

**Estimation of Some Trace Elements in Severe Head Injured Patients**

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**Summary:**

**Objectives:** Severe head injury is the most devastating neurosurgical condition and it is only next to cancers as the leading cause of death in developed countries. Because trace elements (TEs) are involved in most of enzymes that drives the biochemical reactions, so they are considered as a window to the biochemical environment of the body in general and in brain in specific.

**Aim of the Study:** This study measured six TEs (Fe, Zn, Mg, Cu, Mn and Co) in 29 patients with severe head injury (GCS Score 3-9); their ages between 5-50 years. Collection and estimation performed at both Neurosurgical Hospital (NH) in Baghdad and Medical Research Center (MRC) of College of Medicine, Kadhimiyah between January 2004 and August 2004. 17 of healthy Iraqi volunteers of age- and sex- matched were used as a comparable control group in TEs measurement.

**Results:** The analysis showed that serum Cu level has a striking significant positive correlation with GCS ( $P < 0.01$ ) followed by serum Mg ( $P < 0.01$ ), serum Fe ( $P < 0.05$ ) with mode of correlation is linear except for that of serum Fe has three phases of correlation. Serum Mg is the only TE showed statistical significant lower value in patient group than the control group ( $P < 0.01$ ). Zn is the only TE that is correlated with the mode of intake, significantly lower among patient on IVF than those on N/G ( $P < 0.01$ ). Serum zinc correlated in linear relation with serum Mg ( $P < 0.05$ ), serum Fe with serum Mg ( $P < 0.05$ ).

**Keywords:** head injury, trace elements, Glasgow Coma Scale

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**Introduction:**

Trace elements (TEs) are those that in human and animal tissues in milligram/kg amount or less. Correspondingly, human requirements of TEs are reported in milligrams/day<sup>1</sup>. TE action is that TEs are constituents of, or interact with enzymes, cofactors, prosthetic groups or hormones that regulate the metabolism of much larger amounts of biochemical substrates<sup>2</sup>.

**Iron:**

Fe is the most important of the essential TE. Iron is distributed in the body in number of different compartments, including hemoglobin, tissue iron, myoglobin, and a labile pool<sup>3</sup>. It is an essential TE for brain development<sup>4</sup>. Transferrin is synthesized primarily in the liver, but significant amount is also produced in the brain<sup>5</sup>. Fe is found in oligodendrocytes in high density and required for myelin production of CNS<sup>6</sup> and neuromelanin granules in the dopaminergic neurons of the substantia nigra<sup>7</sup> and neuroadrenergic neurons of Locus Coeruleus; a center in the brainstem that regulates consciousness and sleep-wake cycle<sup>8</sup>. Fe is also a cofactor for many proteins that are

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involved in the normal functioning of neural tissue, such as the non-heme iron enzyme tyrosine hydroxylase which is required in dopamine synthesis<sup>9</sup>.

#### **Zinc:**

Zn is second to iron as the most abundant TE in the body<sup>1</sup>. About 80 enzymes in the human body have been shown to be containing Zn. Zn forms a part of the enzymes of superoxide dismutase (SOD) which catalyzes the dismutation of free radical O<sub>2</sub> to H<sub>2</sub>O<sub>2</sub>, therefore reducing the risk of formation of the hydroxyl radical OH, which is the most reactive species<sup>10</sup>. Zn protects the neurons from death due to ischemia; Aβ peptide specifically binds to zinc<sup>11</sup>.

#### **Magnesium:**

Mg catalyzes or activates more than 300 enzymes in the body. It acts an essential cofactor for enzymes concerned with cell respiration, glycolysis, and transmembrane transport of other cations such as Na and Ca. Mg is important for Na-K ATPase<sup>1</sup> and for propagation of nerve impulses (action potential). Mg also activates the Na-K pump, thus maintaining the normal ionic homeostasis across the neuronal membrane<sup>12</sup>.

#### **Copper:**

The major functions of Cu metalloproteins involve oxidation-reduction reactions<sup>1</sup>. It exists in brain as many cuproenzymes i.e. (SOD), tryptophan-2, 3-dioxygenase, lysin oxidase, cytochrome C oxidase, monoamine oxidase, tyrosine, dopamine-β-hydroxylase and d-amino levulinate dehydrogenase<sup>13</sup>. SOD exists mainly in motor neurons and it converts superoxide to H<sub>2</sub>O<sub>2</sub><sup>13</sup>. It is essential for the integrity of axon. Cu deficiency leads to axonal swelling and thus poor conduction. Its deficiency is blamed to be one of etiological factors for neurodegenerative diseases such as Alzheimer's disease and myotrophic lateral sclerosis<sup>12</sup>.

#### **Manganese:**

It forms a part of the enzyme of mitochondrial SOD<sup>10</sup>. It acts as a Ca antagonist and is inhibiting the release of neuromediators into synaptic space, probably because of competition with Ca at the level of Ca channels, thus toxic level of Mn can lead to synaptic transmission failure<sup>14</sup>.

#### **Cobalt:**

Co is essential for human only as an integral part of vitamin B12 (cobalamin)<sup>1</sup>, which is essential for myelination of both central and peripheral myelinated fibers. Cobalt is a regulatory agent of the sympathetic nervous system, limiting arterial blood pressure<sup>15</sup>.

#### **Head Injury:**

The main causes of head injury are road accidents, falls, and assaults<sup>16</sup>. Head injury is classified into open and closed. The secondary and tertiary phases of injury are strongly contributed to by the presence of "secondary insults". Secondary insults are defined as systemic changes resulting from the injury, which can in turn damage the brain further<sup>17</sup>. These insults include hypoxia, hypotension, hypercapnia, anemia, septicemia, and hyperthermia<sup>17</sup>. A state of hyperglycolysis is seen following head injury<sup>18</sup>.

#### **Glasgow Coma Scale:**

The Glasgow Coma Scale (GCS) developed at the University of Glasgow in Scotland in 1974, and is a broad assessment of consciousness in-patients with head injuries<sup>19</sup>. The scale is divided into three subscales: eye opening, best verbal response, and best motor response. Within each subscale are a variety of categories as shown below:

Scoring of Eye Opening	Scoring of Best Motor Response	Scoring of Best Verbal Response
4 Opens eyes spontaneously when the nurse approaches 3 Opens eyes in response to speech (normal or shout) 2 Opens eyes only to painful stimuli (e.g. squeezing of nail beds). 1 Does not open eyes to painful stimuli <sup>20</sup>	6 Can obey a simple command, such as "lift your left hand off the bed" 5 Localizes to painful stimuli and attempts to remove source 4 Purposeless movement in response to pain 3 Flexes elbows and wrist while extending lower legs to pain 2 Extend upper and lower extremities to pain 1 No motor response to pain on any limb <sup>20</sup>	5 Oriented to time, place and person 4 Converses, although confuse 3 Speaks only in words or phrases that make little or no sense 2 Responds with incomprehensible sounds (e.g. groans) 1 No verbal response <sup>20</sup>

The summation of the points of these three subscales indicates the score of GCS. The range of possible scores is 3 to 15. A score of 15 would indicate a fully alert, oriented person, whereas a score of 3, the lowest possible score, would be indicative of a deep

coma<sup>19</sup>. Patients with a score of 3 to 9 are generally considered to be comatose (severe head injury). Patients with moderate head injury (GCS: 9-12), patients with mild head injury (GCS: 13-15)<sup>20</sup>.

**Patients and Methods:**

This study had been conducted between January 2004 and August 2004 performed at both Neurosurgical Hospital (NH) in Baghdad and Medical Research Centre (MRC) of College of Medicine, Kadhimiyah. 29 patients of severe head injury (GCS score from 3 to 9) had qualified for the study; their ages ranged between 5-50 years, 22 males and 7 females. 17 normal healthy Iraqi volunteers of age- and sex- matched were used as a control group in TEs measurements. Patients were evaluated by full medical history to exclude any existing systemic disease that may affect the parameters to be studied (biochemical and hematological), particularly diabetes, anemia, liver disease, renal disease, multiple injuries, and chronic drug intake. Following the admission of the head injured patient to the hospital (NH), the GCS score is evaluated and correlated to each collected sample, 5 ml of venous blood were aspirated aseptically from peripheral veins through venipuncture. Sera

were separated by centrifugation of clotted blood sample at 3000 rpm for 5 minutes then stored in a white disposable test tube inside refrigerator at -20°C, then kept till being forwarded to the laboratory. Assays were done within 2 weeks at the laboratory of MRC by flame emission atomic absorption spectrophotometry (model AA 6200 Schimdu) for TE under study (Zn, Fe, Mg, Cu, Mn and Co). Hemolyzed samples were discarded. 2-5 samples were collected from each patient every 3 days basis as an interval period. Similarly, one serum sample was collected from age- and sex- matched of healthy Iraqi volunteers for TE comparison. A standard calibration curve is drawing. For the measurements of the TEs sera in both groups, the samples are diluted (see table 1). Its absorption is measured by AAs and the resultant values are plotted on the standard calibrator curve for its concentration to be measured.

**Table1. Dilutions to the serum with materials for each trace element**

Trace Element	Dilution Factor	Diluent	Gases
Zinc	10	Deionized water	Air/acetylene
Iron	10	Deionized water	Air/acetylene
Magnesium	50	Lanthanum oxide	Air/acetylene
Copper	10	Deionized water	Air/acetylene
Manganese	1.3	Deionized water	Air/acetylene
Cobalt	1.3	Deionized water	Air/acetylene

**Results:**

**Table 2. Descriptive summary table of the TE in the serum of both control and patient groups (mean ± standard deviation, median, range, and standard error).**

Trace Element	Group	Mean ± SD	Median	Range	Std. Error
Zn (ppm)	Control	8729±.30434	.7600	.91	.07381
	Patient	.7700±.37801	.6700	1.42	.07020
Cu (ppm)	Control	1.0388±313494	1.0388	.98	.07603
	Patient	.8607±.41512	.8000	1.59	.07709
Iron (ppm)	Control	1.1441±.82134	.8200	2.71	.19920
	Patient	1.1617±.67203	.9900	2.97	.12479
Mg (ppm)	Control	41.8235±15.53719	40.0000	51.00	3.76832
	Patient	23.5397±16.53842	17.5000	71.75	3.07111

**Table 3. Independent Samples Test, t-test for Equality of Means of serum TE in both control group and patient (p-value, 95%CI, SE of difference, Mean difference)**

	t-test for Equality of Means						
	95% Confidence Interval of the Difference		Std. Error Difference	Mean Difference	Sig. (2-tailed)	Df	t
	Upper	Lower					
Zn (ppm)	.32026	-.11437	.10783	.1029	.345	44	.955
Cu (ppm)	.4128	-.05660	.11647	.1781	.133	44	1.529
Fe (ppm)	.43171	-.46692	.22295	-.017	.937	44	-.079
Mg** (ppm)	28.24546	8.32229	4.94281	18.2839	.001**	44	3.699

\*\* = Significant at 0.01%

**Table 4. Correlation of TE with each others and with GCS**

	Zn (ppm)	Cu (ppm)	Fe (ppm)	Mg (ppm)
Zn Pearson Correlation(r) (ppm) sig, (1-tailed)	1	.169	-.067	.190*
Cu Pearson Correlation(r) (ppm) sig, (1-tailed)	.169	1	.019	-.126
Fe Pearson Correlation(r) (ppm) sig, (1-tailed)	-.067	.019	1	.194*
Mg Pearson Correlation(r) (ppm) sig, (1-tailed)	.190*	-.126	.194*	1
GCS Pearson Correlation(r) Sig, (1-tailed)	.140	.375**	.220*	.271**

\*. Correlation is significant at the 0.05 level (1-tailed).

\*\* . Correlation is significant at the 0.01 level (1-tailed).

Table 5. Group Statistics. Serum Zinc Level in both types of feedings

	Feed	N	Mean	Std. Deviation	Std. Error Mean
Zn Pat.	IVF*	18	.0394	.31783	.07491
	N/G*	37	.2611	.35557	.05846

**Discussion:**

Trauma is the leading cause of death and disability in people under 45 years of age worldwide<sup>16</sup>. Although severe head injury is the most devastating neurosurgical condition and it is only next to cancers as the leading cause of death in developed countries<sup>21</sup>, but still many measures can be done to reduce its impact on society include early resuscitation, prompt reduction of intracranial pressure, close ICU monitoring and so on. In addition, prognostic factors such as the GCS score, and laboratory parameters (Mg and S-100 protein) play a major role in predicting which patient will get benefit from these sophisticated neurosurgical interference and whom will be<sup>21, 22</sup>. From practical point of view, it is difficult to use these (prognostic factors) on daily practice because either they are expensive such as S-100 protein or technically difficult to apply such as somatosensory evoked potential (SSEP) and visual evoked potential (VEP)<sup>23</sup>.

One of the most important factors that are needed for recovering of injured neurons is proper biochemical environment that will secure a balanced and homeostatic ionic and enzymatic system for re-functioning of injured neurons but yet viable neurons and glial cells<sup>24</sup>. TEs are involved in most of the enzymes that drives the biochemical reactions of the nervous system (such as tyrosine hydroxylases, cytochromes, ATPases, choline esterase, etc), so we decided to study six of TE( Fe, Zn, Cu, Mg, Mn, and Co) and taking them as a window to the biochemical environment of the body in general and nervous system in specific and whether they can be used as a prognostic factor in severe head injured patients or not.

**Copper:**

In this study, Cu is the metal that has statistically the highest significance of correlation with GCS (P=0.000) (Table 4) and the mode of correlation is linear at early stages of illness, and then become nearly flat as the

patients regain their consciousness. It is suggested that the correlation between the patient's outcome and serum Cu is probably due to the vital role of Cu in eliminating the oxidative stress (through metallothionin and SOD) that is the most detrimental factor in severe head injury. The patients have a persistent low score in GCS; there will be a rapid improved group, there is a suitable time to meet the demand of nervous system on one hand and the oxidative stress itself in this group is not might enough to have such impact to lead to rapid consumption of the available Cu, on the other hand. Therefore, the most reliable agent that can be used as a prognostic factor is serum Cu and it is cheaper when compared with S-100 protein and easier to perform the neurophysiological monitoring (SSEP, VER).

**Iron:**

In this study, there will be a significant correlation between serum Fe and GCS at 0.022 (P value <0.05) as shown in Table 4. This correlation takes three distinct phases; Phase I, there is linear positive curve and this happens in the early days after trauma. Phase II, this is represented by the plateau part of the curve and it occurs when there is further improvement in patients level of consciousness. Phase III, this is represented by the second rise in the curve and it happens in the last days of the patient's hospitalization, when the improved group regain their consciousness. In severe head injury there will be a wide spread damage to the axons and their myelin sheaths and as these structures are rich source of Fe so there will be a massive release of Fe into the circulation<sup>25</sup>, this will be reflected as the phase I. Later on as recovery proceeds, there will be no more release of Fe to the circulation and this is reflected as phase II. The final rise of serum Fe in phase III is perhaps of non-neuronal origin but may be due to sequestration of Fe from damaged muscles in the form of myoglobins into the circulation<sup>26</sup> as the patient's movements and



muscle activity are increased when full recovery ensures. So Fe can reliably be used as a possible prognostic indicator in severe head injured patients where a continuous rise in serum Fe without a plateau phase indicates a massive destruction of nervous tissue that is beyond repair (bad prognostic sign), while a plateau separately and rising phases indicates a possible good recovery.

Both serum Fe and serum Mg are statistically significant correlated to each others (Table 4). The relationship between these two metals can be understood on the basis of their common existence in several enzymes e.g. cytochrome oxidase and tyrosine hydroxylase that abundantly in basal ganglia, therefore when there is a brain damage, there will be a release of both of them into the circulation<sup>27</sup>.

#### **Zinc:**

In this study Zn showed two significant correlations, one of these correlations is statistically significant with serum Mg level at 0.045 (P value<0.05) as shown in Table 4. Following brain injury, the extracellular Zn concentration is increased several folds and this will induce neuronal damage through depletion of glutamate and ATP and thus induce apoptotic cell death<sup>28</sup>. The extra Zn is rapidly cleared in renal system and this had been clearly demonstrated in Gliffron (1986) article which showed increasing in urinary excretion of Zn in severe head injury patient<sup>29</sup>. This might explain why serum Zn remains stable during the course of illness regardless to the patient's clinical progression.

Serum Zn is significantly lower in IVF group than with N/G mode of feeding group at 0.004 (P value<0.01) as in table 5 because of IVF is free from T Es and may be due to hemodilution. This might not be significant on short term scale but it becomes very vital on long term basis (more than 3 months) which is not included in this study and this has a profound effect on wound healing, bed sore development, and immune system<sup>9</sup> (not included in this study also).

#### **Magnesium:**

Serum Mg level among patient group is lower than in control group, statistically is highly significant (P value<0.01) as shown in Table 3. In severe head injury, a significant number of neurons die either as a result of

direct trauma or as secondary insult complications<sup>16</sup>. The dead neurons release their contents including free Mg and Mg-containing enzymes to the circulation which are then rapidly cleared by the renal system with resulting decrease in serum Mg. On the other hand, the major homeostatic organ that is responsible for regulation of serum Mg is the hypothalamus<sup>31</sup> which is susceptible to shearing forces that happen in contact injury and to diffuse axonal injury that results from acceleration-deceleration injury<sup>30</sup>. Therefore, low serum Mg in severe head injured patients might reflect the extent of hypothalamic injury and consistently low serum Mg indicates a permanent damage to hypothalamus with prolonged loss of consciousness or death. Kahraman et al (2001) proved that significant decline in serum ionized Mg values were found in the study group immediately after traumatic head injury, and during post-traumatic 5 days ionized Mg levels can be used as a diagnostic and prognostic indicator at the follow-up of traumatic brain injury<sup>31</sup>. In severe head injured patients, there will be a state of hyperglycolysis with subsequent activation of Mg depended pyruvate kinase and enolase. These enzymes will consume the available Mg with resultant reduction in serum Mg<sup>16</sup>.

This study also shows a significant linear correlation between serum Mg and GCS as shown in Table 4 (P value<0.01). In this aspect, once the patients start to recover in term of consciousness, there will be a corresponding increase in serum Mg, but even that increase will not reach the control values at the end of the study when the fully recovered patients have been discharged from hospital. On the other hand; as shown in Table 4, serum Mg is also significantly correlated with serum Fe (discussed in serum Fe).

#### **Conclusions:**

In severe head injury whom GCS 3-9, serum Cu can reliably be used as a prognostic factor due to striking significant positive correlation with GCS followed by Fe and Mg. Serum Mg level is the only TE has a statistically significant lower value in patients with severe head injury than the control group. Serum Zn level is the only TE that is statistically significantly reduced when the patient is kept on IVF alone. There are statistically significant relationships between

serum level of Zn and Mg, Fe and Mg in severe head injured patients.

**Recommendations:**

We recommended for this work to be extended in two directions; horizontally this means inclusion of more patients and for longer follow-up periods, and vertically where more elements are included (e.g. selenium, molybdenum) and more variables are taken into consideration (e.g. wound healing, rate of

infection, bed sore development, jaundice, etc). We recommend supplying the severely head injured patient with Zn rich diet such as meat, fish, and diary products very early in the course of the disease. We must assess the renal function and perform other laboratory tests (e.g. serum creatinine, blood urea, potassium level). We recommend Mg rich diet to be supplied to patients such as leafy green vegetable (chlorophyll).

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