Indonesian Journal of
Tropical and Infectious Disease
Vol. 5. No. 5 May–August 2015

Literature Review

MICRONUTRIENT THERAPY FOR SEPSIS

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ABSTRACT

Micronutrients are nutrients which are needed by the body to perform the function of body. The amounts is less than 100% µg per day and consist of vitamins and minerals. It cannot be synthesized in the body. Research in the US mentioned that the rate prevalence of sepsis is tended to be increased 8.7 % annually. In sepsis, nutrition is one of the important component which could drive the success treatment. Micronutrient, especially a vitamin which is soluble in fats, it would be toxic if the number exceed the capability of body to receive it. Although there are guidance and mutual agreement about sepsis using, it still need to concern on micronutrient which potentially giving bad effect. In sepsis case, micronutrients also determine the success of treatment due to redistribution of vitamin and trace element from circulation to the tissue which involved in the proteins formation and immune system. The conclusions of the latest 7 experiments and 4 random controlled studies of multi-centre support the micronutrients supplementation because it can decrease mortality rate. However, it still need to be aware to the toxicity of fat soluble micronutrient if the doses are excessive.

Key word: *Micronutrients, sepsis, nutrition, mineral, vitamin*

ABSTRAK

Mikronutrien adalah zat gizi (nutrien) yang diperlukan oleh tubuh manusia dalam jumlah kecil yaitu kurang dari 100% µg per hari untuk melaksanakan fungsi fisiologis. Mikronutrien terdiri dari vitamin dan minera dan tidak dapat disintesis oleh tubuh. Penelitian di AS menyebutkan angka kejadian sepsis cenderung meningkat 8,7% setiap tahunnya. Pada sepsis, nutrisi adalah salah satu dari komponen utama yang menentukan keberhasilan pengobatan. Mikronutrien, terutama vitamin larut lemak, membawa risiko toksisitas pada pemberian melebihi dosis standard. Meskipun ada petunjuk dan kesepakatan bersama tentang sepsis, masih diperlukan perhatian pada mikronutien yang berpotensi memberikan dampak buruk. Pada kasus sepsis, mikronutrien juga menentukan keberhasilan pengobatan karena redistribusi vitamin dan diikuti unsur-unsur dari peredaran darah ke jaringan yang terlibat dalam pembentukan protein dan sistem imun. Kesimpulan terhadap 7 percobaan terbaru dan 4 penelitian acak terkontrol multi-centre mendukung suplementasi mikronutrien pada sepsis karena dapat menurunkan angka kematian. Namun demikian, tetap perlu diwaspadai kemungkinan terjadinya toksisitas mikronutrien yang larut dalam lemak jika melebihi dosis.

Kata Kunci: *Mikronutrien, sepsis, nutrisi, mineral, vitamin*

INTRODUCTION

Micronutrient is nutrient substance (nutrients) required by human body in small quantities to give physiological functions. Micronutrient consists of vitamins and minerals/ trace elements which could not be synthesized in the body. Micronutrient is important for body continuously in small quantities, less than 100 µg each day. Different to macronutrient, carb, protein and fat are important for body in large quantities. [1]

Vitamin is an organic substance which could not be synthesized in the body. Trace elements has a role as co-factor for some enzymes such as mineral which has a little amount in the body. The amount of trace elements is about 0.01 % of body mass and the total amount is less than 1 %.[2]

Systemic Inflammatory Response Syndrome (SIRS) occurs redistribution of vitamins and trace elements from circulation to tissues involved in protein synthesis and the immune system. Concentration of iron, selenium, zinc and protein carrier in circulation are decrease while copper and manganese are increase.[1]

In sepsis, nutrition is one of the main component to determine the success of the treatment. Micronutrient is still important beside the optimal carbohydrate, lipid and protein combination. Supplementation micronutrient research on sepsis focused on 5 selenium micronutrient, namely zinc, copper, clusters of vitamin B, vitamin C and E. [1]

Research in the US stated that sepsis occurrence rate is tended to increase 8.7% annually.[3] Since systematic review by Heyland *et al*. at 2005, some experiments was done (including experiment multi-centre greater) so it is increase the micronutrient using.[4] The latest 7 experiments and 4 random controlled studies of multi-centre support the previous findings that showed micronutrient supplementation sepsis is associated with the reduction of mortality rate especially in 28 days.[1]

Although there are guidance and consensus about sepsis using, it still need to concern on micronutrient which potentially giving bad effect. Micronutrient, especially fat soluble vitamin carries toxocity risk if the dose given is exceed the standard. [1]

SEPSIS

According to Surviving Sepsis Campaign 2010 consensus, SIRS defined as 2 or more criteria from a compilation of clinical manifestationand laboratory examination such as temperature more than 38,3°C (101°F) or less than 36,0°C (96,8°F), tachycardia (more than 90bpm), tachypnea (more than 20 times per minute), PCO2 less than 4,3 kPa (32 mmHg), hyperglycemic (glucose of blood >7,77 mmol/L [120 mg/dL]) without record of DM, mental status changed in acute, leucosyte more than 12109/L (12.000/microliter) or less than 4109/L (4000/microlitre) or WBC normal with granulocytes >10%

Metabolic response begin with rising energy of *Resting Energy Expenditure* (REE) catabolism proteins and fats, balance nitrogen negative hyperglycemia and increasing glucose liver production, *Cuthbertson* clearly described the three phases of response when sepsis are, ebb phase when initial shock response decrease metabolism of the body, flow phase (catabolic phase), convalesen phase (anabolic phase) when a body beginning to synthesize ramifications.[4]

On sepsis occurs metabolic changes which called stress metabolism because the influence of inflammatory mediator. In ebb phase and ebb phase, changes that happened could be considered as the basic guidance to give therapeutic action depend on its starting time, composition and also the provision period.[4]

In the early time phases, ebb phase is found and occurs energy conversion at that time. Flow phase which started soon after ebb phase, as distinguished further into two stages: acute flow phase and adaptive flow phase. In acute flow phase, energy needs is increasing even sometimes flashy.[4]

On adaptive flow phase, the healing process started. For optimum recovery, proper indispensable nutrients are needed along the three stages. In acute flow phase where cardiac output and blood pressure are increased, reserve fat and muscle are having a catabolism process and generated energy. Protein in muscle tissue produce an amino acid for liver gluconeogenesis, hormone stress (glucagon, catecholamine and glucocorticoid) is quickly produced and increasing the glucose level. As the parsing of muscle tissue, potassium, phosphorus and sulfur are lost proportionately. Acute flow phase is generally lasting for 3 or 4 days and will end in 7 to 10 days if there is no complication happened. Hyperglicemia often occurs in this phase.[4]

Disorder motility often occurs in sepsis. In a retrospective study, patients with sepsis are having a greater time of gastric emptying (GE) postponement compared with patients with heart disease and failed breath. There are multifactor but mostly are still unclear. Shock, a cytokine, electrolyte disorder, hyperglicemia, underlying disease and treatment. Catecholamine decrease the motility through ß-adrenergic stimulation. Dopamine decrease the acetylcholine and hindered the antrum contraction and prolong the intestine transit time.[5]

Motility of the gastrointestinal normal tract is controlled by the central nervous system (CNS), autonomous nerve, enteric nervous system (ENS) and triggered by peptide located within the walls of the alimentary canal .ENS Neuron system divides into 2 plexus namely plexus mienteric and submucosal. Mienteric plexus located between longitudinal and circular layers that serves as motility agent. Acetylcholine and P-substance transmitter are the main excitatory motoric neurons while nitric oxide (NO), vaso-active and ATP are the main transmitter of inhibitory neurons.[5]

Response neuroendocrine will arise due to sepsis as increased catabolic hormone such as cortisol, glucagon and catecholamine which accompanied by resistance to insulin so that substrate non essential can be turned into energy accelerated healing wounds. There are conclusion process the response of neuroendocrine such as Gluconeogenesis, glucose/glutamin/fatty acid mobilization, proteolysis jaringan peripheral tissue and balance negative nitrogen, increasing REE, retention of water, insulin and GH resistance.[4]

DEFINITION OF MICRONUTRIENT

Micronutrient is an important element which are needed by body in small amount that only 100 mg/day or less than

1 % weight. Micronutriens consists of micromineral and vitamins. Micromineral has iron, cobalt, chromium, bronze iodine, manganese, selenium, zinc and molybdenum as its subtance. Although mineral needs can only 5 % obtained from food, but it is very useful for body organs.[6]

FUNCTION OF MICRONUTRIENT

The role of micronutrients in metabolism process is to maintain the function of body tissue. Hypermetabolism led to an increasing production of Reactive Oxygen Species (ROS) as an impact of increasing oxidative metabolism which can damage cell, mainly on unsaturated fatty acids which are found in the cell membrane and nucleus.[6]

Zinc, iron and selenium are absorbed in duodenum and jejunum while chromium and copper are absorbed in ileum. Micronutrient take part on helping the body to neutralize the negative effects of free radicals. Deficiency micronutrient usually accompanied by more than one drawbacks except zinc, iron and vitamin A. Some interactions could happen in provision of micronutrient. Zinc decrease the absorption of copper while iron decrease the absorption Cu and zinc.[7]

Zinc (Zn)

Several enzymes that play role in setting of oxidant defense including SOD, catalase, and glutathione reductase depend on normal condition of zinc. It is suitable because in sepsis occurs declining capacity of ROS detoxification.[8]

Zinc has a very important role for immune system, oxidative stress response, wound healing process and protecting homeostasis. It is difficult to distinguish between the symptoms of zinc deficiency and sepsis.[9]

Zinc is a co-factor of more than 200 enzyme that play roles in the immune system. It is very important for wound healing process, regenerating new cells and balancing of acid base.[10]

The normal concentration of zinc in the body is between 70-150 mcg/dl. Low concentration of alkaline phosphatase (ALP) represent that the body has a low concentration of zinc. Granting zinc 150 mg/day twice a week for 6 weeks can be lowered the response of lymphocytes stimulation towards fitohemaglutinin as well as it can decreased chemotaxis and bacteria phagocytosis through PMN. Granting 15 mg of zinc can improve response of the body against infection. Zinc become a toxic if it is given in 50 mg/day dose.[9]

Zinc supplementation triggers the decreasing of copper concentration through the competitive interaction in the intestines absorption process. Zinc stimulates enterocyte metallothionein. Metallothionein breaks copper up faster than zinc does so thatas copper can not be transferred and absorbed by the intestines. The excessive provision of zinc is causing anemia deficiency as well as netropenia and lecopenia. Symptoms that appear when indigestion occurs are pain at epigastrium, nauseous, and vomit. Zinc intoxication happens if a dose of 30 mg / day is causing the occurrence of acute phase response and increase IL-6.[11]

IRON (Fe)

On sepsis, the declining iron concentration occurs due to the improving permeability so that transferin move from intravascular into interstitial liquid. Increased production of ferritin in the liver caused by induction IL-6 so that more Fe stored in liver. On sepsis, hepsidin production is increasing and it will inhibit the Fe transporting.[6]

Neutrophils and macrophages need Fe for phagocytosis and intermediate oxygen formation which is toxic in killing bacteria. Reduction of nitroblue tetrazolium and hydrogen peroxide on neutrophils and macrophages are decreasing if lack of iron substance. Iron also taking part in Crebs cycle as a source of essential energy. Several enzymes such as glutathione, peroxidase, catalase and dehidrogenase need the iron as a free radical antidote.[7,12]

The improvement of veins permeability causing a leak, transferin to interstitial fluid. Iron triggers bacterial growth because of its role as an essential nutrients for the growth of bacteria.[6]

Polymorphonuclear (PMN) release laktoferin along inflammatory process and bend the iron than it will be processed by macrophages. Netrofil and macrophages need the iron for phagocytosis and killing bacteria. Otherwise, excessive iron can decrease the ability of macrophages to do phagocytosis. It happens because of the production of free radicals are increasing and damage the peroxydases fat located in phagosom membrane.[12]

Iron is also a growth factor for some bacteria and increase proliferation thoroughly in vivo. Granting iron in parenteral way can inhibit the migration of neutrophi and weaken the host defensibility. Oxidative stress controlled by iron free can trigger inflammatory through some stages, for example is factor-kappa ß(NF-jB). Once it is been activated will cause a mediator inflammatory production like TNF-α, cytokine, etc.[13]

Selenium

In a state of sepsis, the issuance of selenoprotein-P in intravascular is increasing. Selenoprotein-P is a form of

Table 1. Recommendation for Trace Elements in Critical Illness

Trace Element	RDA	Standard Dose		Additional Supplementation
		PN Formula	EN Formula	
Zinc	15 mg	2.5 - 5 mg	11 - 19 mg/L	10 - 30 mg/day
Selenium	50 - 100 mcg	20 - 60 mcg	20 - 70 mcg/L	100 - 400 mcg/day
Iron	0 – 15 mg	0	12 - 20 mg/L	-
Copper	900 mcg	300 - 500 mcg	-	-

Source: S Afr J Clin Nutr 2010;23(1) Supplement: S60[14]

selenium which are rich of protein. One of the uniqueness of selenium is having a dual function as pro-oxidant and as anti-oxidant. Sodium selenite as a pro-xidant while atoms of selenium as an anti-oxidant. Selenium translocation to interstitial cause the improvement of NF kappa B activityso that raises protein during acute phase.[6]

In sepsis there has been a decrease levels of selenium as 40%. Selenoenzymes including glutathione peroxidase (GPx) plays an important role in controlling the process of inflammatory including protection against species reactive oxygen (ROS). The provision of high doses selenium for 9 consecutive days in sepsis and reduce the dose for every 3 days can decrease the number of deaths, score of the APACHE III and serum creatinin.[6,15,16]

Maximum doses of selenium is 400 µg (5µg/kg BB/day) but even granting 800 µg is considered has no side effect report. In some research ,granting 750-1000 µg selenite combined with 800 µg selenium per day in iv and enteral is safer in terms of the dosage provision.[1,15]

According to Kuklinsky, *et al*., granting selenium as a bolus is more effective than as a drip. To reduce the binding of NF-κB with DNA and trigger the apoptosis, it needs high concentration of selenium in plasma that can only be achieved if it granting as a bolus.[15]

Angstwurm *et al*., experimented with selenium by giving high doses for 9 days and got lowered every day. It can fix APACHE III score, decrease creatinin serum and decrease the mortality rate because of sepsis.[16]

Copper

Sepsis is often accompanied by acidosis and release cupric ion from seruloplasmin and another proteins. As the needs of oxygen is increasing which not accompanied by oxygen availability is causing ischemia and acidosis in early sepsis and release cupric ion.[17]

Copper is a essential component of several enzymes like superoxide dismutase (SOD), cytochrome oxidase and some coenzymes. It is needed for free radical detoxification, hem formation, antioxidant effect, immune function and synthesis of collagen. Copper consumption is restricted for liver failure and colestasis patients because it is excrete through the gall bladder and will cause toxicity if it heaped.[11]

Some previous studies show that copper inhibits the activity of activated anticoagulant and protein. In addition, copper trigger the epinephrine oxidation to be inactive and adenokrom which is toxic for the heart.[17]

Copper is important for wound healing process, hematopoiesis and as an anti-oxidant. Besides, it is also as co-factor of metalloenzymes and norepinephrine synthesis. Gastrointestinal absorption is not optimal in this process and having low daily requirement. Copper deficiency can cause neuropathy and pancytopenia. Recommended Dietary Allowance (RDA) for copper in adults is 900 mcg and parenteral dosage is 300 - mcg 500 per day.[7]

Vitamin

In sepsis, the ascorbic levels in plasma and cerebrospinal liquid are decreasing. Vitamin C may decrease the expression of ascorbic iNOS and can overcome radical which produced by immune system. Ascorbic also decrease or prevents endotoxin translocation from intestines and directly bactericydal, also it can increase the GSH concentration in liver circulation. Ascorbic also prevents the enzymes reduction in liver and responsible for any endotoxin cleaning.[18]

The 19 RCT meta-analysis results shows that high doses of vitamin E increase the risk of all causes of mortality and it depends on the doses which begin in 150 IU / days.[1] A research conducted by Crimi *et al*., granting high dose of vitamin C and vitamin E can decrease death rate until 67,5 % to 45,7 %.[6]

Vitamins B1 (thiamine) is co-factor of pyruvic dehydrogenase, an enzyme that responsible for pyruphate conversion into asetil-coenzim A. Lack of thiamine can cause pyruvic failure entering enter the tricarboxylic acid cycle so anaerobic metabolism will happen. Thiamine deficiency is correlated to acidosis lactate tacking.[19]

SUMMARY

Micronutrients are nutrient substance (nutrients) required by human body to perform a physiological function in amounts of less than 100% µg per day and consist of vitamins and trace elements. In sepsis case, micronutrients also determine the success of treatment due to redistribution of vitamin and trace element from circulation to the tissue which involved in the proteins formation and immune system.

The conclusions of the latest 7 experiments and 4 random controlled study of multi-centre support the argument that micronutrients supplementation in sepsis may decrease mortality rate. However, it still need to be particularly aware of the possibility of micronutrients toxicity in fat soluble if the doses is excessive.

Zinc is co-factor of more than 200 enzymes that have a role in the immune system, regeneration new cells and balancing acid bases. Normal level is between 70-150 mcg /dl. The low alkaline phosphatase (ALP) can be used as a parameter that the body has low level of zinc.

In sepsis occurs the improvement production of hepsidin so can block Fe transportation. Neutrofil and macrophages need the iron to do phagocytosis and killing bacteria.

Copper is an essential component of several enzymes e.g. superoxide dismutase (SOD). Copper inhibits the activity of anticoagulant and protein C which has been activated. Recommended Dietary Allowance (RDA) for copper in adults is 900 mcg and parenteral dosage is 300 - 500 mcg per day

Selenium uniqueness is having a dual function as pro-oxidant and anti-oxidant. Granting high doses selenium

in sepsis for 9 consecutive days and decrease the dose every 3 days may lower mortality rates, decrease the score of APACHE III and creatinin serum. Maximum dose of selenium 400 µg (5µg/kg BB/day) but even granting 800 µg is considered has no side effects report.

Vitamin C can lowered the iNOS expression.Vitamin B1 (thiamin) is co-factor of pyruphate dehidrogenase, the enzyme which is responsible for pyruphate conversion into asetil-coenzim A.

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