -Blockade Does Not Prevent Atrial Arrhythmias after Coronary Artery or Valvular Heart Surgery: A Randomized Controlled Trial. Circulation; 120: 163–9.

(41) Corbo J, Esses D, Bijur PE, Iannaccone R, and Gallagher EJ (2001):
Randomized Clinical Trial Of Intravenous Magnesium Sulphate As An Adjunctive Medication For Emergency Department Treatment Of Migraine Headache. Ann Emerg Med; 38:621-7.

(42) Czarnetzki C, Lysakowski C, Elia N, and Tramer MR (2010):
Time Course of Rocuronium-Induced Neuromuscular Block after Pre-Treatment with Magnesium Sulphate: A randomized study. Acta Anesthesiol Scand; 54: 299–306.

(43) Dacey MJ (2001):
Hypomagnesemic Disorders, Grit Care Clinic; 17(1): 155–73.

(44) Demirkaya S, Vural O, Dora B, and Topcuoglu MA (2001):
Efficacy of Intravenous Magnesium Sulphate in Treatment of Acute Migraine Attacks. Headache; 41:171-7.

(45) Dhandapani SS, Gupta A, Vivekanandhan S, Sharma BS, and Mahapatra AK (2008):
Randomized Controlled Trial of Magnesium Sulphate in Severe Closed Traumatic Brain Injury. Indian J Neurotrauma; 5: 27–33.

(46) Do Amaral AF, Rodrigues Junior AL, Terra FJ, Vannucchi H, and Martinez JA (2008):
Effects of Acute Magnesium Loading on Pulmonary Function of Stable COPD Patients. Med Sci Monit; 14: 524–9.

(47) Dorhout Mees SM, Rinkel GJ, Feigin VL, et al. (2007):
Calcium Antagonists for Aneurysmal Subarachnoid Hemorrhage. Cochrane Database Syst Rev; CD000277.

(48) Doyle LW, Crowther CA, Middleton P, and Marret S (2009a):
Magnesium Sulphate for Women at Risk of Preterm Birth for Neuroprotection of the Fetus. Cochrane Database Syst Rev; CD004661.

(49) Doyle LW, Crowther CA, Middleton P, and Marret S (2009b):
Antenatal Magnesium Sulphate and Neurologic Outcome in Preterm Infants: Asystemic Review. Obestetric and gynecology 113(6):1327-1333.

(50) Dube L and Granry JC (2003):
The Therapeutic Use of Magnesium in Intensive Care and Emergency Medicine: A review. Can J Anesth.; 50: 732–46.

(51) Duley L (2009):
The Global Impact of Preeclampsia and Eclampsia. Semin Perinatol; 33: 130–7.

(52) Duley L, Gulmezoglu AM and Henderson Smart DJ (2003):
Magnesium Sulphate and Other Anticonvulsants for Women with Preeclampsia. Cochrane Database. Syst Rev; CD000025.

(53) Durmus M, But AK, Erdem TB, Ozpolat Z, and Ersoy MO (2006):
The effects of Magnesium Sulphate on Sevoflurane Minimum Alveolar Concentrations and Haemodynamic Responses. Eur J Anesthesiol.; 23: 54–9.

(54) Elia N, and Tramer MR (2005):
Ketamine and Postoperative Pain-Aqauntitative Systematic Review Of Randomized Trials.Pain; 113:61-70.

(55) Elin R (1988):
Magnesium Metabolism in Health and Disease. Disease a month 1988; 34: 166–218.

(56) Euser AG and Cipolla MJ (2009):
Magnesium Sulfate for the Treatment of Eclampsia: A Brief Review. Stroke April; 40(4): 1169–1175.

(57) Farouque HM, Sanders P, and Young GD (2000):
Intravenous Magnesium Sulfate For Acute Termination Of Sustained Monomorphic Ventricular Tachycardia Associated With Coronary Artery Disease. Am J Cardiol; 86:1270–2.

(58) Fawcett WJ and Edkins CL (2001):
Pheochromocytoma Diagnosed During Labour. Br J Anesth. 2001; 86: 288–9.

(59) Fawcett WJ, Haxby EJ, and Male DA (1999):
Magnesium, Physiology and Pharmacology. Br J Anesth. 1999; 83: 302–20.

(60) Fine KD, Santa Ana CA, Porter JL and Fordtran JS (1991):
Intestinal Absorption of Magnesium from Food and Supplements. J Clin Invest. 1991; 88: 396–402.

(61) Fisher K, Coderre TJ, and Hagen NA (2000):
Targeting the N-Methyl-D-Aspartate Receptor for Chronic Pain Management. Preclinical animal studies, recent clinical experience and future research directions. J Pain Symptom Manage; 20: 358–73.

(62) Fogarty A, Lewis SA, Scrivener SL, Antoniak M, Pacey S, Pringle M, and Britton J (2003):
Oral Magnesium and Vitamin C Supplements in Asthma: A parallel group randomized placebo-controlled trial. Clin Exp Allergy; 33: 1355–9.

(63) Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. (2006):
ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation; 114: e257–e354.

(64) Ginder S, Oatman B, and Pollack M (2000):
A Prospective Study of I.V Magnesium and I.V Prochlorperazin in the Treatment of Headaches. J Emerg Med; 18:311-15.

(65) Glinas C, Fortier M, Viens C, Fillion L, and Puntillo KA (2004):
Pain Assessment and Management in Critically Ill Intubated Patients: aretrospective study. Am J Crit Care.13 (2):126-135.

(66) Glover ML, Machado C, and Totapally BR (2002):
Magnesium Sulfate Administered Via Continuous Intravenous Infusion In Pediatric Patients With Refractory Wheezing. J Crit Care; 17: 255–8.

(67) Goffaux P, Redmond WJ, Rainville P, and Marchand S (2007):
Descending Analgesia-When The Spine Echoes What The Brain Expects. Pain.130 (1-2):137-143.

(68) Gordon DB, DahI JL, Miaskwski C McCarberg B, Todd KH, Paice JA, Lipman AG, Bookbinder M, Sanders SH, Turk DC, and Carr DB (2005):
American Pain Society Recommendations for Improving the Quality of Acute and Cancer Pain Management: American Pain Soceety Quality of Care Task Force. Arch Intern Med.; 165(4):1574-1580.

(69) Grace Kong J., Gabe Tsang, Brandon Togioka Kanupriya, Kumar Jean, Pierre Ouanes, and Christopher Wu (2011):
Analgesic Efficacy of Intravenous Magnesium Infusion: a metaanalysisReg Anesth Pain Med Spring; 184.

(70) Guler A, Satilmis T, Akinci SB, Celebioglu B, and Kanbak M (2005):
Magnesium Sulfate Pretreatment Reduces Myoclonus After Etomidate. Anesth Analg.; 101:705–9.

(71) Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, and Trohman RG (2007):
Current Concepts in the Mechanisms and Management of Drug-Induced QT Prolongation and Torsade De Pointes. Am Heart J;153(6):891-9.

(72) Gupta K, Vohra V and Sood J (2006):
The Role of Magnesium as an Adjuvant during General Anesthesia. Anesthesia; 61:1058–63.

(73) Gupta SD, Mitra K, Mukherjee M, Roy S, Sarkar A, Kundu S, Goswami A, Sarkar UN, Sanki P, and Mitra R (2011):
Effect of Magnesium Infusion on Thoracic Epidural Analgesia. Saudi J Anesth; 5(1): 55–61.

(74) Gyamlani G, Parikh C, and Kulkarni AG (2000):
Benefits of Magnesium in Acute Myocardial Infarction: Timing is crucial. Am Heart J; 139: 703.

(75) Halhali A, Wimalawansa SJ, Berentsen V, Avila E, Thota CS, and Larrea F (2001):
Calcitonin And Parathyroid Hormone-Related Peptides In Preeclampsia: Effects of magnesium sulfate. Obstet Gynecol; 97: 893–7.

(76) Hasegawa AE and Zacny JP (1997):
The Influence of Three L-Type Calcium Channel Blockers on Morphine Effects in Healthy Volunteers. Anesth Analg; 85: 633–8.

(77) Hassan TB, Jagger C and Barnett DB (2002):
A Randomized Trial to Investigate the Efficacy of Magnesium Sulphate for Refractory Ventricular Fibrillation. Emerg Med J.2002; 19: 57–62.

(78) Herbert Koinig, Thomas Wallner, Peter Marhofer, Harald Andel, Klaus Horauf, and Nikolaus Mayer (1998):
Magnesium Sulfate Reduces Intra- and Postoperative Analgesic Requirements. Anesth Analg; 87:206-10.

(79) Herroeder S, Schönherr ME, De Hert SG, and Hollmann MW (2011):
Magnesium–Essentials for Anesthesiologists. Anesthesiology; 114: 971–93.

(80) Hollmann MW, Liu HT, Hoenemann CW, Liu WH, and Durieux ME (2001):
Modulation of NMDA Receptor Function by Ketamine and Magnesium. Part II: Interactions with Volatile Anesthetics. Anesth Analg; 92:1182–91

(81) Hoshino K, Ogawa K, Hishitani T, Isobe T, and Etoh Y (2006):
Successful Uses of Magnesium Sulfate for Torsades De Pointes in Children with Long QT Syndrome. Pediatr Int; 48(2):112-7.

(82) Hruby A, Ngwa JS, Renström F, Wojczynski MK, Ganna A, Hallmans G, Houston DK, Jacques PF, Kanoni S, Lehtimäki T, Lemaitre RN, Manichaikul A, North KE, Ntalla I, Sonestedt E, and Tanaka T et al. (2013):
Higher Magnesium Intake Is Associated with Lower Fasting Glucose and Insulin, with No Evidence of Interaction with Select Genetic Loci, in a Meta-Analysis of 15 CHARGE Consortium Studies· American Society for Nutrition. J. Nutr. March 1, 2013 vol. 143 no. 3 345-353.

(83) Huether SE and McCance KL (2004):
Understanding Pathophysiology. 3rd ed. St Louis, MO: Mosby; 333.

(84) Huijgen HJ, Soesan M, Sanders R, Mairuhu WM, Kesecioglu J, and Sanders GT (2000):
Magnesium Levels in Critically Ill Patients. What should we measure? Am J Clin Pathol.; 114: 688–95.

(85) Hwang JY, Na HS, Jeon YT, Ro YJ, Kim CS and Do SH (2010):
I.V. Infusion of Magnesium Sulphate during Spinal Anesthesia Improves Postoperative Analgesia. Br J Anesth; 104: 89–93.

(86) Idama TO and Lindow SW (1998):
Magnesium Sulphate: A Review of Clinical Pharmacology Applied to Obstetrics. Br J Obstet Gynecol. 1998; 105: 260–8.

(87) In Gyu Choi, Young Soon Choi, Yong Ho Kim, Jin Hye Min, Young Keun Chae, Yong Kyung Lee, So Woon Ahn, Young Shin Kim, and Aerena Lee et al. (2011):
The Effects of Postoperative Brachial Plexus Block Using $MgSO_4$ on the Postoperative Pain after Upper Extremity Surgery. Anesthesiology; 114: (4): 971–993.

(88) Iseri LT (1990):
Role of Magnesium in Cardiac Tachyarrhythmias. Am J Cardiol; 19; 65(23): 47K–50K.

(89) J Physiol (2005):
Epithelial Magnesium Transport in Intestine and Kidney July 15; 566(Pt 2): 301–308.

(90) Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, Chalfin DB, Masica MF, Bjerke HS, Coplin WM, Crippen DW, Fuchs BD, Kelleher RM, Marik PE, Nasraway SA Jr, Murray MJ, Peruzzi WT, Lumb PD (2002):
Task Force of the American College of Critical Care Medicine (ACCM) of the society of the Critical Care Medicine (SCCM), American Society of health-system pharmacists (ASHP), American college of chest Physicians. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult.Critical Care Med.; 30(1):119-141.

(91) James MF and Cronje L (2004):
Pheochromocytoma Crisis: The use of magnesium sulfate. Anesth Analg; 99: 680–6.

(92) James MFM (2009):
Magnesium: An Emerging Drug in Anesthesia. Br J Anesth; 103:465-9.

(93) Jee D, Lee D, Yun S and Lee C (2009):
Magnesium Sulfate Attenuates Arterial Pressure Increase during Laparoscopic Cholecystectomy. Br J Anesth.; 103 (4): 484–489.

(94) Jeffrey L Saver (2011):
Field Administration of Stroke Therapy– Magnesium (FAST-MAG) Trial, www.clinicaltrials.gov, by University of California, Los Angeles, USA, last updated on December 12, 2011.

(95) Jodka P, and Heard SO (2005):
Management of Acute Pain in the Intensive Care Unit. In: Fink MP, Abraham E, Vincent J, Patrick PM, eds. text book of Critical Care. 5th ed.Philadelphia, PA: Elsevier Saunders; 13-16.

(96) Jose A (2008):
Curiel-Garcia, Martha Rodriguez-Moran, Fernando Guerrero-Romero: Hypomagnesemia and mortality in patients with type 2 diabetes. Magnesium Research; 21 (3): 163-6

(97) Kafadar AM, Sanus GZ, Is M, Coskun A, Tanriverdi T, Hanimoglu H, and Uzan M (2007):
Prolonged Elevation of Magnesium in the Cerebrospinal Fluid of Patients with Severe Head Injury. Neurol Res; 29: 824–9.

(98) Kang WS, Yun HJ, Han SJ, Kim HY, Kim DK, Lim JA, Woo NS, and Kim SH (2011):
The Effects of Magnesium on the Course of Atrial Fibrillation and Coagulation in Patients with Atrial Fibrillation Undergoing Mitral Valve Annuloplasty. Korean J Anesthesiol. September; 61(3): 210–215.

(99) Kara H, Sahin N, Ulusan V, and Aydogedu T (2002):
Magnesium Infusion Reduces Postoperative Pain. Eur J Anaesthesiology; 19:52-6.

(100) Kausalya PJ, Amasheh S, Gunzel D, Wurps H, Müller D, Fromm M, and Hunziker W (2006):
Disease-Associated Mutations Affect Intracellular Traffic And Paracellular Mg^{+2} Transport Function Of Claudin-16. J Clin Invest; 116: 878–91.

(101) Kaya S, Kararmaz A, Gedik R, and Turhanoglu S (2009):
Magnesium Sulfate Reduces Postoperative Morphine Requirement After Remifentanil-Based Anesthesia. Med Sci Monit; 15: I5–I9.

(102) Kaye P and O'Sullivan I (2002):
The Role of Magnesium in the Emergency Department. Emerg Med J; 19:288-291.

(103) Keith W Muir and Kennedy R Lees (1998):
Dose Optimization of Intravenous Magnesium Sulfate after Acute Stroke American Heart Association; 29: 918-923.

(104) Keogh E and Herdenfeldt M (2002):
Gender, Coping and the Perception of Pain. Pain; 97:195-201.

(105) Keus F, Ahmed Ali U, Noordergraaf GJ, Roukema JA, Gooszen HG, and Van Laarhoven CJHM (2007):
Anaesthesiological Considerations in Small-Incision and Laparoscopic Cholecystectomy in Symptomatic Cholecystolithiasis: implications for pulmonary function. A randomized clinical trial. Acta Anesthesia Scand; 51:1068-70.

(106) Kim JE, Jeon JP, No HC, Choi JH, Lee SH, Ryu KH, and Kim ES (2011):
The Effects of Magnesium Pretreatment on Reperfusion Injury during Living Donor Liver Transplantation**.** Korean J Anesthesiol. June; 60(6): 408–415.

(107) Kissin I (2000):
Pre-Emptive Analgesia. Anesthesiology; 93: 1138–43.

(108) Kissin I, Bright CA, and Brabley EL Jr (2000):
The Effect of Ketamine on Opioid-Induced Acute Tolerance: Can It Explain Reduction of Opioid Consumption With Kitamine-Opioid Analgesic Combinations? Anesth Analg; 91: 1483-8.

(109) Ko SH, Lim HR, Kim DC, Han YJ, Choe H, Song HS. (2001):
Magnesium Sulphate Does Not Reduce Postoperative Analgesic Requirements. Anesthesiology; 95:640-6.

(110) Konrad M, Schlingmann KP, and Gudermann T (2004):
Insights into the Molecular Nature of Magnesium Homeostasis. Am J Physiol Renal Physiol.; 286: 599–605.

(111) Kranke P, Eberhart LH, Roewer N, and Tramer MR (2004):
Single-Dose Parenteral Pharmacological Interventions for the Prevention of Postoperative Shivering – A Quantitative Systematic Review of Randomized Controlled Trials. Anesth Analg; 99:718-27.

(112) Kroin JS, Mc Carthy RJ, Von Roenn N, Schwab B, Tuman KJ, and Ivankovich AD (2000):
Magnesium Sulfate Potentiates Morphine Antinociception At The Spinal Level. Anesth Analg; 90: 913–7.

(113) Lake CL, Hines RL, and Blitt CD (2001):
Clinical Monitoring: Practical Applications or Anesthesia and Critical Care.WB.

(114) Landymore RW, Marble AE, and Fris J (1994):
Effect of Intermittent Delivery of Warm Blood Cardioplegia on Myocardial Recovery. Ann Thorac Surg. May; 57(5): 1267–72.

(115) Laurie Barclay (2009):
Antenatal Magnesium Sulfate May Be Neuroprotective Medscape Medical News Cochrane Database Syst Rev. Published online January 21.

(116) Laurila J, Laurila PA, Saarnio J, Koivukangas V, Syrijala H, and Alakokko T (2006):
Organ System Dysfunction Following Open Cholecystectomy For Acute Calculus Cholecystitis In Critically Ill Patients. Acta Anesthesia Sand; 50:173-9.

(117) Lee DH and Kwon IC (2009):
Magnesium Sulphate Has Beneficial Effects as an Adjuvant during General Anaesthesia for Caesarean Section. Br J Anaesth. 2009 Dec; 103(6):861-6.

(118) Levaux CH, Bonhomme V, Dewandre P Y, Brichant J F, and Hans P (2003):
Effect of Intraoperative Magnesium Sulphate on Pain Relief and Patient Comfort after Major Lumber Orthopedic Surgery. Anesthesia; 58:131-135.

(119) Lichtor JL (2006):
Anaesthesia for Ambulatory Surgery. In: Barash PG, Cullen BF, Stoelting RK, eds. Clinical anesthesia, 5th ed. Philadelphia: Lippincott Williams &Wilkins: 1242-1243.

(120) Lu JF and Nightingale CH. (2000):
Magnesium Sulfate in Eclampsia and Pre-Ecalmpsia: Pharmaco-Kinetic Principles. Clin pharmacokinet; 38:305-14.

(121) Lyell DJ, Pullen K, Campbell L, Ching S, Druzin ML, Chitkara U, Burrs D, Caughey AB, El-Sayed YY (2007):
Magnesium Sulfate Compared with Nifedipine for Acute Tocolysis of Preterm Labor: A randomized controlled trial. Obstet Gynecol; 110: 61–7.

(122) Lysakowski C, Dumont L, Czarnetzki C, and Tramer MR (2007):
Magnesium as an Adjuvant to Postoperative Analgesia: A Systematic Review of Randomized Trials. Anesth Analg; 104:1532-9.

(123) Mac Kay AP, Berg CJ, and Atrash HK (2001):
Pregnancy-Related Mortality from Preeclampsia and Eclampsia. Obstet Gynecol; 97: 533–8.

(124) Mack WJ, Kellner CP, Sahlein DH, Ducruet AF, Kim GH, Mocco J, Zurica J, Komotar RJ, Haque R, Sciacca R, Quest DO, Solomon RA, Connolly ES, and Heyer EJ (2009):
Intraoperative Magnesium Infusion during Carotid Endarterectomy: A double-blind placebo-controlled trial. J Neurosurg.; 110: 961–7.

(125) Maheshwari AV, Blun YC, Shekhar L, Ranawat AS, Ranawat CS (2009):
Multimodal Pain Management after Total Hip and Knee Arthroplasty at the Ranawat Orthopaedic Center. Clin Orthop Relat res; 467:1418-23.

(126) Mami AG, Ballesteros JR, Fritz KI, Kubin J, Mishra OP, Delivoria-Papadopoulos M (2006):
Effects of Magnesium Sulfate Administration during Hypoxia on Cam Kinase IV and Protein Tyrosine Kinase Activities in the Cerebral Cortex of Newborn Piglets. Neurochem Res; 31: 57–62.

(127) Mannino DM, Homa DM, Akinbami LJ, Moorman JE, Gwynn C, and Redd SC (2002):
Surveillance for Asthma in the United States, 1980–1999. MMWR Surveill Summ; 51: 1–13.

(128) Marino PL (2007):
Magnesium. The ICU Book: third edition, Lippincott Williams &Wilkins, New York, section 9, chapter 34, 625-38.

(129) Mauskop A and Altura BM (1998):
Role of Magnesium in the Pathogenesis and Treatment of Migraine. Clin Neurosci.1998; 5(1): 24–7.

(130) Mavrommati PD, Gabopoulou ZT, Papadimos CN, Petsikopoulos MG, Vrettou VA, Konstantinidou MG, and Velmachou KG (2004):
The Perioperative Infusion of Low Doses of Sulphate Reduces Analgesic in Patients Undergoing Hernioplasty. Acute Pain; 5:81-7.

(131) Mc Lean RM (1994):
Magnesium and its therapeutic uses: a review. Am J Med.1994; 96: 63–76.

(132) McGrath PA and Brown SC (2003):
Pain in Children. In: Kanner R, ed. Pain Management Secerts. 2nd ed. Philadelphia, PA: Hanley & Belfus; 2003:180-194.

(133) McKee JA, Brewer RP, Macy GE, Borel CO, Reynolds JD, Warner DS (2005):
Magnesium Neuroprotection Is Limited In Humans with Acute Brain Injury. Neurocrit Care; 2: 342–51.

(134) Memiş D, Turan A, Karamanlioğlu B, Süt N, Pamukçu Z (2002):
The Use of Magnesium Sulphate to Prevent Pain on Injection of Propofol. Anesth Analg; 95:606-8.

(135) Mentes O, Harlak A, Yigit T, Balkan A, Balkan M, Cosar A, Savaser A, Kozak O, Tufan T (2008):
Effect of Intraoperative Magnesium Sulphate Infusion on Pain Relief after Laparoscopic Cholecystectomy. Acta Anesthesiol Scand.; 52: 1353–9.

(136) Mikkelsen S, Dirks J, Fabricius P, Petersen KL, Rowbotham MC, Dahl JB (2001):
Effect of Intravenous Magnesium on Pain Secondary Hyperalgesia Associated with the Heat/Capsacin Sensitization Model in Volunteers. Br J Anesth; 86:871-3.

(137) Minami T, Adachi T, and Fukuda K (2002):
An Effective Use of Magnesium Sulfate for Intraoperative Management of Laparoscopic Adrenalectomy for Pheochromocytoma in a Pediatric Patient. Anesth Analg; 95: 1243–4.

(138) Moran JL, Gallagher J, Peake SL, Cunningham DN, Salagaras M, Leppard P (1995):
Parenteral Magnesium Sulfate Versus Amiodarone in the Therapy of Atrial Tachyarrhythmias: A prospective randomized study. Crit Care Med.1995; 23: 1816–24.

(139) Morgan GE, Mikhail MS, and Murray MJ (2006):
Pain Management.In Clinical Anaesthesiology, 4th Ed, the McGraw-Hill, 18:359-410.

(140) Muir KW, Lees KR, Ford I, and Davis S (2004):
Magnesium for Acute Stroke (Intravenous Magnesium Efficacy in Stroke Trial): Randomized controlled trial. Lancet; 363: 439–45.

(141) Munro Seelig MS: Magnesium requirements in human nutrition. Magnesium-Bull 1981; 3: suppl, 1: 26–47.

(142) Nand Kishore Kalra, Anil Verma, Apurva Agarwal, and Hd Pandey (2011):
Comparative Study of Intravenously Administered Clonidine and Magnesium Sulfate on Hemodynamic Responses during Laparoscopic Cholecystectomy. J Anesthesiol Clin Pharmacol. Jul-Sep; 27(3): 344–348.

(143) Nassar AH, Sakhel K, Maarouf H, Naassan GR, and Usta IM (2006):
Adverse Maternal and Neonatal Outcome of Prolonged Course of Magnesium Sulfate Tocolysis. Acta Obstet Gynecol Scand; 85: 1099–103.

(144) Nicholas J. Wilkes, Susan V. Mallett, Tim Peachey, Carmelo Di Salvo, and Robin Walesby (2002):
Correction of Ionized Plasma Magnesium During Cardiopulmonary Bypass Reduces the Risk of Postoperative Cardiac Arrhythmia. Anesth Analg.; 95: 828-34.

(145) O'Flaherty JE and Lin CX (2003):
Does Ketamine Or Magnesium Affect Post Tonsillectomy Pain In Children? Pediatr Anesth; 13: 413–21.

(146) Omote K, Sonoda H, Kawamata M, Iwasaki H, Namiki A (1993):
Potentiation of Antinociceptive Effects of Morphine by Calcium-Channel Blockers at the Level of the Spinal Cord. Anesthesiology; 79: 746–52.

(147) Ozalevli M, Cetin TO, Unlugenc H, Guler T, Isik G (2005):
The effect of Adding Intrathecal Magnesium Sulphate to Bupivacaine-Fentanyl Spinal Anesthesia. Acta Anesthesiol Scand; 49: 1514–1523.

(148) Ozcan PE, Tugrul S, Senturk NM, Uludag E, Cakar N, Telci L, and Esen F (2007):
Role of Magnesium Sulfate in Postoperative Pain Management for Patients Undergoing Thoracotomy. J Cardiothorac Vasc Anesth; 21: 827–31.

(149) Pasero C and McCaffrey M (2002):
Pain In the Critically Ill: New Information Reveals That One of the Simplest Procedures-Turning-Can Be the Most Painful One. Am J Nurs; 102(1):59-60.

(150) Pasero C and McCaffrey M (2005):
No Self-Report Means No Pain-Intensity Rating: Assessing Pain In Patients Who Cannot Provide A Self-Report. Am J Nurs. 105 (10):50-53.

(151) Peikert A, Wiliuizig C and Kohne-Volland R (1996):
Prophylaxis of Migraine with Oral Magnesium; Results from a Prospective, Multi-Center, Placebo-Controlled and Double-Blind Randomized Study. Cephalalgia; 16(4): 257–63.

(152) Peterson RC, Hammarstrom JM, and Seal II RR (2006):
Alpersite (Mg, Cu)SO_4•7H_2O, A New Mineral of the Melanterite Group, and Cuprian Pentahydrite: Their Occurrence within Mine Waste. American Mineralogist 91(2-3):261-269.

(153) Pfaffenrath V, Wessely P, Meyer C, Isler HR, Evers S, Grotemeyer KH, Taneri Z, Soyka D, Göbel H, and Fischer M (1996):
Magnesium in the Prophylaxis of Migraine–A Double-Blind Placebo-Controlled Study. Cephalalgia; 16 (6): 436–40.

(154) Pinard AM, Donati F, Martineau R, Denault AY, Taillefer J, Carrier M (2003):
Magnesium Potentiates Neuromuscular Blockade With Cisatracurium During Cardiac Surgery. Can J Anesth; 50: 172–8.

(155) Pogatzki-Zahn EM and Zahn PK (2006):
From Preemptive to Preventive Analgesia. Curr Opin Anaesthesiol; 19: (5):551-555.

(156) Polderman KH, Bloemers FW, Peerdeman SM, and Girbes AR (2000):
Hypomagnesemia and Hypophosphatemia at Admission in Patients with Severe Head Injury. Crit Care Med; 28: 2022–5.

(157) Portenoy RK (2003):
Neuropathic Pain. In: Kanner R, ed. Pain Management Secrets. 2nd ed. Philadelphia, PA: Hanley& Belfus; 147-170.

(158) Pranskunas A, Vellinga NA, Pilvinis V, Koopmans M, and Boerma EC (2011):
Microcirculatory Changes during Open Label Magnesium Sulphate Infusion in Patients with Severe Sepsis and Septic Shock. BMC Anesthesiology, 11:12.

(159) Quamme GA (1986):
Renal handling of magnesium: Drug and hormone interactions. Magnesium 1986; 5: 248–272.

(160) Rayssiguier Y, Gueux F and Weiser D (1986):
Effect of magnesium deficiency on lipid metabolism in rats fed a high carbohydrate diet. J Nutr. 1986; 111(11): 1876–83.

(161) Rouse DJ, Hirtz DG, Thom E, Varner MW, Spong CY, Mercer BM, Iams JD, Wapner RJ, Sorokin Y, Alexander JM, Harper M, Thorp JM Jr, Ramin SM, Malone FD, Carpenter M, Miodovnik M, Moawad A, O'Sullivan MJ, Peaceman AM, Hankins GD, Langer O, Caritis SN, Roberts JM (2008):
A randomized Controlled Trial of Magnesium Sulfate for the Prevention of

Cerebral Palsy. N Engl J Med. 2008 Aug 28; 359(9):895-905. doi: 10.1056/NEJMoa0801187.

(162) Rowe BH and Camargo CA Jr (2008):
The Role of Magnesium Sulfate in the Acute and Chronic Management of Asthma. Curr Opin Pulm Med; 14: 70–6.

(163) Rowe BH, Bretzlaff JA, Bourdon C, Bota GW, and Camargo CA Jr (2000):
Magnesium Sulfate for Treating Exacerbations of Acute Asthma in the Emergency Department. Cochrane Database Syst Rev; CD001490.

(164) Ryu JH, Sohn IS, and Do SH (2009):
Controlled Hypotension for Middle Ear Surgery: A Comparison between Remifentanil and Magnesium Sulphate. Br J Anaesth; 103:490-5.

(165) Sağsöz N and Küçüközkan T (2003):
The Effect of Treatment on Endothelin-1 Concentration and Mean Arterial Pressure in Preeclampsia and Eclampsia. Hypertens Pregnancy; 22: 185–91.

(166) Sales CH, Pedrosa LF, Lima JG, Lemos TM and Colli C (2011):
Influence of Magnesium Status and Magnesium Intake on the Blood Glucose Control in Patients with Type 2 Diabetes. Clin Nutr. 2011, Jan 3.

(167) Santoro GM, Antoniucci D, Bolognese L, Valenti R, Buonamici P, Trapani M, Santini A, Fazzini PF (2000):
A Randomized Study of Intravenous Magnesium in Acute Myocardial Infarction Treated with Direct Coronary Angioplasty. Am Heart J; 140: 891–7.

(168) Saris NE, Mervaala E, Karppanen H, Khawaja JA, and Lewenstam A (2000):
Magnesium. An Update on Physiological, Clinical and Analytical Aspects. Clin Chim Acta.; 294: 1–26.

(169) Sasaki R, Hirota K, and Roth SH Yamazaki M (2002):
Extrecellar Magnesium Ion Modifies the Actions of Volatile Anesthetics in Area CAI of Rat Hippocampus in Vitro. Anaesthesiology; 96:681-7.

(170) Saver JL, Kidwell C, Eckstein M and Starkman S (2004):
Prehospital Neuroprotective Therapy for Acute Stroke; Results of the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) pilot trial. Stroke; 35: 106–8.

(171) Schauf B, Mannschreck B, Becker S, Dietz K, Wallwiener D, and Aydeniz B (2004):
Evaluation of Red Blood Cell Deformability and Uterine Blood Flow in Pregnant Women with Preeclampsia or IUGR And Reduced Uterine Blood Flow Following the Intravenous Application of Magnesium. Hypertens Pregnancy; 23: 331–43.

(172) Schenk P, Vonbank K, Schnack B, Haber P, Lehr S, and Smetana R (2001):
Intravenous Magnesium Sulfate for Bronchial Hyperreactivity: A Randomized Controlled, Double-Blind Study. Clin Pharmacol Ther; 69: 365–71.

(173) Schreiber JU, Lysakowski C, Fuchs-Buder T, Tramèr MR (2005):
Prevention of Succinylcholine-Induced Fasciculation and Myalgia: A Meta-Analysis of Randomized Trials. Anesthesiology; 103: 877–84.

(174) Schulz-Stübner S, Wettmann G, Reyle-Hahn SM, and Rossaint R (2001):
Magnesium as A Part of Balanced General Anaesthesia with Propofol, Remifentanil and Mivacurium: A Double-Blind, Randomized Prospective Study in 50 Patients. Eur J Anaesthesiology; 18:723-9.

(175) Schwarz RE and Nevarez KZ (2005):
Hypomagnesemia after Major Abdominal Operations in Cancer Patients: Clinical Implications. Arch Med Res; 36: 36–41.

(176) Sen AP and Gulati A (2010):
Use of Magnesium in Traumatic Brain Injury. Neurotherapeutics; 7: 91–9.

(177) Seyhan TO, Tugrul M, Sungur MO, Kayacan S, Telci L, Pembeci K and Akpir (2006):
Effect of Three Different Dose Regimens of Magnesium on Propofol Requirements, Hemodynamic Variables and Postoperative Pain Relief in Gynecological Surgery. Br J Anaesth; 96:247-52.

(178) Shareghi GR and Agus ZS (1982):
PTH-Sensetive magnesium transport in the rabbit cortical thick ascending limb of Henle, Kidney int.1982; 16: 837A.

(179) Shashi Kiran, Rachna Gupta, and Deepak Verma (2011):
Evaluation of a Single-Dose of Intravenous Magnesium Sulphate for Prevention of Postoperative Pain after Inguinal Surgery. Indian Journal of Anesthesia; 55: (1): 31–35.

(180) Shepherd J, Jones J, Frampton GK, Tanajewski L, Turner D, and Price A (2008):
Intravenous Magnesium Sulphate and Sotalol for Prevention of Atrial Fibrillation after Coronary Artery Bypass Surgery: A systematic review and economic evaluation Health Technol Assess; 12: iii–95.

(181) Shimosawa T, Takano K, Ando K and Fujita T (2004):
Magnesium Inhibits Norepinephrine Release by Blocking N-Type Calcium Channels at Peripheral Sympathetic Nerve Endings. Hypertension; 44: 897–902.

(182) Sibai B, Dekker G and Kupferminc M (2005):
Preeclampsia. Lancet; 365: 785–99.

(183) Sibai BM (2004):
Magnesium Sulfate Prophylaxis in Preeclampsia: Lessons Learned From Recent Trials. Am J Obstet Gynecol; 190: 1520–6.

(184) Simhan HN and Caritis SN (2007):
Prevention of preterm Delivery. New England Journal of Medicine 357(5); 477-487.

(185) Simpson JI, Eide TR, Schiff GA, Clagnaz JF, Hossain I, Tverskoy A, and Koski G (1994):
Intrathecal Magnesium Sulphate Protects the Spinal Cord from Ischemic Injury During Thoracic Aortic Cross Clamping. Anesthesiology 1994; 81(6): 1493–9.

(186) Singh DK, Jindal P, and Singh G (2011):
Comparative Study of Attenuation of the Pain Caused By Propofol Intravenous Injection, By Granisetron, Magnesium Sulfate and Nitroglycerine. Saudi J Anesth; Jan-Mar; 5(1): 50–54.

(187) Singhi SC, Singh J and, Prasad R (2003):
Hypo- and Hypermagnesemia in an Indian Pediatric Intensive Care Unit. J Trop Pediatr; 49: 99–103.

(188) Skorodin MS, Tenholder MF, Yetter B, Owen KA, Waller RF, Khandelwahl S, Maki K, Rohail T, and D'Alfonso N (1995):
Magnesium Sulfate in Exacerbations of Chronic Obstructive Pulmonary Disease. Arch Intern Med; 155: 496–500.

(189) Standley CA, Whitty JE, Mason BA, and Cotton DB (1997):

Serum Ionized Magnesium in Normal Preeclamptic Gestation. Obstet Gynecol; 89: 24–7.

(190) Stanik-hutt JA (2003):
Pain Management in the Critically Ill. Crit. Care Nurse.23 (2):99-103.

(191) Steinlechner B, Dworschak M, Birkenberg B, Grubhofer G, Weigl M, Schiferer A, Lang T, and Rajek A (2006):
Magnesium Moderately Decreases Remifentanil Dosage Required For Pain Management After Cardiac Surgery. Br J Anesth Apr; 96(4): 444–9.

(192) Stippler M, Fischer MR, Puccio AM, Wisniewski SR, Carson-Walter EB, Dixon CE, and Walter KA (2007):
Serum and Cerebrospinal Fluid Magnesium in Severe Traumatic Brain Injury Outcome. J Neurotrauma; 24: 1347–54.

(193) Takano Y, Sato E, Kaneko T, Sato I (2000):
Antihyperalgesic Effect of Intrathecally Administered Magnesium Sulphate in Rats; 84:175-9.

(194) Telci L, Esen F, Akcora D, Erden T, Canbolat AT, Akpir K (2002):
Evaluation of Effects of Magnesium Sulphate in Reducing Intraoperative Anaesthetic Requirements. British Journal of anaesthesia; 89:594-602.

(195) Temkin NR, Anderson GD, Winn HR, Ellenbogen RG, Britz GW, Schuster J, Lucas T, Newell DW, Mansfield PN, Machamer JE, Barber J, and Dikmen SS (2007):
Magnesium Sulfate for Neuro-Protection after Traumatic Brain Injury: A Randomized Controlled Trial. Lancet Neurol; 6: 29–38.

(196) Terrone DA, Rinehart BK, Kimmel ES, May WL, Larmon JE, and Morrison JC (2000):
A Prospective, Randomized, Controlled Trial of High and Low Doses Of $MgSO_4$ for Acute Tocolysis. Am J Obestet Gynecol.; 182:1477-1482.

(197) Thomas J, Millot JM, Sebille S, Delabroise AM, Thomas E, Manfait M, Arnaud MJ (2000):
Free and Total Magnesium in Lymphocytes of Migraine Patients-Effect of Magnesium-Rich Mineral Water Intake. Clin Chim Acta; 295(i-2): 63–75.

(198) Toraman F, Karabulut EH, Alhan HC, Dagdelen S, Tarcan S (2001):
Magnesium Infusion Dramatically Decreases the Incidence of Atrial Fibrillation after Coronary Artery Bypass Grafting. Ann Thorac Surg; 72:

1256–61.

(199) Touyz RM (2004):
Magnesium in Clinical Medicine. Front Biosci 2004; 9: 1278–93.

(200) Toyoshima C and Mizutani T (2004):
Crystal structure of the calcium pump with a bound ATP analogue. Nature 2004; 430: 529–35.

(201) Tramer MR and Glynn CJ (2002):
Magnesium Bier's Block for Treatment of Chronic Limb Pain: A Randomized, Double-Blind, Cross-Over Study. Pain; 99: 235–41.

(202) Tramer MR and Glynn CJ (2007):
An Evaluation of A Single Dose of Magnesium to Supplement Analgesia after Ambulatory Surgery: Randomized Controlled Trial. Anesth Analg; 104: 1374–9.

(203) Tramer MR, Schneider J. Marti RA and Rifat K (1996):
Role of Magnesium Sulphate in Postoperative Analgesia. Anaesthiology; 84:340-7.

(204) Turan A, Memiş D, Karamanlioğlu B, Güler T, Pamukçu Z (2005):
Intravenous Regional Anesthesia Using Lidocaine and Magnesium. Anesth Analg; 100:1189-92.

(205) Türkyilmaz C, Türkyilmaz Z, Atalay Y, Söylemezoglu F, and Celasun B (2002):
Magnesium Pretreatment Reduces Neuronal Apoptosis in Newborn Rats in Hypoxiaischemia. Brain Res; 955: 133–7.

(206) Ueshima K (2005):
Magnesium and Ischemic Heart Disease: A Review of Epidemiological, Experimental, and Clinical Evidences: Magnesium Research; 18 (4): 275-84.

(207) Unlugenc H, Guenduez M, Oezalevi M, and Akman H (2002):
A Comparative Study on The Analgesic Effect of Tamadol, Tramadol Plus Magnesium, and Tramadol Plus Ketamine for Postoperative Pain Management after Major Abdominal Surgery. Act Anaesthesiology Scand; 46:1025-30.

(208) Ustün ME, Gürbilek M, Ak A, Vatansev H, and Duman A (2001):

Effects of Magnesium Sulphate on Tissue Lactate and Malondialdehyde Levels in Experimental Head Trauma. Intensive Care Med; 27: 264-268.

(209) van den Bergh WM, Algra A, van Kooten F, Dirven CM, van Gijn J, Vermeulen M, and Rinkel GJ (2005):
Magnesium Sulfate in Aneurysmal Subarachnoid Hemorrhage: A Randomized Controlled Trial. Stroke; 36: 1011–5.

(210) Vedat Cinar, Rasim Mogulkoc, Abdulkareem Kasim Baltaci and polat (2008):
Adrenocorticotropic Hormon and Cortisol Levels in Athelets and Sedentary Subjects at Rest and Exhaustion: Effect of Magnesium Supplementation. Biol Trace Elem Res; 121:215-220.

(211) Voets T, Nilius B, Hoefs S, van der Kemp AW, Droogmans G, Bindels RJ, and Hoenderop JG (2004):
TRPM6 forms the Mg^{+2} Influx Channel Involved in Intestinal and Renal Mg^{+2} Absorption. J Biol Chem; 279: 19–25.

(212) Wadhwa A, Sengupta P, Durrani J, Akça O, Lenhardt R, Sessler DI, and Doufas AG (2005):
Magnesium Sulphate Only Slightly Reduces the Shivering Threshold in Humans. Br J Anaesth; 94:756-62.

(213) Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD (2004):
Placebo-Induced Changes in FMRI in the Anticipation and Experience of Pain. Science; 303(5661):1162-1167.

(214) Walder RY, Landau D, Meyer P, Shalev H, Tsolia M, Borochowitz Z, Boettger MB, Beck GE, Englehardt RK, Carmi R, and Sheffield VC (2002):
Mutation of TRPM6 Causes Familial Hypomagnesemia with Secondary Hypocalcemia. Nat Genet; 31: 171–4.

(215) Wee KSL, Zhang Y, Khanna S, and Low CM (2007):
Immunolocalization of NR3B Subunit of the N-Methyl-D-Aspartate Receptor in the Adult Rat Central Nervous System, SfN Abstract, November.

(216) Whelan CT, Jin L, and Meltzer D (2004):
Pain and Satisfaction with Pain Control in Hospitalized Medical Patients: No Such Thing as Low Risk. Arch Intern Med.; 164:175-180.

(217) Wilson RB, Erskine C, and Crowe PJ (2000):
Hypomagnesemia and Hypocalcemia after Thyroidectomy: A prospective study. World J Surg; 24: 722–6.

(218) Witlin AG, Friedman SA and Sibai BM (1997):
The Effect of Magnesium Sulphate Therapy on the Duration of Labor in Women with Mild Preeclampsia at Term: A randomized double blind placebo-controlled trial. Am J Obstet Gynecol; 176: 623–7.

(219) Wong GK, Poon WS, Chan MT, Boet R, Gin T, Ng SC, and Zee BC (2010):
Intravenous Magnesium Sulphate for Aneurysmal Subarachnoid Hemorrhage (IMASH): A randomized Double-Blinded Placebo-Controlled Multicenter Phase III Trial. Stroke; 41: 921–6.

(220) Woolf CJ and Thompson SW (1991):
The induction And Maintenance of Central Sensitization Is Dependent on N-Methyl-D-Aspartic Acid Receptor Activation; Implications for the Treatment of Post-Injury Pain Hypersensitivity States. Pain; 44: 293–9.

(221) Wu TJ, Teng RJ and Tsou KI (1995):
Persistent Pulmonary Hypertension of the Newborn Treated with Magnesium Sulfate in Premature Neonates. Pediatrics 1995; 96: 472–4.

(222) Yasuyuki Kawagoe, Hiroshi Sameshima, Tsuyomu Ikenoue, Ichiro Yasuhi, and Tatsuhiko Kawarabayashi (2011):
Magnesium Sulfate as a Second-Line Tocolytic Agent for Preterm Labor: A Randomized Controlled Trial in Kyushu Island. Journal of Pregnancy; Article ID 965060

(223) Ying SQ, Fang L, Xiang MX, Xu G, Shan J, and Wang JA (2007):
Protective Effects of Magnesium against Ischemia-Reperfusion Injury through Inhibition of P-Selectin In Rats. Clin Exp Pharmacol Physiol; 34: 1234–9.

(224) Young Hee Shin, Soo Joo Choi, Hui Yeon Jeong and Myung Hee Kim (2011):
Evaluation of Dose Effects of Magnesium Sulfate on Rocuronium Injection Pain and Hemodynamic Changes by Laryngoscopy and Endotracheal Intubation**.** Korean J Anesthesiol. May; 60(5): 329–333.

(225) Zarauza R, Sáez-Fernández AN, Iribarren MJ, Carrascosa F, Adame M, Fidalgo I, and Monedero P (2000):

A Comparative Study with Oral Nifedipine, Intravenous Nimodipine, and Magnesium Sulphate in postoperative Analgesia. Anesth Analg; 91:938-43.

(226) Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, et al. (2006): ACC/AHA/ESC 2006 Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol; 48: 247–346.

وقد تم أخذ عينات دم من الوريد قبل تخدير المرضى، وبعد بداية فتح الجلد، ثم قبل الإنتهاء من خياطة الجلد فى نهاية العملية الجراحية، ثم حللت هذه العينات لتحديد نسبة الكورتيزول والجلوكوز فى الدم. أيضاً تم قياس ضغط الدم، وسرعة ضربات القلب خلال الفترات السابق ذكرها. ثم بعد خروج المريض من غرفة العمليات تم قياس الفترة من نهاية العملية إلى طلب المريض إلى المسكنات، ونسبة الألم بإستخدام المقياس التمثيلى البصرى (VAS)، ومقياس الإرتعاش، وفترة بقاء المريض بالمستشفى بعد العملية، ثم حللت النتائج إحصائياً.

وقد بينت النتائج أن عقار سلفات الماغنسيوم له تأثير فعال على نسبة الكورتيزول والجلوكوز فى الدم أثناء العمية الجراحية، بالإضافة إلى تأثيره الفعال على تقليل حدة الألم وكمية إستهلاك المسكنات وتقليل نسبة الإرتعاش بعد العملية الجراحية، وبالتالى تقليل فترة بقاء المريض بالمستشفى.

ملخص البحث

مما لا شك فيه أن علاج آلام ما بعد العملية الجراحية يعتبر من أهم الأولويات بالنسبه للمرضى حيث إنها تؤثر سلباً أوإيجاباً على نتائج العملية الجراحية، فالتحكم أو القضاء على آلام ما بعد العملية يؤدى إلى نتائج أفضل، وسرعة فى الشفاء ويقلل من فترة إقامة المريض فى المستشفى مما يقلل من النفقات والمستهلكات المصروفة على المريض. وعقار سلفات الماغنيسوم يعمل من خلال عدة محاور أو آليات أهمها أنه يغلق بعض مستقبلات الآلام (نيمدا) بالإضافة إلى أنه له تأثير مهدئ للأعصاب مما يساعد فى عدم الشعور بالألم.

وفى هذه الدراسة تم دراسة تأثير مدى فاعلية عقار سلفات الماغنسيوم على علاج آلام ما بعد عمليات أسفل البطن عن طريق إعطائه بالحقن الوريدى المستمر قبل إجراء العملية الجراحية ، وتمت الدراسة على 90 مريض تتراوح أعمارهم من 20 إلى 50 عام. وقد تقسيم المرضى إلى ثلاث مجموعات متساوية العدد (30).

المجموعة الأولى (F): تم إعطائها عقار الفنتانيل بجرعة 2 ميكروجم/كجم، مضافاً إلى 100 مم محلول ملح 0.9% وذلك بالحقن الوريدى المستمر قبل بداية التخدير بـ 30 دقيقة.

المجموعة الثانية (M): تم إعطائها عقار سلفات الماغنسيوم بجرعة 50 ملل جم/كجم (3 جم)، مضافاً إلى 100 مم محلول ملح 0.9% وذلك بالحقن الوريدى المستمر قبل بداية التخدير بـ 30 دقيقة.

المجموعة الثالثة (FM): تم إعطائها عقار سلفات الماغنسيوم بجرعة 50 ملل جم/كجم (3 جم) + عقار الفنتانيل بجرعة 2 ميكروجم/كجم، مضافاً إلى 100 مم محلول ملح 0.9% وذلك بالحقن الوريدى المستمر قبل بداية التخدير بـ 30 دقيقة.

جامعــة بنــها
كليـــة الطـب
قســم التخدير والعناية المركزة

تأثير سلفات الماغنسيوم بالحقن الوريدي المستمرعلى إزالة آلام ما بعد عمليات أسفل البطن

رسالة مُقدمة
للحصول على درجة الدكتوراة
فى التخدير والعناية المركزة

مُقدمة من

الطبيب/ **محمد سعيد مصطفى المليجى**
ماجستير التخدير والعناية المركزة
كلية الطب - جامعة بنها

تحت إشـــراف

أ.د. محمد على حموده
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كلية الطب - جامعة بنها

كليــة الطب ـ جامعــة بنها
جمهوريــة مصر العربيــة
2013