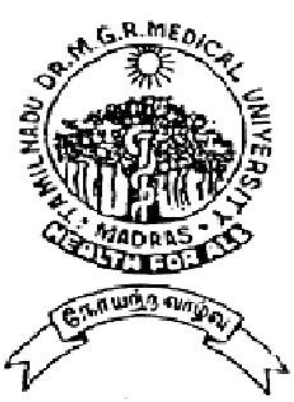
SERUM MAGNESIUM LEVELS AS A PROGNOSTIC MARKER IN SYSTEMIC INFLAMMATORY RESPONSE SYNDROME IN INTENSIVE MEDICAL CARE UNIT OF GOVERNMENT RAJAJI HOSPITAL

Dissertation submitted in partial fulfillment of the
requirement for the award of the degree of

DOCTOR OF MEDICINE

Branch I – GENERAL MEDICINE

April 2013



THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY,

CHENNAI, TAMILNADU.

CERTIFICATE

This is to certify that the dissertation entitled **"SERUM MAGNESIUM LEVELS AS A PROGNOSTIC MARKER IN SYSTEMIC INFLAMMATORY RESPONSE SYNDROME IN INTENSIVE MEDICAL CARE UNIT OF GOVERNMENT RAJAJI HOSPITAL"** is a bonafide work of **Dr. AZEEM AHAMED** in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine Branch I examination to be held in **April 2013**.

Dr.VT.PREMKUMAR MD.,
Professor
Department of Medicine
Government Rajaji Hospital
Madurai Medical College
Madurai.

Dr.MOSES K.DANIEL MD.,
Professor and HOD,
Department of Medicine
Government Rajaji Hospital,
Madurai Medical College,
Madurai.

DECLARATION

I, **Dr. AZEEM AHAMED,** solemnly declare that, this dissertation **"SERUM MAGNESIUM LEVELS AS A PROGNOSTIC MARKER IN SYSTEMIC INFLAMMATORY RESPONSE SYNDROME IN INTENSIVE MEDICAL CARE UNIT OF GOVERNMENT RAJAJI HOSPITAL"** is a bonafide record of work done by me at the Department of General Medicine, Government Rajaji Hospital, Madurai, under the guidance of **Dr. VT. PREMKUMAR M.D.,** Professor, Department of General Medicine, Madurai Medical college, Madurai. This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulations for the award of Degree of Doctor of Medicine (M.D.), General Medicine Branch-I, examination to be held in April 2013.

Place: Madurai

Date: **DR.AZEEM AHAMED**

ACKNOWLEDGEMENT

I would like to thank **Dr.N MOHAN MS., Dean,** Madurai, Medical College, for permitting me to utilise the hospital facilities for the dissertation.

I also extend my sincere thanks to **Prof.Dr.MOSES.K.DANIEL M.D**, Head of the Department and Professor of Medicine for his constant support during the study.

I would like to express my deep sense of gratitude and thanks to my Unit Chief, my guide and Professor of Medicine, **Dr.V T PREMKUMAR**. **M.D**., for his valuable suggestions and excellent guidance during the study.I would also like to thank chief of IMCU ,Professor .**Dr.DHARMARAJ MD** for his valuable advice and support during the study.

I thank the Assistant Professors**,Dr.KS MANIAPPAN M.D**., **DrM.SOORIYAKUMAR, M.D.,Dr.SC VIVEKANANTHAN MD** for their valid comments, guidance and suggestions.

I wish to acknowledge all those, including my post graduate colleagues, my parents who have directly or indirectly helped me complete this work with great success. Last but definitely not the least, I thank all the patients who participated in this study for their extreme patience and co-operation.

CONTENTS

INTRODUCTION

Systemic Inflammatory Response Syndrome (**SIRS**) is an inflammatory condition which affects multiple systems in the body and often occurs as a response which is immunologically mediated by the protective immune system to infectious agent. SIRS is closely associated with sepsis, a state wherein the patients satisfy the criteria for systemic inflammatory response syndrome and also when its etiology is suspected to be of infectious nature. Systemic inflammatory response syndrome is a critical state and is associated with systemic inflammatory response , multiple organ injury and organ failure.

Definition

Systemic inflammatory response syndrome	
Finding	**Value**
Temperature	<36 °C (96.8 °F) or >38 °C (100.4 °F)
Heart rate	>90/min
Respiratory rate	>20/min or PaCO2<32 mmHg (4.3 kPa)
WBC count.	$<4x10^9$/L (<4000/mm³) or $>12x10^9$/L (>12,000/mm³), or >10% bands

Two or more of the above clinical or laboratory findings should be present to make a diagnosis of SIRS and may have a non infectious cause.

Magnesium plays a vital role in sepsis and systemic inflammatory response syndrome **(SIRS)** especially in seriously decompensated patients in the intensive medical care unit[10]. Hypomagnesemia has been found to be associated with progression towards occurrence of functional impairment of multiple organs and systemic inflammatory response syndrome in patients treated in Intensive medical care unit[38]. Magnesium deficiency leads on to aggravated production of cytokines which favour inflammation. Also production of endothelins is increased.

In certain experiments related to sepsis it was demonstrated that there is aggravated mortality in the setting of ongoing magnesium depletion or deficiency and administration of magnesium supplements may have a protective response on challenge with endotoxins [31,32,33] . The effect was owing to the fact that there was decreased production of cytokines which are favouring inflammatory response in the system. These cytokines are Tumor necrosis factor alpha and Interleukin 6 .

Magnesium deficiency has been reported in individuals afflicted with a wide spectrum of different disease states which comprise infectious

diseases like cerebral malaria, multi drug resistant malaria, leptospirosis, tetanus, kidney related sepsis and infections, cellulitis, meningoencephalitis, lung parenchymal infections, pulmonary tuberculosis and invasive aspergillosis, hepatic encephalopathy, acute fulminant hepatitis or cirrhosis, acute kidney injury due to intravascular volume depletion and septicaemia, pre-existing kidney disease, respiratory decompensation due to chronic obstructive pulmonary disease, lung involvement as in ILD and acute respiratory distress syndrome , heart failure due to coronary artery disease or other valvular pathology, cerebrovascular injury due to cerebrovascular ischemia or hemorrhage, snake bite related sepsis and poisonings for example OPC compounds and drug overdosage[37].

Many factors lead on to magnesium depletion in seriously decompensated individuals admitted to ICU like decreased assimilation of magnesium, nasogastric aspiration, lack of adequate amount of the nutrient in certain feeding formulations or Total Parenteral Nutrition compounds, use of certain medicines like diuretics, gentamycin, amikacin , and amphotericin-B which leads on to the loss of this vital mineral through the kidneys.

Hypermagnesemia is observed less frequently in clinical practice and it may be due to iatrogenic or kidney diseases [37]. Magnesium depletion in the system has been found to present with a wide variety of clinical

features such as ventricular and atrial tachycardias, heart failure, coronary artery constriction, unexpected cardiac mortality, certain skeletal and respiratory muscle decompensation, broncho constriction, convulsions, and also certain other neurologic manifestations and a wide spectrum of associated electrolyte disturbances like deficiency of potassium calcium ,sodium and phosphate[36].

Hypomagnesemia is supposed to be one among the frequently encountered electrolyte abnormalities seen among the ICU patients[37]. Also hypomagnesemia has been found to be related to increased duration of hospital stay and 30 day mortality[5,17,37]. It is also associated with increased possibility of respiratory failure and mechanical ventilation in ICU patients with sepsis and SIRS and increased duration of stay under mechanical ventilatory support[28,29,30].

The present study was undertaken with the aim of estimating serum magnesium levels in the patients who undergo treatment in the medical intensive care unit satisfying the diagnostic criteria for systemic inflammatory response syndrome and to assess the clinical outcome in these patients with relation to the serum magnesium levels.The clinical progress is aimed to be assessed in patients with low magnesium levels duration of ICU stay, need for ventilator support and its outcome, and mortality rate.

AIM OF THE STUDY

The aim of this study is

1. Estimating serum magnesium concentrations in patients with Systemic Inflammatory Response Syndrome (**SIRS**) in the medical ICU .
2. Correlating serum magnesium concentrations with prognosis of SIRS patients.
3. To assess the clinical outcome in patients found to have abnormal magnesium levels in relation to duration of ICU stay, mortality rate, need for mechanical ventilation and duration of ventilator support.
4. To analyse the other clinical and biochemical data obtained during the study in SIRS patients and to arrive at conclusions.

REVIEW OF LITERATURE

MAGNESIUM

Magnesium is an essential divalent cation found in the cell[20]. It is crucial in the normal neuromuscular activity of human body . The magnesium found inside the cell forms an essential ATP bound complex and is a vital cofactor in a spectrum of different enzymes, nucleic acids and transporters required for normal cellular function, replication & energy metabolism[11,20]. Normal range of serum magnesium is maintained within the range of 1.5- 2 meq/L or (1.7-2.4 mg/dl) . 30% of this magnesium is protein bound & 15 % is bound to phosphate.

50 % of the total body magnesium is located in bone, & only one half is insoluble in mineral phase. Most of the extraskeletal magnesium is present within the cells, and the total concentration is 5 mM & 95% is bound to proteins & other macromolecules.

The normal magnesium content in the diet is about 6-15 mmol / day[20]. Absorption of magnesium takes place mainly in the jejunum & ileum which is 30-40 % of the total dietary magnesium. The factor which affects intestinal magnesium absorptive efficiency is 1,25 (OH)2D. Urinary

magnesium excretion is 4 mmol/d or 100mg/day and almost same as nett intestinal absorption.

About 20% of magnesium that is filtered gets absorbed in the PCT or proximal convoluted tubule and remaining 60% is reabsorbed in ascending thick limb of loop of Henle and 5-10% in DCT or Distal convoluted Tubule.

Reabsorption of magnesium in the thick ascending limb is enhanced by parathormone but inhibited by hypercalcemia or hypermagnesemia which also activates the CaSR receptor in this nephron segment[20].

HYPOMAGNESEMIA:

Hypomagnesaemia is often an under diagnosed electrolyte abnormality in day to day practice and its importance cannot be undervalued[37].

There are several causes of hypomagnesaemia in day to day clinical practice and these include intractable vomiting, diarrhea, malabsorption syndrome, intestinal drainage, decreased renal tubular magnesium reabsorption, and movement of the nutrient from the ECF to the cell, bone and third space.

Hypomagnesaemia is found in acquired kidney diseases like tubulo interstitial disease, acute tubular necrosis, obstructive uropathy and in kidney transplantation.

Chronic alcoholism has been found to be associated with dietary magnesium deficiency and in turn leading on to hypomagnesaemia[37].

Poorly controlled Diabetes mellitus is associated with hypomagnesemia which is due to decreased tubular magnesium reabsorption and persistent glycosuria with osmotic diuresis[35].

Recovery from Diabetic ketoacidosis causes hypomagnesemia. Other conditions are starvation & respiratory acidosis. The mechanism in these conditions is due to rapid shifts of magnesium from extracellular fluid into the intracellular fluid.

Magnesium depletion in the human system has been found to be associated with sepsis and systemic inflammatory response syndrome.

Hypomagnesemia is also associated with burns which are extensive, acute pancreatitis,excessive sweating and also in pregnancy & lactation.

Hypomagnesemia can also be caused by drugs like pentamidine, amphotericin B, cyclosporine, foscarnet, diuretics, cisplatin and cetuximab-which is an EGF receptor inhibitory antibody[20].

Hypomagnesaemia is associated with certain rare genetic disorders like primary infantile hypomagnesemia, hypomagnesemia with secondary hypocalcemia caused by gene mutations in TRPM 6 &TRPM 7 genes[26].

Other genetic magnesium wasting syndromes include Gitelman syndrome. Gitelman syndrome is caused by inactivating mutations of genes encoding the DCT NaCL co-transporter.

Other syndromes are Bartter's syndrome, autosomal recessive renal hypomagnesemia with hypercalciuria and autosomal dominant renal hypomagnesemia with hypocalciuria[24,25].

In Bartter's syndrome, mutation of genes encoding proteins required for cTAL Na-K-2 Cl transport is seen. There is mutation of the genes encoding paracellin-1 in autosomal recessive renal hypomagnesemia with hypercalciuria and mutation of gene encoding DCT- Na^+ K^+ ATPase gamma subunit in autosomal dominant renal hypomagnesemia with hypocalciuria.

HYPOMAGNESEMIA IN INTENSIVE CARE UNIT PATIENTS

Magnesium deficiency in the intensive care unit patients has three main causes[16,18,19].

They are

1. Increased renal losses
2. Reduced intestinal absorption.
3. Compartmental redistribution

1. Due to loss through the kidneys are

Specific tubular defect:

- ATN or Acute Tubular Necrosis
- Interstitial nephritis
- Post obstructive diuresis
- After renal transplantation

Drug induced

- Amphotericin B
- Foscarnet

- ❖ Cyclosporin- A
- ❖ gentamycin
- ❖ Pentamidine
- ❖ cisplatin
- ❖ CSF or Colony stimulating factor

The endocrine causes are diabetic ketoacidosis, alcoholic ketoacidosis hyperaldosteronism, hyperthyroidism,hyperparathyroidism & SIADH.

2. Due to the distribution of magnesium are

Acute respiratory alkalosis

Hungry bone syndrome

Administration of epinephrine

Acute pancreatitis

Blood transfusion

Also, extensive burns

increased sweating

cardiopulmonary bypass surgery

alcohol dependence syndrome

1. **Gastrointestinal causes include**

    Nutritional disturbances

    Refeeding syndrome

    TPN

Impaired intestinal absorption:

Malabsorptive states

Short bowel syndrome

Chronic diarrhea

Pancreatitis

Prolonged nasogastric suction

Biliary, intestinal fistula.

CLINICAL FEATURES OF HYPOMAGNESEMIA

Hypomagnesemia is associated with a wide variety of clinical manifestations, especially in the central nervous system and cardiovascular system.

The features include convulsions, generalised muscle weakness, ataxia, nystagmus, vertigo, apathy, tremors & tetany.

It can also cause certain psychiatric manifestations like depression, psychosis, irritability and even it may lead on to delirium.

Severity of symptoms may not correlate with the serum magnesium levels.

In the cardiovascular system, hypomagnesemia causes life threatening arrhythmias like ventricular arrhythmias and also sinus tachycardia and other supraventricular tachycardias [20].

ECG findings include prolonged PR or QT intervals, flat T waves or inverted T waves and straight ST segment.

In the presence of other electrolyte abnormalities like hypocalcemia and hypokalemia, magnesium should be administered, for favorable clinical outcome.

TREATMENT OF HYPOMAGNESEMIA

Hypomagnesemia may be classified as mild asymptomatic type and severe type.

Oral magnesium supplements like magnesium chloride, magnesium hydroxide, and magnesium oxide is usually given to treat mild asymptomatic hypomagnesaemia in divided dosages and upto 20-30 mmol/ day (40-60 meq/ day)

Severe hypomagnesemia is treated parenterally with intravenous magnesium chloride as an intravenous administration of 50 mmol/ day which is to be continued, if renal function is normal. If GFR is reduced, infusion is lowered by 50-75%. There should be close monitoring of serum magnesium at intervals of 12 hours to one day during treatment and it is continued for several days. Calcium, potassium & phosphate supplementation is important in patients with hypomagnesemia. Vitamin D deficiency should be treated with oral or parenteral vitamin D.

Administration of intravenous magnesium alone may worsen hypophosphatemia leading on to neuromuscular symptoms or rhabdomyolysis due to rapid PTH secretion.

HYPERMAGNESEMIA

Hypermagnesemia is rarer than hypomagnesemia and is seen mostly in the setting of kidney disease. Mild hypermagnesemia is seen in some patients with hypothermia, hypoadrenalism ,hypothyroidism,and with increased reabsorption in cTAL due to Ca SR mutations in familial hypocalciuric hypercalcemia. Massive soft tissue injury can push large amounts of magnesium into the extracellular fluid in patients with shock, sepsis, burns or cardiac arrest.

Causes of hypermagnesemia

1.Increased mobilization from tissues

a) burns

b) cardiac arrest

c) trauma

d) shock

e) sepsis.

2.Increased magnesium intake

a) parenteral magnesium

b) urologic irrigants,cathartics

3.Decreased excretion

a) familial hypocalciuric hypercalcemia

b) renal failure

Other causes are :

a) hypothyroidism

b) hypothermia

c) hypoadrenalism

CLINICAL FEATURES

An early sign of hypermagnesemia is hypotension that does not respond to vasopressors or volume expansion. Vasodilation and neuromuscular blockade are quite prominent in hypermagnesemia ie. Serum magnesium >2 mmol/L(>4 meq/L).

At serum magnesium > 4 mmol/L respiratory failure, paralysis, coma with hypoactive tendon reflexes,intestinal ileus, facial flushing, mydriasis bradycardia are seen.

ECG findings are increased duration of PR interval, QRS, QT interval, heart blocks and at magnesium concentrations>10 mmol/L, asystole is seen.

TREATMENT OF HYPERMAGNESEMIA

The treatment depends on the clinical scenario.

In the setting of renal injury renal replacement therapy in the form of hemodialysis may be indicated .Intravenous volume replacement is required in other situations. Enemas or cathartics which do not contain any magnesium may be needed to remove ingested magnesium from the alimentary tract. Intravenous calcium in the dose range 100-200 mg in a time period ranging one to two hours leads on to the clinical recovery of many patients. Aggresive rehydration may be required in some cases.

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)

Systemic inflammatory response syndrome is an inflammatory condition which affects various systems of the body. Fever or hypothermia, leucocytosis and leucopenia, tachycardia and tachypnea are the important clinical signs of the systemic response that is termed the systemic inflammatory response syndrome[20].

SIRS can be due to infectious or non infectious etiology[20]. An individual with SIRS is considered to be in a state of sepsis if infection is suspected or proven.

When sepsis is seen to be associated with impairment of function of organs away from the origin of infection, the patient is said to have severe sepsis.

If severe sepsis is associated with hypotension which could not be treated by intravenous fluid therapy then septic shock is the diagnosis .

Definitions:

1. SIRS : Defined by the presence of two or more of the following conditions.
    1. Fever (oral temperature > 38^0c) or hypothermia (<36^0c)
    2. Tachypnea (> 24 breaths / Min)

3. Tachycardia (Heart rate >90 beats / min)
4. Leucocytosis (>12,000/ mm3)

   leucopenia (<4000/mm3)

   or >10% bands; may have a non infectious etiology.

For confirming the diagnosis of SIRS two or more of the criteria mentioned above should be met. The above mentioned criteria was proposed in 1992 in the American College of Chest Physicians / Society of Critical Care Medicine Consensus Conference[20].

Sepsis:

SIRS which has a proven or suspicious microbial cause.

Severe sepsis:

Sepsis with one or more signs of organ dysfunction.

for example

1. **Cardiovascular:**

   Systolic arterial blood pressure less than 90 mm Hg or mean arterial pressure less than 70 mm of Hg that responds to administration of intravenous fluids.

2. **Renal:**

   Urine output <0.5 ml/ kg per hour for 1 hour despite adequate fluid resuscitation.

3. **Respiratory:**

   Pa 0_2/ FI 0_2 less than or equal to 250 or in case of lung being the only affected organ less than or equal to 200.

   Hematologic:

   Thrombocytopenia which is count less than 80000 / μL or 50% decrease in platelet count from highest value recorded over last 3 days.

4. **Unexplained metabolic acidosis**: A pH less than or equal to 7.30 or base deficit greater than or equal to 5.0 meq/l and plasma lactate >1.5 times upper limit of normal.

5. **Adequate fluid resuscitation:**

   Pulmonary Artery Wedge Pressure greater than or equal to 12 mm Hg or central venous pressure greater than or equal to 8 mm Hg.

Septic Shock:

Sepsis with hypotension (Arterial systolic blood pressure < 90 mm Hg or 40 mm Hg less than patient's normal blood pressure) for atleast 1 hour despite resuscitation or need for vasopressors to maintain systolic blood pressure > 90 mm Hg or mean arterial pressure > 70 mm Hg.

Refractory septic shock:

Septic shock that goes on for more than one hour and which does not improve with administration of vasopressor agents and intravenous fluids.

Multiple Organ Dysfunction Syndrome (MODS)

When there is impairment of function of more than one organ and it is required to intervene promptly for maintenance of homeostasis.

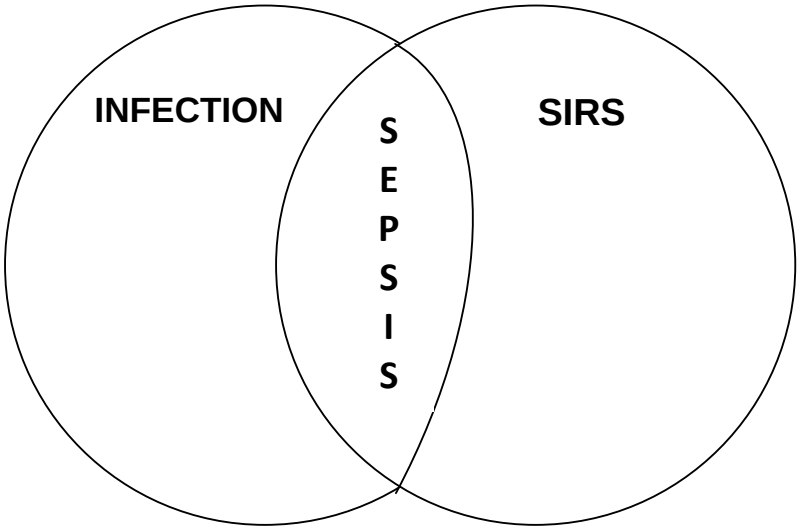
SIRS may have non- infections causes like extensive soft tissue injury, massive burns, pancreatitis and haemorrhage.

Other etiologies are:

1. Post operative states
2. Anaphylaxis
3. Drug overdose
4. Cardiac tamponade
5. Pulmonary embolism
6. Adrenal insufficiency

Pathophysiology of SIRS and sepsis:

Sepsis is systemic inflammatory response syndrome with suspicious or proven infectious etiology.



Sepsis is usually triggered by infectious agent like fungi or bacteria which does not lead on to any disease affecting many of the systems in a person with intact immunity.

The body will respond with a vigorous inflammatory reaction that results in severe sepsis, yet fails to kill the invaders.

SIRS is a consequence of the combined effect of the inflammatory mediators involved in acute phase reaction response in the body.

Inflammatory response

Inflammation is a part of the biologic response of the vascular tissue to pathogens , harmful irritants and damaged cells .

The phenomenon called inflammation involves vasodilatation which leads on to an increase in the blood flow to the involved organ, increased permeability of capillary wall and transmigration of inflammatory cells into the target site. There is triggering of protective immune mechanism and the cells, plasma enzymes, and clotting factors and complement entities. This activation is equal to the extent of the cellular injury.

The local signs in inflammatory response like rubor, tumor, calor, dolor and functio laesa are classically seen.

Acute phase response

The acute phase response is the inbuilt unique adaptive response to tissue damage. They are a set of responses brought out by humoral mediators and certain other factors, especially cytokines which favour inflammation like interleukin1, interleukin 2, interleukin 6 and tumor necrosis factor alpha .

The acute phase reactant proteins comprise a set of proteins which increase or decrease in response to inflammation. They are broadly divided as positive acute phase reactant proteins and negative acute phase reactants. The positive acute phase reactant proteins are ferritin, C-reactive protein, ceruloplasmin, haptoglobulin, serum amyloid A and complement factors. The negative acute phase reactants are albumin, transthyretin, transferrin, retinol binding protein.

The acute phase response is vital in maintaining homeostasis in water temperature, and ion balance.and removal of irreversibly damaged tissue, and regenerative and reparative processes .

Systemic inflammatory response syndrome is a complicated response as compared to acute phase response .Systemic inflammatory response syndrome can lead on to much complicated disturbances in the normal homeostatic mechanism leading on to potential damaging effect on the system.

SIRS, independent of the cause can have the same pathogenetic mechanisms and there can be small variations in the effects which are described. Inflammatory response is the response of the body to insults which are not specific and are due to infectious diseases, chemicals or external traumatic insults. The inflammatory process is a complicated

response which invoves cellular and humoral responses and the complement and cytokine related systems.

The association between systemic inflammatory response syndrome and these complicated interactions are :

1. After an inciting stimulus , localised cytokines are generated with the aim of producing inflammation and then helps in repair of wounds and activation of the system invoving the reticuloendothelial cells .

2. The cytokines get access to the circulatory system and leads on to a better effect. This leads to stimulation of factors involved in activation of macrophages and platelets and certain growth factors. The acute phase reaction is well adjusted by decreased proinflammatory mediators and due to the production and action of certain factors which are antagonistic.

3. In case there is no achievement of homeostasis there is a response involving the system and the cytokines which are destructive. This leads on to stimulation of several systems and also the reticuloendothelial system and consequent disturbances in the circulatory system and there is impairment of function of the organs.

The inflammatory system is activated by stimuli like infectious diseases, inflammatory stimuli and traumatic insults. Endotoxin or exotoxin initiates the inflammatory system when systemic inflammatory response is due to infectious diseases. A wide spectrum of cytokines are generated by

the endothelium, monocytes and macrophages. Tumor necrosis factor alpha and interleukin 1 released leads on to the splitting of nuclear factor kB inhibitor. After the absence of inhibitor,nuclear factor Kb leads on to release of mRNA ,later on leading to the generation of cytokines which are favouring inflammation. Interferon gamm ,interleukin 6 and 8 are proinflammatory cytokines released if viruses are responsible for inflammation .Interferon gamma is generated from the tissues devastated by the viral insult.

Tumor necrosis factor alpha & interleukin 1 leads on to hyperthermia and generation of certain stress responses like for example stimulation of vasopressin and the renin-AT system. Interleukin 1 and tumor necrosis factor alpha can lead on to pulmonary pathology and hemodynamic failure if they are acting at the same time and not when acting singly.

Infectious diseases lead on to hyperthermia due to release of tumor necrosis factor alpha more than in the case of traumatic injury. C-reactive protein is generated due to the release of cytokines like interleukin 6.
There is stimulation of the clotting system, complement system and production of platelet activating factor, leukotrienes and complement system.

Several inflammatory peptides lead on to the production of certain cytokines and lead on to dilatation of blood vessels and aggravated blood vessel permeability .Good examples are complements 3a and 5a.

Certain factors lead on to endothelial injury and several organ systems are badly affected. Leukotriene B4 is responsible for this effect as also prostaglandin compounds.

For comprehending the future consequences of SIRS the association between clotting response and inflammatory syndrome is vital . Tissue factor leads on to thrombin genesis and thus initiation of clotting pathway and thus inflammatory response is aggravated. Cytokines like interleukin 1 and tumor necrosis factor alpha act on endothelium and lead on to tissue factor production. Thus the process of inflammation is activated in part also by the clotting cascade. Due to the production of PAI-1,splitting of fibrin is inhibited by interleukin 1 and tumour necrosis factor alpha. Splitting of fibrin is impaired by interleukin 1 and tumor necrosis factor alpha by producing plasminogen activator inhibitor-1.

The complement cascade is vital in the clotting mechanism of body. Uncontrolled clotting factor activation can lead on to vascular obstruction with blood clots later leading on to multi system failure.This is because anti clotting mechanisms of body like APC is affected.

There is activation of clotting system due to the process of sepsis and it is more critical than due to other insults. There is disruption of homoeostasis leading to dominant clotting pathway activation.

Symptomatology of SIRS

Hyperthermia

The temperature controlling centre in the hypothalamus is acted upon by the cytokines and the thermogenic factors due to sepsis which change the fixed temperature set point to a much higher one .The factors which generate more heat are activated and there is a decrease in the loss of heat from our body. This regulation of set point goes on till the body responds with its inbuilt immunological mechanism and also due to the effect of therapy with medications.

Tachycardia

In sepsis the metabolic demand of the target tissues is increased and the demand for oxygen to the organ systems is increased .Increased heart rate is one mechanism to increase the oxygen supply to the vital organs. Also there will be hypotension due to the action of cytokines which inhibits the firing activity of baroeceptors therefore natural high activity of sympathetic centre is prominent. So the heart rate is increased by this mechanism also in sepsis.

There is increased contractility of the myocardium due to this effect.

Decreased blood pressure

There is a drop in blood pressure because of the dilation of small blood vessels in the periphery which can be attributed to the action of the cytokines and certain factors which favour inflammation leading on to dilatation of the

blood vessels. Also there is an inhibitory effect of these mediators on the cardiovascular system.

Tachypnea

The reason for increase in respiratory rate in SIRS is complicated .In SIRS or sepsis there is aggravated demand of oxygen to the tissues and vital organs and hence there is a need to increase the ventilatory response so as to absorb more oxygen into the circulation. Breathing which is shallow and fast is brought out as a compensatory temperature regulating response. Hypocapnia is seen in hyperventilatory response and respiratory alkalosis occurs in the system as a result of hypocapnia.

Effect on leucocytes

As a result of release of cytokines favouring inflammation the leucocytes in the marrow get activated and hence proliferate and mature which leads on to adequate immunological protection and young immature leucocytes are produced and sent into the circulation from the marrow for protective function.

Leucopenia

There is a decrease in number of leucocytes as a result of certain phases of inflammation like leucocyte rolling, leucocyte adhesion and transmigration. The leucocytes are not promptly replaced from the bone marrow and leads on

to leucopenia in case of sepsis .The normal leucocyte count might not be replenished in such a stress situation in the bone marrow of human body.

The progression and consequences of SIRS depends on the effect of response of inflammatory and anti inflammatory mechanisms in body at tissue level and multisystem level. The body has got a counter inflammatory response process against the systemic inflammatory syndrome which is supposed to oppose and correct the effects of systemic inflammatory response on body as a whole. This mechanism is based on the fact that body stimulates it to oppose SIRS and both of them operate at the same time. The balance between the SIRS and the anti inflammatory syndrome is a proof of the balance between adequate inflammation and the level of suppression of body's immunity.

Interleukins 4 and 10 decrease the release of interleukins 1,6 and 8 and tumor necrosis factor alpha.The antagonists to Tumor necrosis factor alpha and interleukin 1 are generated which act on these cytokines and lead to dysfunction and receptor blockade.The ultimate result of the interaction of proinflammatory and anti inflammatory responses will decide the prognosis of a seriously ill individual with SIRS.

The associated disease conditions will affect the response of an individual to such stress or insults. Both inflammatory and anti inflammatory responses occur simultaneously and there should be a homeostasis maintained

even after the inflammatory and anti inflammatory response by the system. If the balance is destroyed there is a possibility of severe SIRS leading to tissue destruction and end organ damage and mortality .Another possibility is that there can be suppressed immunity leading on to other opportunistic insults and further leading on to death of the individual.

End organ damage in SIRS

The causes for end organ damage in sepsis are

1. dilatation of blood vessels
2. increase in vascular permeability
3. destruction of endothelium and production of certain mediators and microthrombus in the small blood vessels leading to DIC.
4. free radical release by the polymorphs.
5. generation of certain proteolytic enzymes by polymorphs.
6. nitric oxide synthesis by the enzyme nitric oxide synthetase.

Pulmonary system

Respiratory failure is frequently encountered in systemic inflammatory response syndrome and leads on to the clinical manifestations like increased respiratory rate, hypoxia and alkalosis. It further deteriorates the condition of the patient leading to acute lung injury and ARDS. The pathogenetic mechanism is that there is injury to endothelium in the lung capillary vessels

and this leads on to exudation of inflammatory cell rich fluid into the alveoli and interstitium. The cytokines increase the vascular permeability .There is destruction of pneumocytes which are supposed to produce surfactant and and also the integrity of the alveoli and basement membrane is also lost. This later on leads to atelectiasis in the lungs.

Cardiovascular system

Cytokines act on the cardiovascular system to cause the cardiac complications of SIRS.Nitric oxide is produced by nitric oxide synthetase and it is the cause for peripheral vasodilation which occurs in the system and there is in turn drop in the blood pressure. NO is produced from L-Arginine in endothelium of blood vessels by the enzyme. The drop in blood pressure may not improve with aggressive volume replacement, inotropic agents and vasoconstrictor agents. There is increased cardiac output due to hypotension. There is increased heart rate and stroke volume as the afterload decreases. There is depression of myocardial contractility due to the action of cytokines in SIRS. Myocardial depression is due to the action of nitric oxide .In what manner the myocardium responds to beta adrenergic drugs is also dependent on nitric oxide.

Kidneys

Acute kidney injury in SIRS is due to multitude of factors[20].The normal autoregulatory function of renal afferent and efferent arterioles is affected and

so blood supply to the kidneys and the GFR is decreased significantly.There is disturbance of the autoregulatory function in sepsis and SIRS.The decreased hemoperfusion is due to the effect of cytokines and volume loss which is not absolute.

The blood pressure of the patient need not predict the blood flow to the kidneys. Certain factors which constrict the blood vessels are produced as a result of inflammatory factors and the renin- AT- aldosterone system. Some of the factors have a renoprotective effect and others have an adverse effect.

Like in the case of other organs the kidneys are susceptible to white blood cell mediated cell injury and accumulation of polymorphs and generation of certain free radical species and proteolytic enzymes.

Gastrointestinal tract

In the gastrointestinal tract, there is decreased blood supply to the organs and the normal protective barrier is lost due to this decreased hemoperfusion to the gut. The real danger is when the bacteria seen inside the lumen of gut gets transported to the systemic circulation .The endotoxins also transmigrate in a similar manner.

Then there is a real risk of septicaemia and further aggravation of the condition of the patient. There may also be hemodynamic decompensation worsening as a result.

Metabolic dysfunction

Hypoxemia and elevated lactic acid levels are a consequence of the changes that occur in the hemodynamics due to the effects of inflammatory state leading on organ hypoperfusion and redirection of the blood. The novel approach to treatment of such conditions is to increase oxygen supply to the vital organs and avoid cell death. Nitric oxide mediates this effect at the level of mitochondria and thus electron transport process is affected at receptor for cytochrome oxidase. Then there is increased production of free radicals and decreased oxygen delivery to the tissues.

Coagulopathy

Coagulopathy is seen in SIRS due to the action of cytokines on clotting mechanism of the body[20].DIC or disseminated intravascular coagulation leads on to both thrombosis and hemorrhage and leads on to end organ failure. The extrinsic pathway mediated by tissue factor is involved in the coagulopathy seen in SIRS.

The tissue factor is responsible for the activation and is the cofactor for factor VIIa and activation of factors IX and X of the extrinsic pathway. Tissue factor is produced by endothelium and macrophages as a response to interleukins 6 and 8, complements and endotoxin. The clotting system is activated and anti clotting system is inhibited to certain extent. An important factor in the anti clotting mechanism is antithrombin III. Another vital factor

in anti clotting system is the thrombomodulin which is produced by endothelium and causes lysis of fibrin .Thrombin- thrombomodulin compound leads on to the activation of protein C with protein S and factors 5 and 8 are inactivated. In patients with SIRS there is decreased thrombomodulin under the effect of certain inflammatory factors and also protein S levels are decreased.

MAGNESIUM AND SIRS

Magnesium levels in Systemic Inflammatory Response Syndrome patients in the intensive care unit has been the important part of this study.

Several studies have been done to demonstrate the prevalence of abnormalities in serum magnesium levels in seriously ill patients upon admission to medical Intensive Care Unit[36]. Among the critically ill patients malnutrition is a widely acknowledged issue that may aggravate underlying illnesses and increase the risk of complications, so it is essential to have a nutritional assessment upon admission to the intensive care unit to identify the patients at risk and to guide nutritional supplementation during the stay in ICU[36,39] .

Magnesium deficiency is an often found electrolyte abnormality found in seriously ill patients [37].

The prevalence of magnesium deficiency ranges from 11 to 61% as reported in certain international studies and it has various effects on morbidity & mortality[6] .

Magnesium deficiency is also associated with worse clinical outcome among patients under intensive care.

There is dysfunction of heart and blood vessels as a result of magnesium depletion and SIRS in the intensive care unit patients[40]. Hypomagnesemia is also associated with other chronic diseases states. Association with diabetes mellitus has been reported which is as a result of loss of this mineral through the kidney route along with glycosuria.[13] It has been found that magnesium depletion and resistance to the action of insulin on its receptors is related[35] .

Administration of magnesium may lead to lesser requirement of insulin[34,35]. An important factor responsible for magnesium deficiency is chronic alcohol abuse. 30% of the hospital admissions with alcohol intoxication have been found to have hypomagnesemia and 85% in cases with delirium tremens[10]. Magnesium deficiency in alcoholics may be as a result of multiple causes like malnutrition, pancreatitis, alcohol withdrawal syndrome and abnormality in renal tubules due to alcoholism and further leading on to loss of magnesium through the kidneys[10].

Hypomagnesemia was found to be associated with 33% of patients with chronic liver disease and alcoholism by Soliman et al[5].Magnesium deficiency is associated with sepsis & SIRS in intensive care unit[37].

Immunoregulatory effects of hypomagnesemia and magnesium has been increasingly reported [9]. There is data available which shows that reduction in magnesium in the cells and in the circulation can have certain vital clinically relevant effects in sepsis and shock states[31,32].

Hypomagnesaemia promotes inflammatory tissue injury by increased production of free radical species and synthesis of cytokines. Circulating free magnesium ions are supposed to antagonise the action of calcium and affect the entry of calcium into the cells in states of sepsis as proposed by Altura et al[41]. Hypomanesemia leads on to calcium to move from the sarcoplasmic reticulum of muscle cells in experimental animals at a magnesium level of 0.3 to 3 millimol. It was found that low ionized magnesium leads to increased voltage gated calcium current[27]. It was found that intracellular calcium increases when magnesium concentration in tissues decrease in an endotoxin shock experiment on mice. Magnesium deficiency leads on to abnormal cellular calcium entry during SIRS and which will lead on to aggravated free cytoplasmic calcium and in the mitochondria which leads on to death of the cells.

Due to the fact that much amount of magnesium in the cells is attached to adenosine triphosphate, in the setting of SIRS decreased production of ATP will cause releasing of magnesium ions in the cells[32,33]. Later on levels of ionised magnesium increases and magnesium is removed from the cell.

It leads on to

(1) decreased sodium potassium ATPase function .

(2) decreased potassium ion channels.

(3)defective calcium channels in the cell membrane and sarcolemma..

The above said effects can explain the aggravated danger of endotoxin increase which is encountered in experimental animals in magnesium deficiency and also protection offered by magnesium administration . Magnesium controls vital immune function like stimulation of the macrophages, destruction of bacteria and polymorph cell adhesion, increased lymphocytes and monocyte bound by endotoxin..

There is alteration in binding of DNA to transcription elements which are supposed to inhibit the gene stimulation for the proinflammatory cytokines. Also it was researched and found by Mak et al that there is release of NO or nitric oxide in experiments on mice .The production of NO was due to the activation of synthetase enzyme and also the enzyme which is sensitive to calcium.

The cellular toxic consequences of nitric oxide are due to its combining with superoxides to produce per-oxynitrates.

The process of oxygen assimilation in the cell and mitochondrial system is affected due to the inhibition of haeme containing enzymeswhich further aggravates cell death and tissue injury .The vast amount of information that is coming out has shed light on the fact that prompt identification of hypomagnesemia and correction with prompt magnesium administration may in the long run lead to favourable results.This may be due to the fact that magnesium has vital role to play in the normal metabolic process of human body. A lot of research is needed towards the aspect mentioned in future times.

MATERIALS AND METHODS

The study was done with the aim of estimating the serum magnesium levels in Systemic inflammatory response syndrome patients in the Intensive Care Unit and assessing the prognostic value of serum magnesium in these patients.

DESIGN OF STUDY

Observational analytical study.

STUDY POPULATION:

The study was conducted at the medical intensive care unit of Government Rajaji Hospital, Madurai on 50 patients after getting institutional ethical committee approval. Informed written consent was obtained from each patient before being included in the study.

INCLUSION CRITERIA

The patients admitted to the Intensive Medical Care Unit of Government Rajaji Hospital, Madurai ,who satisfy the diagnostic clinical criteria for Systemic Inflammatory Response Syndrome during the period from April 2012 to October 2012.

EXCLUSION CRITERIA

1. Patients with chronic kidney disease.
2. Patients on diuretic therapy.
3. Patients with history of alcohol abuse.
4. Patients receiving magnesium supplements. or magnesium containing antacids.
5. Chronic diarrhea or malabsorptive states.
6, H/o recent myocardial infarction less than 6 months.

DATA COLLECTION

A total of 50 ICU patients were included in the study after obtaining informed written consent .Detailed history and history of other underlying disease conditions including hypertension ,diabetes mellitus, ischemic heart diseases, chronic kidney disease,chronic diarrhea was taken. History of chronic drug intake, and other systemic illness were obtained. History of fever and breathlessness was noted. Temperature and other vital signs were recorded.

Detailed clinical examination was done for each patient. The diagnosis of systemic inflammatory response syndrome was confirmed for each patient before he/she was included in the study.

LABORATORY INVESTIGATIONS

Complete blood count and differential cell count

serum creatinine

S.bilirubin,

Serum magnesium

serum sodium

Serum potassium

Calmagite dye method for quantitative estimation of serum magnesium

Test principle:

Under alkaline conditions magnesium ions react with calmagite dye to form a reddish complex which is measured spectrophotometrically at 530 nanometer. Intensity of the colour produced is directly related to the serum magnesium concentration .To eliminate the interference of calcium during estimation, EDTA is included in the reagent. Cyanide prevents interference by heavy metals and there is induction of surfactant system to prevent interference by proteins.

Magnesium + Calmagite-- ->Red coloured complex

Test procedure:

Three test tubes labeled Blank, Standard and Test are prepared as in table.

In test tubes	blank	standard	test
Calmagite reagent	1.0 ml	1.0 ml	1.0 ml
Standard reagent	-	10 ml	
Patient's sample	-	-	10 ml
Distilled water	10 ml	-	-

Three test tubes are incubated at room temperature (22-28ºC). The absorbance of Test (AT), Standard (AS) and Blank (AB) are read at 530nm in spectrophotometer. Magnesium concentration is calculated by the following formula.

Magnesium concentration (mEq/L) = (AT-AB / AS-AB) x 2

Serum magnesium concentration is expressed in mg/dl by linearity of 1 mEq/L = 1.2 mg/dl.

The patients are the divided into 3 groups based on the levels of serum magnesium as :

Normal : 1.3 to 2.5 meq/L.

Hypomagnesemia : less than 1.3 meq/L.

Hypermagnesemia : >2.5 meq/L.

The patients were followed up in the study regarding mortality rate and other aspects like duration of ICU stay ,necessity of mechanical ventilation and period under ventilator support.

STATISTICAL TOOLS

The data which was collected as regards the patients included in the study were recorded in a Master Chart.

Statistical analysis:

Analysis was performed with **SIGMA STAT 3.5** version statistical package. All continuous variables were presented as mean ±standard deviation if they were normally distributed. Differences in the normally distributed variables were assessed using the *t*-test and the ONE WAY ANOVA for dependent variable and chi square test. Comparisons between the two individual groups were performed using the unpaired *t*-test (parametric). All tests were two-sided and a probability value of $p < 0.05$ was considered statistically significant.

RESULTS

TABLE – 1

AGE DISTRIBUTION

Age in years	No.of cases	Percentage
< 20	3	6
21 – 40	22	44
41 – 60	16	32
> 60	9	18
Total	50	100

In the study, 50 patients were included and 22 patients (44 %) were in the 21-40 yrs age group. The mean age of the study population was 42.92 $\pm$ 16.69 years.

The median age was 41 yrs.

The lowest age was 14 years and highest age was 79 years.

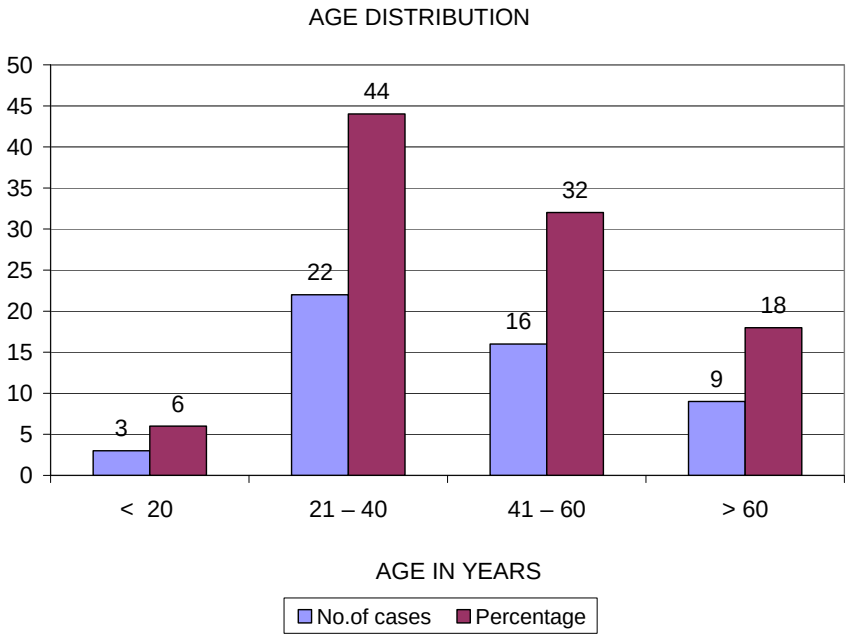

AGE DISTRIBUTION
50
45
40
35
30
25
20
15
10
5
0
3
6
22
44
16
32
9
18
< 20
21 – 40
41 – 60
> 60
AGE IN YEARS
No.of cases
Percentage

TABLE – 2

SEX DISTRIBUTION

SEX	No.of cases	Percentage
Male	35	70
Female	15	30
Total	50	100

70 % of the patients in the study group were male (35) and 30 % were females.(15)

SEX DISTRIBUTION

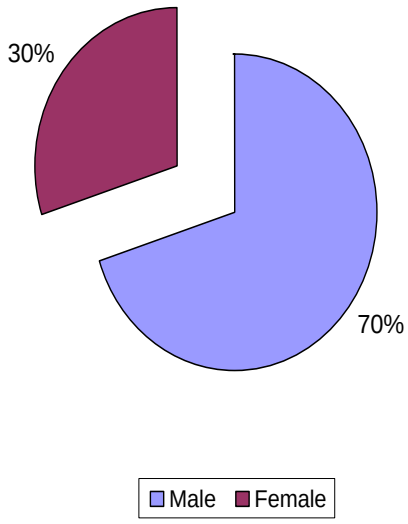


TABLE – 3

SERUM MAGNESIUM IN SIRS

Serum magnesium	No.of cases	Percentage
< 1.3	33	66
1.3 – 2.5	14	28
> 2.5	3	6
Total	50	100

In the study , 66 % patients(33) were in the hypomagnesemia group and 28 % (14)patients were in the normomagnesemia group .3 patients had hypermagnesemia.

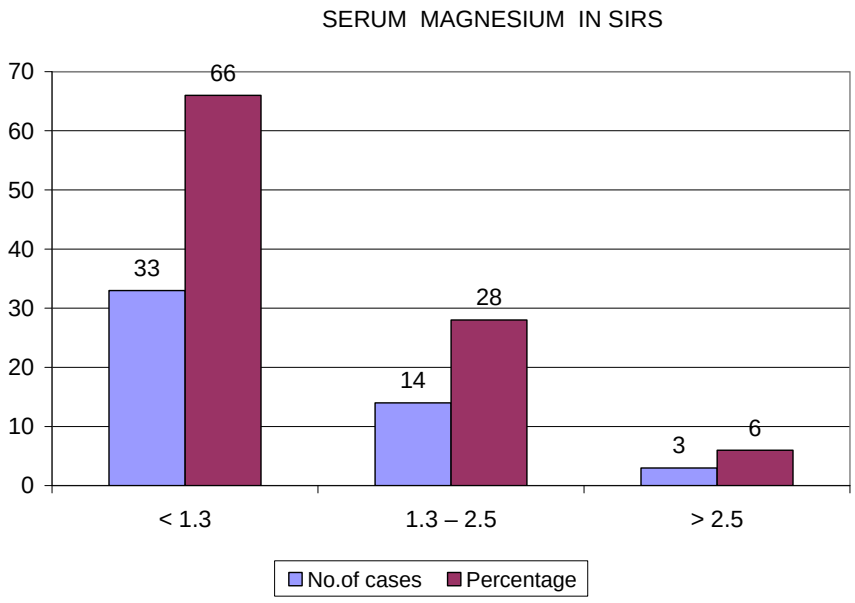

SERUM MAGNESIUM IN SIRS
70
60
50
40
30
20
10
0
66
33
28
14
3
6
< 1.3
1.3 – 2.5
> 2.5
No.of cases
Percentage

TABLE 4

MORTALITY RATE IN SIRS

Magnesium	Mortality			
	Yes	Percentage	No	Percentage
< 1.3 (33)	27	81.8	6	18.2
1.3 – 2.5 (14)	2	14.3	12	85.7
> 2.5 (3)	0	0	3	100

The mortality rate in the hypomagnesemia group was 81.8 % whereas it was 14.3 % in the normomagnesemia group Significant greater mortality rate was observed in the hypomagnesemia group when compared to the normomagnesemia group.

(P value = 0.037)

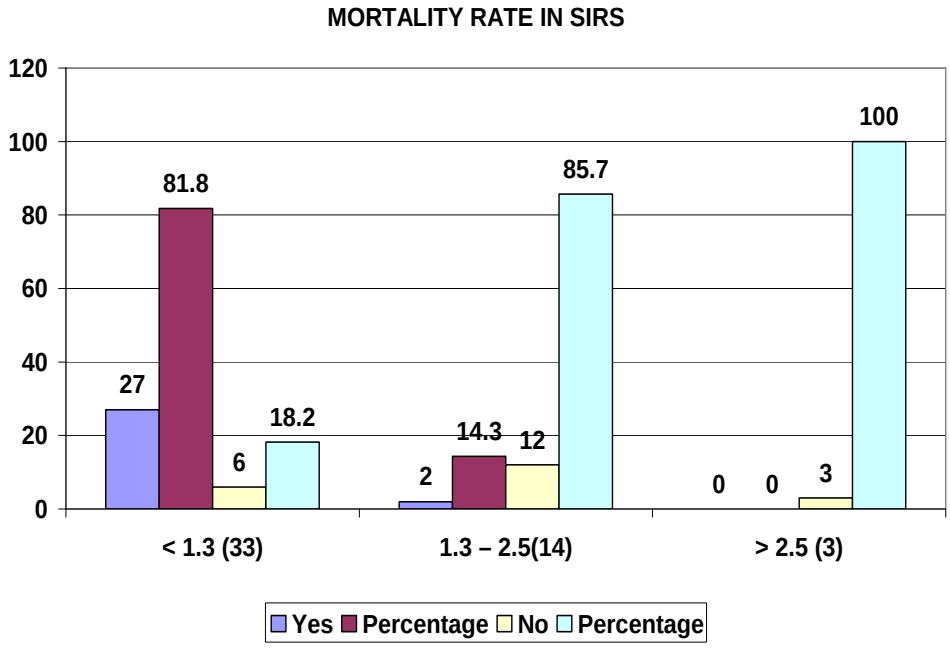

MORTALITY RATE IN SIRS
120
100
80
60
40
20
0
27
81.8
6
18.2
2
14.3
12
85.7
0
0
3
100
< 1.3 (33)
1.3 – 2.5(14)
> 2.5 (3)
Yes
Percentage
No
Percentage

TABLE 5

SERUM MAGNESIUM AND DURATION OF ICU STAY

OF SIRS PATIENTS

Magnesium	Mean duration
< 1.3 (33)	5.424
1.3 – 2.5 (14)	5.286
> 2.5 (3)	5.333

The mean duration of ICU stay for patients in the hypomagnesemia group was 5.424 days and in the normomagnesemia group it was 5.286 days. The difference was not found to be statistically significant. (P value = 0.865).

SERUM MAGNESIUM AND DURATION OF ICU STAY OF SIRS PATIENTS

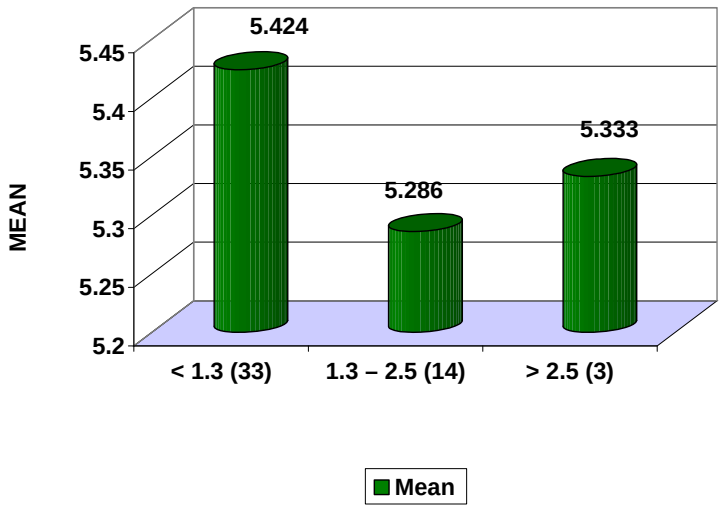


TABLE – 6

SERUM MAGNESIUM AND NEED FOR MECHANICAL VENTILATION IN SIRS

Magnesium	Ventilation Needed	
	No.of cases	Percentage
< 1.3 (33)	25	66
1.3 – 2.5 (14)	1	7.1
> 2.5 (3)	0	0

Among 33 patients with hypomagnesemia 25 patients required mechanical ventilation and it was 66 %. Among 14 patients in normomagnesemia group, 1 patient required ventilatory support.

The difference is statistically significant. (P = < 0.001) .

SERUM MAGNESIUM AND NEED FOR VENTILATION IN SIRS

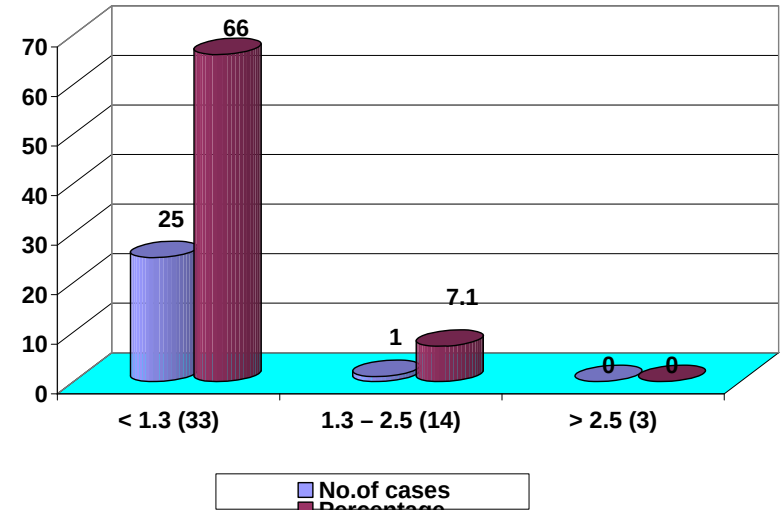


TABLE – 7

SERUM MAGNESIUM AND DURATION OF MECHANICAL VENTILATION IN SIRS

Magnesium	Duration of Ventilation
	Mean
< 1.3 (33)	3.45 days
1.3 – 2.5 (14)	2 days
> 2.5 (3)	0

The mean duration of mechanical ventilatory support for the hypomagnesemia group was 3.45 days and in the normomagnesemia group was 2 days. The difference is found to be statistically significant. (P value = < 0.001)

SERUM MAGNESIUM AND DURATION OF VENTILATION IN SIRS

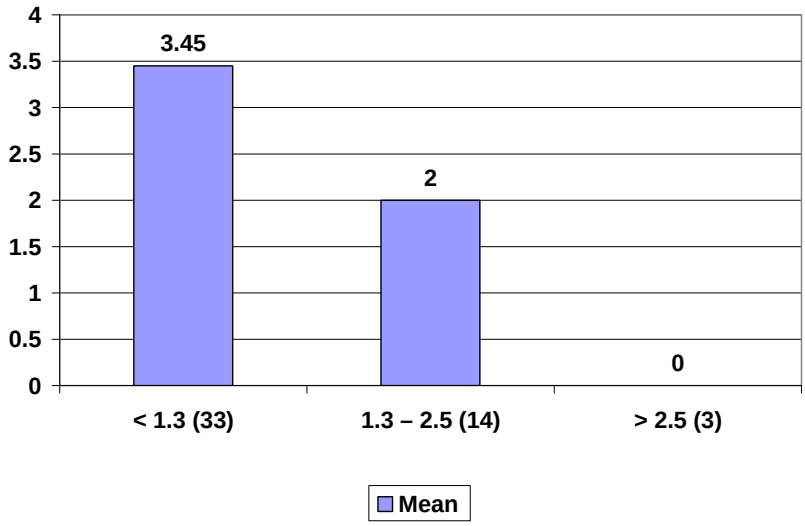


TABLE – 8

SERUM MAGNESIUM AND HYPONATREMIA

Magnesium	SERUM SODIUM LEVEL	
	< 135 meq/l	> 135meq/l
< 1.3 (33)	15 (45.4%)	18 (54.6%)
1.3 – 2.5 (14)	7 (50.0%)	7 (50.0%)
> 2.5 (3)	2 (66.7%)	1 (33.3%)
Total	24	26

Serum sodium levels were measured to look for incidence of hyponatremia in the study group. 45.4 % of the hypomagnesemia group had hyponatremia while 50 % of the normomagnesemia group had hyponatremia. The difference was not found to be statistically significant. (P value = 0.591)

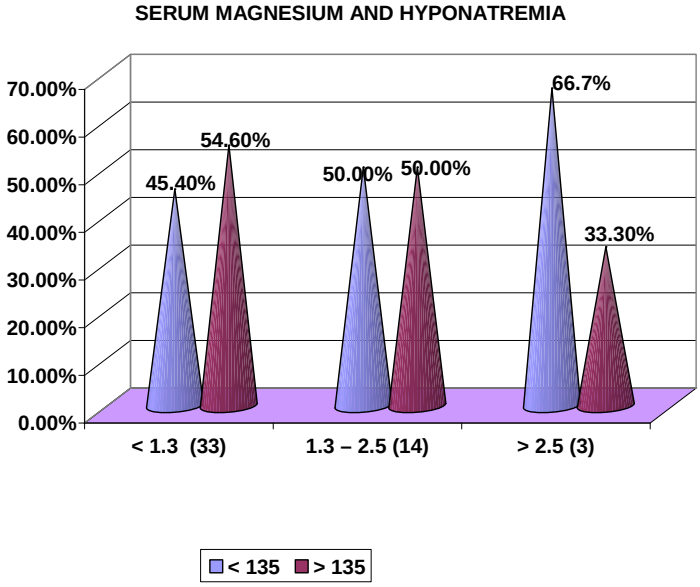

SERUM MAGNESIUM AND HYPONATREMIA
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
45.40%
54.60%
50.00%
50.00%
66.7%
33.30%
< 1.3 (33)
1.3 – 2.5 (14)
> 2.5 (3)
< 135
> 135

TABLE – 8

HYPOKALEMIA AND SERUM MAGNESIUM

Magnesium	SERUM POTASSIUM LEVEL	
	< 3.5meq/l	> 3.5 meq/l
< 1.3 (33)	13 (39.3%)	20 (60.7%)
1.3 – 2.5 (14)	10 (71.4%)	4 (28.6%)
> 2.5 (3)	3 (100%)	0
Total	26	24

Serum potassium levels were measured in the study. 39.3 % of the patients (13) in the hypomagnesemia group had hypokalemia while 71.4 % of the patients in the normomagnesemia group had hypokalemia . Three patients in the hypermagnesemia group had hypokalemia in the study. The difference among the hypomagnesemia and normomagnesemia group was not statistically significant. (P value = 0.387)

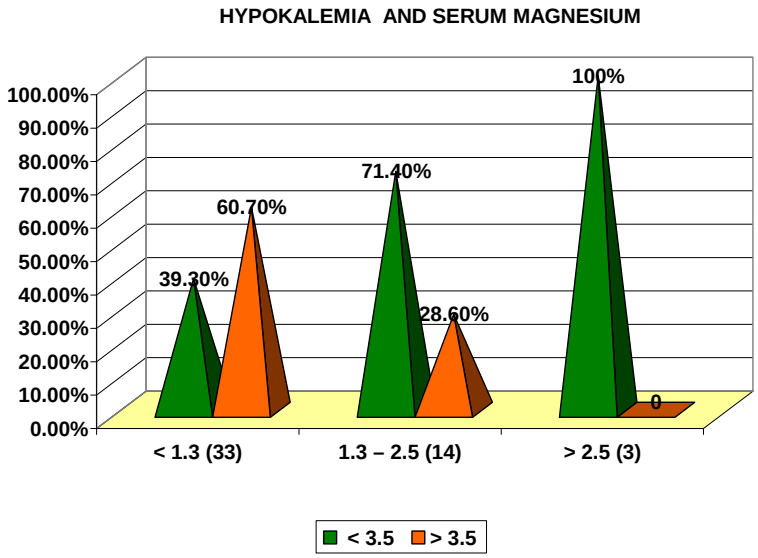

HYPOKALEMIA AND SERUM MAGNESIUM
100.00%
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
39.30%
60.70%
71.40%
28.60%
100%
0
< 1.3 (33)
1.3 – 2.5 (14)
> 2.5 (3)
< 3.5
> 3.5

TABLE – 9

SERUM MAGNESIUM AND DIABETES MELLITUS

Magnesium	DIABETES	
	Yes	No
< 1.3 (33)	12 (36.3%)	21 (63.7%)
1.3 – 2.5 (14)	6 (42.8%)	8 (57.2%)
> 2.5 (3)	1 (33.4%)	2 (66.6%)
Total	19	31

36.3 % of the patients in the hypomagnesemia group had diabetes mellitus while 42.8 % in the normomagnesemia group were diabetic. One patient in the hypermagnesemia group was diabetic. The difference among

hypomagnesemia and normomagnesemia group was not found to be statistically significant. (P = 0.982)

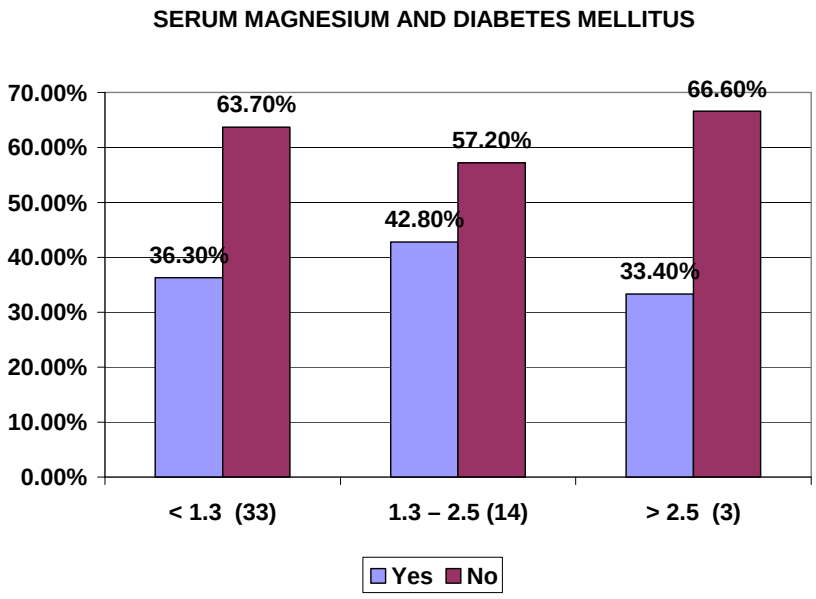


TABLE – 10

HYPERTENSION AND SERUM MAGNESIUM

Magnesium	HYPERTENSION	
	Yes	No
< 1.3 (33)	11 (33.3%)	22 (66.7%)
1.3 – 2.5 (14)	5 (35.7%)	9 (64.3%)
> 2.5 (3)	0	3 (100%)
Total	16	34

33.3 % of the patients in the hypomagnesemia group were hypertensive and 35.7% patients in the normomagnesemia group were hypertensive. The difference was found to be not significant.(P = 0.387)

HYPERTENSION AND SERUM MAGNESIUM

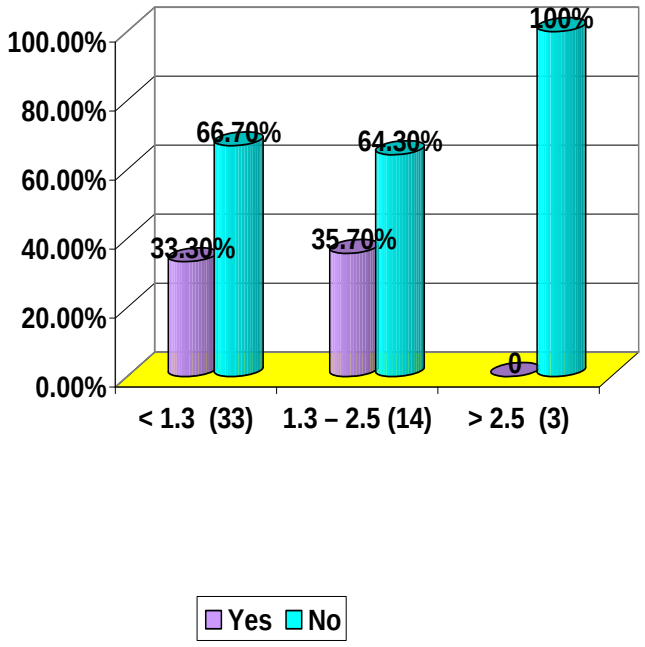


TABLE -11

SERUM BILIRUBIN IN SIRS

Serum Bilirubin	
Lowest	0.8
Highest	1.5
Mean	1.042

The lowest value of serum bilirubin recorded was 0.8 mg/dl and the highest value recorded was 1.5 mg/dl with a mean serum bilirubin value of 1.042 mg/dl.

TABLE -12

SERUM CREATININE IN SIRS

Serum Creatinine	
Lowest	0.7
Highest	3
Mean	1.2

The highest serum creatinine recorded was 3 mg/dl and the lowest value was 0.7 mg/dl .The mean value of serum creatinine was 1.2 mg/dl.

TABLE - 13

TEMPERATURE

Temperature(F)	No.of cases	Percentage
< 100.4	2	4
100.4 – 102.4	47	94
> 102.4	1	2

The mean temperature value was 101.35 degree F 94 % of the patients (47) were in the recorded temperature range of 100.4- 102.4 degree F.

TABLE - 14

HEART RATE

Heart Rate	No.of cases	Percentage
90 – 100	21	42
101 – 110	21	42
> 110	8	16

The mean heart rate was 103.52 per minute.

42 % patients had heart rate in the range 101-110 and 16 % had heart rate > 110 per minute.

TABLE - 15

RESPIRATORY RATE

Respiratory Rate	No.of cases	Percentage
< 26	17	34
27 – 30	23	46
> 30	10	20

Mean respiratory rate value was 28.52/min.

46 % patients were in the 27-30 range for respiratory rate and 34% patients had respiratory rate less than 26.

20 % patients had respiratory rate greater than 30 /min.

TABLE -16

LEUCOCYTOSIS IN SIRS

Leucocytosis	No.of cases	Percentage
Yes	27	54
No	23	46
Total	50	100

In the study 27 patients had leucocytosis which was 54 % .

LEUCOCYTOSIS IN SIRS

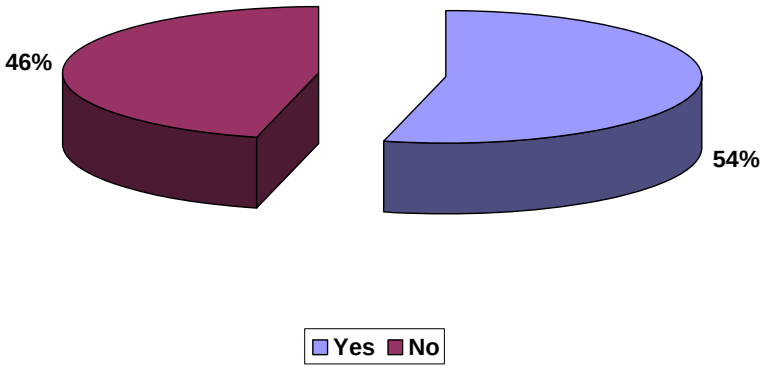


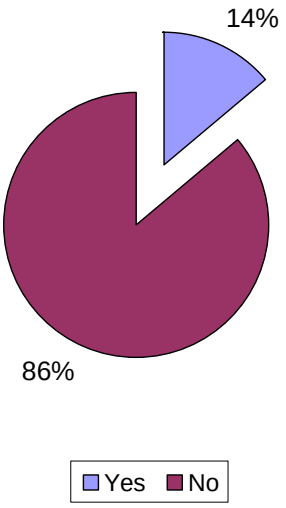
TABLE- 17

LEUCOPENIA IN SIRS

Leucopenia	No.of cases	Percentage
Yes	7	14
No	43	86
Total	50	100

In the study 7 cases had leucopenia on blood investigation which came to 14 %.

LEUCOPENIA IN SIRS



DISCUSSION

Magnesium is a vital electrolyte in the normal metabolism of the human body. The deficiency of magnesium can lead on to disastrous consequences if not detected at the right time and is supposed to be an important underestimated electrolyte abnormality especially in the intensive care unit setting. Sepsis is an independent risk factor for developing hypomagnesemia during ICU stay as reported by Soliman et al[5].

The deficiency of magnesium has been associated with the occurrence of Systemic Inflammatory Response Syndrome (SIRS)[10,38]. Sepsis , which is SIRS which has got an infectious etiology is supposed to be associated with hypomagnesemia according to the research by Soliman et al[5].

The purpose of this study was to estimate serum magnesium levels in the SIRS patients who have been admitted to the medical intensive care unit and to assess the prognostic value of serum magnesium in these patients.

The study was done on 50 patients and the mean age in this particular study was 42.92 $\pm$ 16.69 yrs .Most of the patients in the

study was in the age group 0f 21-40 yrs and the least number were in the age group less than 20 yrs.

In the study 35 patients (70%) were males and 15 were female(30%). The association between magnesium deficiency and mortality rate and clinical improvement while in ICU was dealt upon mainly in this study.

Several previous studies on critically ill adults and children have shown the association of hypomagnesemia and increased occurrence of mortality, increased morbidity ,increased duration of ICU and hospital stay and increased duration of mechanical ventilation .

In this study which was done on 50 patients admitted to the intensive care unit hypomagnesemia was found in 66 % patients and hypermagnesemia was found in 6 % patients. Magnesium depletion is associated with increased release of proinflammatory cytokines as in inflammatory states and in sepsis[9].

The previous studies have measured the total serum magnesium and the prevalence of hypomagnesemia was in the range of 14 to 70 %[3,37]. The prevalence of magnesium deficiency in seriously ill patients in a study done by Mousavi et al in Tehran, Iran was 33 % and in the same study 13.2% patients had hypermagnesemia[36]. There has been

studies which show that the prevalence of hypomagnesemia varies from 14 to 66 %.. Abnormal levels of magnesium has been found in several previous studies which were done on critically ill adult patients and children .

Hypermagnesemia is usually rarer compared to hypomagnesemia and in this study 6 % of the patients had hypermagnesemia[37]. Previous studies have shown that it was in the range of 4- 14 %[37]. Musavi et al have reported 13.2 % incidence of hypermagnesemia in the study conducted in Tehran[36]. Hypermagnesemia though it is rare has been found to be associated with increased mortality and morbidity in critically ill patients. The release of magnesium after cell injury or cell death into the extracellular fluid may be the explanation for this phenomenon.

The association between serum magnesium levels and mortality while in the intensive care unit was an important aspect of this study.

In this study in patients with hypomagnesemia the mortality rate was 81.8 % and in patients with normal serum magnesium levels the mortality rate was found in this study to be 14.3 % and was found to be statistically significant. The association between magnesium levels and mortality rate has been found to vary in different studies[1,2,6,17]. Also

magnesium supplementation may be beneficial in lowering the mortality rate.

In the study conducted by Soliman et al it was found that there was increased mortality rate in the setting of hypomagnesemia occurring in the intensive care unit[5].In the study conducted by Guerin et al it was found that there was no difference in ICU mortality between patients with hypomagnesemia and patients with normal serum magnesium levels[2].

There was higher mortality among patients with higher than normal serum magnesium levels according to the study done by Guerin et al[2].

In the study done by Chernow et al a higher mortality rate (41 % vs 13 %) was significantly found in patients with magnesium deficiency as against patients with normal serum magnesium levels[17]. Similar results were found in studies done by Safavi et al and Rubiez et al[1,6].

The higher mortality rate in patients with hypomagnesemia may be due to multiple other factors also like cardiac rhythm disturbances and hypokalemia[37]. Also the association of hypomagnesemia with sepsis and SIRS may be another cause for the observed increased mortality rate in the study. Deheinzelin et al had reported on the outcome of seriously ill

cancer patients with relation to serum magnesium levels in a study[4].The study which has been done here mainly focusses on the seriously ill SIRS patients who have been admitted to the ICU .

The difference in the duration of ICU stay was studied and it was found that in the patients with low magnesium levels the mean duration of ICU stay was 5.424 , in the normomagnesemia group it was 5.286. The hypermagnesemia group had mean duration of ICU stay of 5.333. The difference was not found to be statistically significant in this study.

Soliman et al had reported that that there was no difference in the duration of stay in the intensive care unit among the three different groups mentioned above[5]. However patients who developed magnesium depletion while staying in the ICU were found to have more duration of stay there [5].

The duration of stay in the ICU was found to be a risk factor for developing hypomagnesemia and its complications in other studies . Hypomagnesemia patients had longer length of mechanical ventilation and ICU stay according to Musavi et al [36].

Magnesium depletion in the extracellular fluid has been associated with respiratory muscle weakness and respiratory failure and this later leads on to difficulty in weaning a patient from the ventilator[9]. The

present study showed that the patients with hypomagnesemia needed mechanical ventilation more than the patients with normomagnesemia.

Prolonged mechanical ventilator dependence has been reported in hypomagnesemia patients in previous studies[28] . In this study duration of mechanical ventilation was significantly more in the hypomagnesemia group than in the patients with normal serum magnesium levels.

Fiaccordori et al in his study had shown that patients with hypomagnesemia needed ventilator support for more days[28].It was researched and reported by Molloy et al that on administering magnesium to patients who had hypomagnesemia ,weakness of the muscles of respiration improved when compared to the normomagnesemic controls[29].

Safavi et al had also reported that in patients with hypomagnesemia mechanical ventilation duration was longer than in normomagnesemia group[6]. In a study done by Munoz et al it was found that in neonatal intensive care unit the neonates needed ventilator support more frequently if they were in the hypomagnesemia group than in the normomagnesemic group[12,30]. Also there have been several national studies done touching on the topic of magnesium levels and prognosis of the pediatric patients[7,8].

Magnesium depletion also has been found to be associated with diabetes mellitus and is supposed to be due to depletion by the renal route that usually occurs along with glycosuria[37].

Hypomagnesemia has been associated with development of insulin resistance and a strong relation has been found between magnesium deficiency and Diabetes .Specific tubular defect in the thick ascending limb of loop of henle has been found which is associated with the reabsorption of magnesium ion and it has been researched and reported recently.

Increased urinary magnesium excretion due to hyperglycemia and osmotic diuresis may contribute to hypomagnesemia in diabetes[34]. Serum levels of magnesium have been found by several investigators to correlate inversely with fasting blood glucose concentration and the percentage of HbA1C.In the present study it was found that 36.3% of the patients in the hypomagnesemia group were diabetics and 42.8% in the normo magnesemia group were diabetics. One patient in the hypermagnesemia group was found to be diabetic. The association between diabetes and magnesium deficiency was not found to be statistically significant in the present study.

In the study done by Rodriguez et al it was found out that magnesium supplementation can lead on to decreased insulin requirements[35]. Another study done by Chernow et al has stressed on the point that magnesium supplementation can lead on to better glycemic control[17] .

Hypomagnesemia has been found to be associated with hypertension. The study done by Kawano et al had shed light on the association between hypertension and magnesium deficiency[36]. The above mentioned study had studied the effect of magnesium supplementation in hypertensive patients[36].

In the present study it was found that 33.3 % of patients in the hypomagnesemia group were hypertensives. 35.7% patients in the normomagnesemia group were hypertensive individuals .The association between hypertension and magnesium levels were not found to be statistically significant. In the study done by Safavi et al it was found that association between hypomagnesemia and hypertension is poor.

The effect of magnesium supplementation on control of hypertension has not shown a consistent relationship. Hypomagnesemia increases arteriolar tone and thus tissue hyperperfusion which is supposed to be a homoeostatic function is affected.The failure of this

homeostatic function leads on to hypoperfusion states which leads on to end organ damage in the brain and the cardiovascular system.

Hypomagnesemia has also been found to be associated with many other electrolyte abnormalities[9,15,23]. It was the study by Whang et al which reported that hypomagnesemia was seen in 42 % patients with hypokalemia, 27% patients with hyponatremia, 22 % patients with hypocalcemia and 29% patients with hypophosphatemia[21,22]. Serum sodium and potassium levels were also estimated in the study .

In the present study it was found that hypokalemia was seen in 39.3% of the patients with hypomagnesemia.71.4 % of the patients in normomagnesemia group had hypokalemia. The difference in the 2 groups were not found to be statistically significant.

The relevance of hypokalemia in the setting of hypomagnesemia in a critically ill SIRS patient is that hypokalemia will not respond to supplementation unless magnesium depletion in the extracellular space is detected and corrected promptly. It may be due to the fact that there is increased loss of potassium through the kidneys in this condition and also the membrane ATPase function is defective.

Also there can be underlying diseases causing deficiency of both the electrolytes and associated with diuretic therapy ,diarrhea and

vomiting. In the present study the association between hypokalemia and hypomagnesemia was not significant.

The association between hyponatremia and hypomagnesemia has been reported in previous studies. Safavi et al had reported this association in a study done in Isfahan, Iran.In the present study hyponatremia was seen in 45.4% of the patients in the hypomagnesemia group. 54.6 % of the patients had serum sodium levels above the lower limit.

Hyponatremia was seen in 50 % of the patients in the normomagnesemia group.Two patients in the hypermagnesemia group had hyponatremia.

In the present study the association between hyponatremia and hypomagnesemia was not found to be statistically significant.

In the study the mean serum bilirubin value obtained was 1.042 mg/dl. Also serum creatinine had a mean value of 1.2 mg/dl. In the study,leucocytosis was found in 54 % cases and leucopenia was seen in 14%.

SUMMARY

The present study was done with the important purpose of ascertaining whether serum magnesium levels had any prognostic significance in patients who are diagnosed as systemic inflammatory response syndrome .The study was done in the seriously ill patients in the critical care unit. The inference from the study was that magnesium depletion was found to be associated with significant greater mortality rate (with p value 0.037).Also the patients in the hypomagnesemia set had more incidence of being put on mechanical ventilator support due to respiratory system decompensation. (p value <0.001) The duration of being on ventilator support was also significantly more in the patients with hypomagnesemia in the present study than in those who had normal serum magnesium concentrations.(p value <0.001). The number of days spent in ICU was also compared and it was found out that there was no significant difference in the hypomagnesemia and normomagnesemia groups (p value 0.865).

There was no significant association of hypomagnesemia and other electrolyte abnormalities like hyponatremia and hypokalemia in the present study. Also the association between magnesium levels and chronic disease states like Diabetes mellitus and hypertension were not significant.

CONCLUSION

1. Serum magnesium levels have prognostic value in the patients diagnosed as SIRS in the ICU setting.

2. Serum magnesium concentration shows association with increased mortality rate in the critical care unit.

3. There is significant greater need for mechanical ventilation and increased duration of stay under ventilator support in the patients with lower magnesium levels.

4. The duration of ICU treatment was not significantly related with the serum magnesium concentration.

5. No significant association between hypomagnesemia and systemic hypertension could be reported.

6. No significant association between magnesium deficiency and Diabetes mellitus could be found out in this study.

BIBLIOGRAPHY

1. Rubeiz G J,Hardy D, Thil-Baharozean M et al: Association of hypomagnesemia and mortality in acutely ill medical patients. Crit Care Med 1993;21:203-209.

2. Guerin C,Cousin C: Serum &erythrocyte magnesium in critically ill patients.Intensive care med1996;22:724-727.

3. Huijigen H J ,Sosan M,Sander et al :Magnesium levels in critically ill patients:what should we measure?Am J Clin Patholo 2000;114:688-695.

4. Deheinzelin D, Negri E M, Salem M Z et al: Hypomagnesemia in critically ill cancer patients: a prospective study of predictive factors.Braz J med Biol Res 2000;33:1443-8.

5. Soliman HM ,Mercen D et al: Development of ionized hypomagnesemia is associated with higher mortality rate.Crit care med 2003;31:1082-7.

6. Safavi M, Honarmand A: Admission hypomagnesemia –impact on mortality and morbidity in critically ill patients. Middle East J Anaesthesiol 2007;19:645-60.

7. Singhi S C,Singh J,Prasad R:Hypo and Hypermagnesemia in an Indian pediatric intensive care unit.Journal of tropical pediatrics.2003;7:235-7.

8. Deshmukh C T , Gaurav M N,S A Rane: Hypomagnesemia in pediatric population in an ICU. JPGM 2000;46:179-180.

9. Zaloga G P, Wilken R: A simple method of determining physiologically active magnesium and calcium concentrations in critically ill patients.Crit Care Med 1987,15:813-816.

10. Paul Marino :Fluid and electrolyte disorders- magnesium.The ICU Book, 2nd ed. Philadelphia, Lippincott Williams and Wilkins 2004;660-672.

11. Varley H :Iodine,iron,copper,sulphur and magnesium.Practical Clinical Biochemistry, 4th ed. 481-482.

12. Salem M, Munoz,Chernow:Hypomagnesemia in critical illnesses. Critical Care Clinics 1991;7:225-252.

13. Michel J D: Hypomagnesemic disorders.Critical Care Clinics 2001;17:155-173.

14. James W.Van Hook:Hypermagnesemia ,Critical Care Clinics 1991;7:215-223.

15. Zaloga, Robert P: Calcium ,phosphorus & magnesium disorders. Textbook of Critical Care,Fourth edition ,Philadelphia, W B Saunder 2000;862-875.

16. Ryzen E ,Wagers P W,Singer et al: Hypomagnesemia in ICU population. Criti Care Med 1985;13:19-21.

17. Chernow B,Banberger ,Stoiko et al: Magnesium deficiency in postoperative ICU. Chest 1989;95:391-397.

18. Reinhart R A ,Desbien et al : Magnesium deficiency in the patient entering ICU. Criti care med 1989;13:506-507.

19. Balsteri F J: Magnesium metabolism in critically ill.Criti care Clinics 1985;5:217-226.

20. Robert Munford S,Richard Bringhurst F,Marie B Demay et al . Magnesium metabolism /Severe sepsis and septic shock. Harrison's Principles of Internal Medicine 18 th edition,pages 2223 and 3089-92 ,Mc graw Hill 2011.

21. Whang R, Aikawa,Oei T O et al: Predictors of clinical hypomagnesemia -hypocalcemia,hypokalemia , hypophosphatemia. Arch internal medicine 1984;144:1794-6.

22. Whang R, Dykner ,Flink et al: Magnesium depletion as a cause of refractory potassium repletion. Arch internal medicine 1985;145:1686-1689.

23. Web,Schade D S: Magnesium deficiency as a cause of persistent hypokalemia. JAMA 1975;233:23-24.

24. Browne E M,Chen C :Calcium,magnesium and control of PTH secretion. Bone Miner 1989;5:249-257.

25. Rude R K, Singer ,Oldam S B: Functional hypoparathyroidism and Parathormone end organ resistance in human magnesium deficiency. Clin Endocrinol 1976;5:209-224.

26. Graber M L, Schultman G: Hypomagnesemic hypocalcemia independent of parathyroid hormone. Ann Intern Med 1986;104:804-

27. Koch SM, Warter , Mehlorn U: The simultaneous measurement of total and ionized calcium in intensive care unit . J Crit Care 2002;17:203-5.

28. Fiaccordori E, Delcanale , Coffrini et al: Muscle and serum magnesium in pulmonary ICU. Crit Care Med 1988;16:751-60.

29. Molloy ,S Dingra,F sloveen et al: Hypomagnesemia and respiratory muscle power. Am Rev Respir Dis 1984;129:497-8.

30. Munoz R,khilnaani P, Ziegler J et al: Ultra filterable hypomagnesemia in neonates admitted to the ICU. Crit Care Med 1994;22:815-20.

31. Salem M, Kasinsky N, Munoz et al: Progressive magnesium deficiency and increased mortality from endotoxin challenge: protective effects of acute magnesium replacement therapy. Criti Care Med 1995;23:108-18.

32. Harkema JM, Choudhary IH: Magnesium –ATP in the treatment of shock, sepsis and ischemia. Criti Care Med 1992;20:263-75.

33. Wang P, Morison M H et al: Mechanism of the beneficial effects of ATP –magnesium chloride following trauma ,hemorrhage &resuscitation.: Downregulation of proinflammatory cytokines release. J Surg Res 1992;52:364-71.

34. Tosiello :Hypomagnesemia and Diabetes– a review of clinical implications. Arch Internal Medicine 1996;156:1143-8.

35. Rodrigues M, Romeiro et al : Oral magnesium supplementation improves insulin sensitivity and metabolic control in Type 2 Diabetes. Diabetes Care 2003;15:1045-49.

36. Syedali javaad Musavi,Saeed Salimi ,Mehdi Rezaai: Serum magnesium levels :impact on the outcome of patients admitted to the ICU.Tanaffos 2010 9(4),28-33.

37. Limaye CS, Londhe ,M Y Nadkar, Borges:Hypomagnesemia in critically ill medical patients. JAPI January 2011,volume 59.

38. Jean Louis Vincent.Annual update of intensive care medicine. 2008 edition

39. Hulst J M, Zimerman L J,Tibbol D ,Joosten K,van Goudoever , Zimmermann LJ.The role of initial monitoring of routine biochemical marker in critically ill patients. J Nutri Biochem 2006; 17 (1): 57- 62.

40. Tofaletti J.Physiology and regulation .Ionised magnesium,calcium,lactate levels in critical care setting.Am J Clin Pathol 1995 Oct ,104(4suppl 1)s88-94

41. Altura BM, Altura B. Role of magnesium in pathophysiologic process & clinical utility of magnesium ion selective electrodes. Scand J Clini Lab invest suppl; 224:211-234, 1996.

LIST OF ABBREVIATIONS

SIRS	Systemic Inflammatory Response Syndrome
ATP	Adenosine Triphosphate
WBC	White Blood Cell
ILD	Interstitial Lung Disease
OPC	Organophosphorus Compound
ICU	Intensive Care Unit
PCT	Proximal Convoluted Tubule
DCT	Distal Convoluted Tubule
ECF	Extracellular Fluid
EGF	Epidermal Growth Factor
ATN	Acute Tubular Necrosis
CSF	Colony Stimulating Factor
SIADH	Syndrome of Inappropriate Antidiuretic Hormone
TPN	Total Parenteral Nutrition
GFR	Glomerular Filtration Rate
PTH	Parathormone
MODS	Multiple Organ Dysfunction Syndrome
PAI-1	Plasminogen Activator Inhibitor -1
APC	Activated Protein C
DIC	Disseminated Intravascular Coagulation
ARDS	Acute Respiratory Distress Syndrome
DNA	Deoxyribonucleic Acid.
EDTA	Ethylene Diamine Tetra acetic Acid

PROFORMA

Serial No:

Patient Details

Name:

Hospital IP no:

Age:

Sex:

Address:

Date of admission:

H/o presenting illness:

fever

breathlessness

symptoms relevant to the illness

duration of ICU stay

Past History:

Diabetes mellitus

Hypertension

Ischemic heart disease

Chronic kidney disease

Pulmonary tuberculosis.

h/o Malabsorption or chronic diarrhea

Drug history:

h/o diuretic drug use

H/o magnesium supplementation

Use of magnesium containing antacids.

Personal History*:*

Alcohol consumption

/smoking

Examination:

General Examination

Level of consciousness and orientation

Pallor /icterus /cyanosis

Clubbing /lymphadenopathy/pedal edema.

Vital parameters:

Pulse rate :

Heart rate:

Blood pressure:

Respiratory rate:

Temperature :

System examination:

Cardiovascular system

Respiratory system

Central Nervous System

Abdomen

Investigations:

1. Blood Urea and Serum creatinine

2.serum magnesium

3.serum sodium

4.serum potassium

5.total leucocyte count

6.differential leucocyte count.

7.serum bilirubin.

S.No.	Name	IP No.	age	sex	heart rate	respiratory rate	temperature	Leucocytosis	Leucopenia	Diabetes	Hypertension	S.sodium	s.potassium	s magnesium	**Duration of icu stay**	ventilated /not	duration of ventilation	mortality	S.bilirubin	s creatinine
1	KANNAIYYA	64474	45	M	100	30	101	YES	NO	YES	NO	124	3	1.5	7	NO	NO	YES	1.5	1.2
2	MUTHU	62215	72	M	102	28	102	YES	NO	YES	YES	135	4	1.6	10	NO	NO	NO	0.9	1
3	THANKAM	62236	27	F	122	26	100.6	YES	NO	NO	NO	127	3.5	1.2	5	YES	3	YES	1	1.4
4	AMIR	65226	38	M	90	24	101	YES	NO	NO	NO	135	3.4	3.2	2	NO	NO	NO	1	2
5	ARUMUGAM	60845	47	M	96	32	100.4	YES	NO	YES	YES	136	3.5	1	5	YES	3	YES	1.4	0.9
6	THANGAMANI	59078	42	M	96	30	102	NO	NO	YES	YES	126	3.5	1.1	8	YES	8	YES	1	1.5
7	PANDISELVI	62378	55	F	98	36	101	YES	NO	NO	YES	133	3.6	1.2	10	YES	10	YES	1	1
8	SIVANANDI	57435	28	M	96	26	101	NO	NO	NO	NO	136	3.5	1.1	5	NO	NO	NO	1.2	1
9	RAMALINGAM	56743	65	M	102	28	102	YES	NO	YES	YES	134	3.7	1	9	YES	9	YES	0.9	1.1
10	REVATHI	62254	14	F	112	30	101	NO	YES	NO	NO	130	3.4	1.2	3	NO	NO	YES	1.2	1
11	CHANDRAN	55902	45	M	108	24	101	NO	YES	NO	NO	135	3.4	2.5	3	NO	NO	NO	1	2.2
12	PONNAPPAN	62287	23	M	104	26	101	NO	YES	NO	NO	126	3.5	1.9	3	NO	NO	NO	1.2	1
13	MANOJ	54322	26	M	112	28	102	NO	NO	NO	NO	133	3	1.5	5	NO	NO	NO	1.3	0.8
14	SIVARAJ	57345	17	M	96	26	102	YES	NO	NO	NO	133	3	1	10	YES	10	YES	1	1
15	SRINIVASAN	71929	45	M	98	28	104	YES	NO	NO	NO	136	3.5	0.8	2	YES	2	YES	1	1
16	VELAPPAN	56789	25	M	100	28	102	NO	NO	NO	NO	134	3.7	1.2	6	YES	3	YES	1	1
17	KARUPPU	58769	40	M	104	30	101	YES	NO	YES	NO	138	3	2	1	NO	NO	NO	0.9	1
18	KARTHICK	56430	72	M	110	26	100.8	YES	NO	YES	YES	136	3.5	0.9	4	YES	4	YES	0.9	1
19	BALU	67553	31	M	106	28	101	NO	NO	NO	NO	137	3.4	4.6	6	NO	NO	NO	1	1.3
20	GURUSAMI	67549	66	M	114	24	101	NO	YES	YES	NO	125	3.8	0.9	5	NO	NO	YES	1	1

21	NATHAN	55772	34	M	100	26	102	NO	NO	NO	NO	133	3.5	1	3	YES	3	YES	1	1
22	SRUTHI	65421	40	F	102	32	101	YES	NO	YES	NO	126	3.2	5.5	8	NO	NO	NO	1	1.3
23	FAREED	65476	24	M	116	36	101	NO	NO	NO	NO	133	3.6	1.1	5	NO	NO	NO	0.9	0.7
24	PONNAIYASAMY	67009	20	M	118	30	102	YES	NO	NO	NO	135	3.8	1	6	YES	3	YES	0.9	1
25	BALAN	62430	25	M	114	26	101	YES	NO	NO	NO	137	4	1.1	10	YES	10	YES	1	0.8
26	MALATHI	67892	52	F	100	28	101	YES	NO	NO	NO	133	3.9	2	5	NO	NO	NO	1	1
27	PONNAMMA	57333	34	F	102	30	100.6	YES	NO	YES	NO	138	4	1.2	6	YES	4	YES	1	1.4
28	GOPALAN	67778	38	M	106	32	101	YES	NO	NO	NO	132	3.5	2.1	3	NO	NO	NO	1.5	2.3
29	PUSHPAM	60098	65	F	116	28	101	NO	NO	YES	YES	137	3.8	1.8	9	NO	NO	NO	1	1.3
30	MARISAMI	69879	56	M	102	26	102	YES	NO	YES	YES	136	3.6	1	4	YES	2	YES	0.9	1.2
31	CHINNAIYA	50088	44	M	106	32	101	YES	NO	YES	YES	124	3.9	1	7	YES	6	YES	1	1
32	SETHU	67871	45	M	100	36	102	NO	NO	NO	NO	137	3.5	1.1	3	YES	3	YES	1	0.9
33	KAALI	55667	79	F	110	32	100.4	NO	NO	YES	YES	140	4.1	1.1	6	YES	4	YES	0.8	0.9
34	SUMITHAN	68000	56	M	104	30	101	YES	NO	NO	YES	141	4.1	2.5	7	NO	NO	NO	1	1.8
35	PRAVEEN	67001	42	M	100	24	102	YES	NO	NO	NO	142	4	0.9	2	NO	NO	NO	1.1	1.3
36	KRISHNAMMA	60001	29	F	98	26	102	YES	NO	NO	NO	136	3.4	0.8	3	NO	NO	NO	1.2	1
37	CHELLAM	65000	30	F	96	28	101	NO	YES	NO	NO	134	4.2	0.9	5	YES	4	YES	1	1
38	HARISAMY	64426	70	M	98	30	101	NO	NO	YES	YES	135	4.2	1.1	2	YES	2	YES	1	1
39	SEETHA	60032	56	F	100	24	101	NO	NO	YES	YES	138	4	1.5	6	YES	2	YES	0.9	1
40	AJITH	56010	37	M	104	32	102	YES	NO	NO	NO	139	3.8	1.1	2	YES	2	YES	0.8	1.2
41	MANI	64499	63	M	104	32	102	NO	YES	YES	YES	130	3.4	1	4	YES	3	YES	1.2	1.2
42	ANISH	67721	33	M	106	30	101	NO	NO	NO	NO	138	3.6	1.1	11	YES	8	YES	0.8	1.4
43	PONNAYAN	54999	39	M	94	28	101	YES	NO	NO	NO	133	3.6	1.8	5	NO	NO	NO	1	3
44	LAKSHMANAN	66661	26	M	96	26	101	YES	NO	NO	NO	138	3.7	1	6	YES	3	YES	1	1

45	KANTHI	55555	32	F	100	28	102	NO	YES	NO	NO	142	4.3	1	8	NO	NO	YES	0.9	0.9
46	NARAYANAN	66605	59	M	102	26	101	NO	NO	YES	YES	138	3.6	1.1	7	NO	NO	YES	1	0.7
47	REEMA	67713	21	F	106	28	102	YES	NO	NO	NO	136	3	0.9	4	YES	2	NO	1.2	0.9
48	RAJU	68888	48	M	108	24	101	NO	NO	YES	YES	138	3.8	1.7	5	NO	NO	NO	1.4	2.1
49	MANIYAMMA	60003	73	F	102	30	102	NO	NO	NO	NO	141	3.7	1.2	3	YES	3	NO	1.2	1.3
50	RAJAMMA	62222	53	F	100	28	101	YES	NO	NO	NO	133	3.9	2	5	NO	NO	NO	1	1

Ref. No. 3104/E4/3/2012

Govt.Rajaji Hospital,Madurai.20.
Dated: 29.03.2012

Institutional Review Board / Independent Ethics Committee.
Dr. A. Edwin Joe, M.D (FM), BL.,
Dean, Madurai Medical College & 2521021 (Secy)
Govt Rajaji Hospital, Madurai 625020.
Convenor
grhethicssecy @gmail.com.

Sub: Establishment-Govt. Rajaji Hospital, aMadurai-20-
Ethics committee-Meeting Agenda-communicated-regarding.

The Ethics Committee meeting of the Govt. Rajaji Hospital, Madurai was held at 11.00 Am to 1.00Pm on 29.03.2012 at the Dean Chamber, Govt. Rajaji Hospital, Madurai. The following members of the committee have been attended the meeting.

---

1. Dr.N.Vijayasankaran,M.ch(Uro.) 094-430-58793 0452-2584397	Sr.Consultant Urologist Madurai Kidney Centre, Sivagangai Road,Madurai	Chairman
2. Dr.P.K. Muthu Kumarasamy, M.D., 9843050911	Professor & H.O.D of Medical, Oncology(Retired)	Member Secretary
3. Dr.T.Meena,MD 094-437-74875	Professor of Physiology, Madurai Medical College	Member
4. Dr. S. Thamilarasi, M.D (Pharmacol)	Professor of pharmacology	
5. Dr.Moses K.Daniel MD(Gen.Medicine) 098-421-56066	Professor of Medicine Madurai Medical College	Member
6. Dr.M.Gobinath,MS(Gen.Surgery)	Professor of Surgery Madurai Medical College	Member
7. Dr.S. Dilshadh, MD(O&G) 9894053516	Professor of OP&Gyn Madurai Medical College	Member
8. Dr.S.Vadivel Murugan., M.D, 097-871-50040	Professor of Medicine Madurai Medical College	Member
9. Shri.M.Sridher,B.sc.B.L. 099-949-07400	Advocate, 2, Deputy collectors colony 4th street KK Nagar, Madurai-20.	Member
10. Shri.O.B.D.Bharat,B.sc., 094-437-14162	Businessman Plot No.588, K.K.Nagar,Madurai.20.	Member
11.Shri. S.sivakumar,M.A(Social) Mphil 093-444-84990	Sociologist, Plot No.51 F.F, K.K Nagar, Madurai.	Member

Following Projects were approved by the committee

Sl. No	Name of P.G.	Course	Name of the Project	Remarks
1.	Azeem Ahamed	PG, M.D (genl Med)	Serum magnesium in the systemic inflammatory response syndrome.	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain Confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution to Government.
2. She/He should inform the institution Ethical Committee in case of any change of study procedure site and investigation or guide.
3. She/He should not deviate for the area of the work for which applied for Ethical clearance. She/He should inform the IEC immediately, in case of any adverse events pr Serious adverse reactions.
4. She/he should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and apply for if any Extension of time is required She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the word or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

DEAN

To
All the above members and Head of the Departments concerned.
All the Applicants.

turnitin

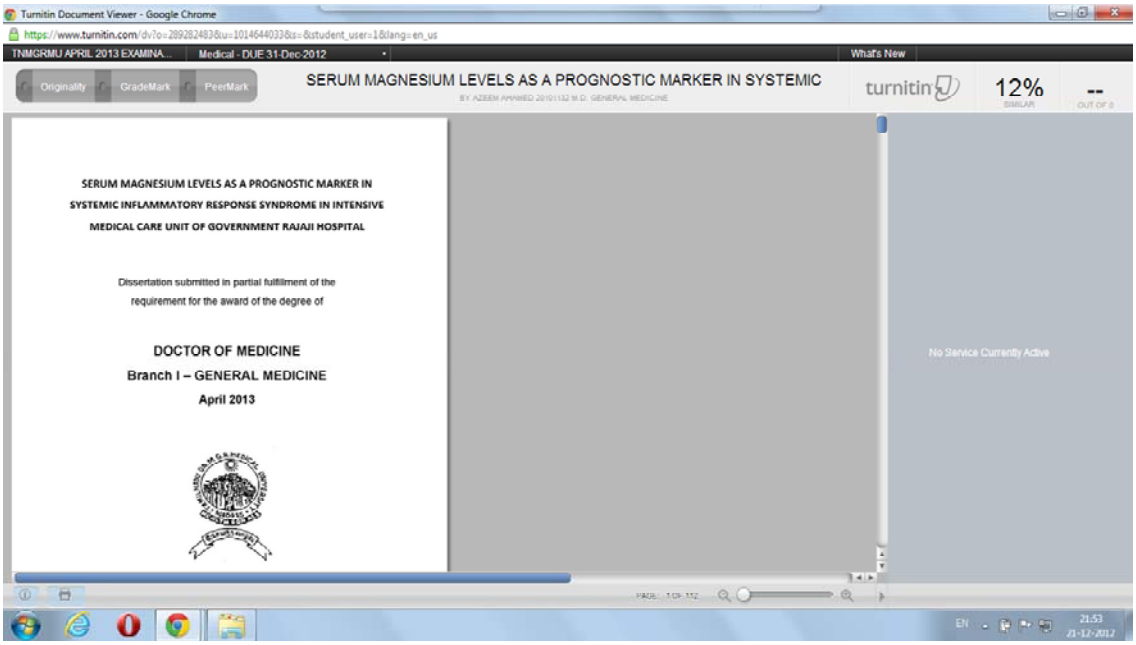
Your digital receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

Paper ID	289282483
Paper title	SERUM MAGNESIUM LEVELS AS A PROGNOSTIC MARKER IN SYSTEMIC INFLAMMATORY RESPONSE SYNDROME IN INTENSIVE MEDICAL CARE UNIT OF GOVERNMENT RAJAJI HOSPITAL
Assignment title	Medical
Author	Azeem Ahamed 20101132 M.D. General Medicine
E-mail	azeem20@gmail.com
Submission time	21-Dec-2012 12:17AM
Total words	12391

First 100 words of your submission

SERUM MAGNESIUM LEVELS AS A PROGNOSTIC MARKER IN SYSTEMIC INFLAMMATORY RESPONSE SYNDROME IN INTENSIVE MEDICAL CARE UNIT OF GOVERNMENT RAJAJI HOSPITAL Dissertation submitted in partial fulfillment of the requirement for the award of the degree of DOCTOR OF MEDICINE Branch I – GENERAL MEDICINE April 2013 THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI, TAMILNADU. CERTIFICATE This is to certify that the dissertation entitled "SERUM MAGNESIUM LEVELS AS A PROGNOSTIC MARKER IN SYSTEMIC INFLAMMATORY RESPONSE SYNDROME IN INTENSIVE MEDICAL CARE UNIT OF GOVERNMENT RAJAJI HOSPITAL" is a bonafide work of Dr. AZEEM AHAMED in partial fulfillment of the university regulations of the Tamil Nadu Dr....


Turnitin Document Viewer - Google Chrome
https://www.turnitin.com/dv?o=289282483&u=1014644033&s=&student_user=1&lang=en_us
TNMGRMU APRIL 2013 EXAMINA...
Medical - DUE 31-Dec-2012
What's New
Originality
GradeMark
PeerMark
SERUM MAGNESIUM LEVELS AS A PROGNOSTIC MARKER IN SYSTEMIC
turnitin
12%
SIMILAR
--
OUT OF 0
SERUM MAGNESIUM LEVELS AS A PROGNOSTIC MARKER IN
SYSTEMIC INFLAMMATORY RESPONSE SYNDROME IN INTENSIVE
MEDICAL CARE UNIT OF GOVERNMENT RAJAJI HOSPITAL
Dissertation submitted in partial fulfillment of the
requirement for the award of the degree of
DOCTOR OF MEDICINE
Branch I – GENERAL MEDICINE
April 2013
No Service Currently Active
EN
21:53
23-12-2012