THE EFFECT OF ENRICHED L-GLUTAMINE COMPLEMENTARY FOOD ON CELLULAR IMMUNITY PROFILE AND MORBIDITY SCORE OF UNDERWEIGHT 6 MONTH INFANTS [1]

Endang S. Sunaryo [2] and Rimbawan [3]

ABSTRACT

Growth faltering is widely prevalent in developing world including Indonesia. The prevalence of mild and moderate Protein Energy Malnutrition is also extremely high reaching more than 20 % in Indonesia. Faltering in weight begins at about age 3 mo and continues rapidly until about 12 mo. Thereafter, it continues to decline at a slower pace until about 18 mo with a subsequent catch-up pattern.

The enriched L-Glutamine Complementary Food containing 0.3 g/kg body weight or 2.5 g/ 25 g CF was developed from cereals, milk protein, mungbean, milk fat and mixture of vegetable oils. Using animal rat experimental, additional L-Glutamine CF could enhance better integrity of jejunum in which improve the lymphoid proliferation and further prevent *E coli* penetration.

The experimental study using double blind randomized trial was conducted in 19 villages supervised by medical doctors of 6 community health centres in 4 sub districts of Bogor, West Java. Three groups of totally 143 infants of 6 months ± 1 week were involved in the study. The respective infants were healthy infants with slightly underweight. Each group were assigned to receive different intervention during 3 mo i.e MPG (Enriched L-Glutamine CF), MPK (Control CF) and MPP (No Enriched L-Glutamine CF). The CF was given daily after reconstituted with boiled water, 7 days a week, 2 packs @ 25g CF per day for 12 weeks (3 mo duration).

Cellular Immunity Profiles indicated by lymphocytes T, lymphocytes B and natural killer. Enriched L-Glutamine CF (MPG) improved lymphocytes T, T helper and T suppressor better compared to MPK and MPP designated by percentage differences of the cellular immunity profiles between beginning and ending of the intervention. Though protein influenced the blood profiles particularly leucocytes, erythrocytes and haemoglobins development, enrichment L-Glutamine in MPG postulated beneficial improving on Iron Deficiency Anaemia reduction 42,8 % better than 14,2 % in case of MPP, while MPK no change in prevalence.

Improvement of the cellular immunity profiles in MPG could reduces morbidity score significantly ($p<0.05$) by 239 ± 302; better than MPP (314 ± 357) and MPK (345 ± 468). Morbidity score calculated using portfolio by multiplying score of disease risk with duration of illness. From logistic regression analysis point of view , L-Glutamine CF has potential opportunity in improving immunity 4.3 times compared to control. Besides L-Glutamine CF, morbidity score negative influenced by care giving behaviour (OR 0.46), mother's education (OR 0.43) and CF intake (OR 0.30).

Key words : L-Glutamine. Complementary Food. Cellular Immunity. Morbidity Score. Infant

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1) Presented at the Ajinomoto Seminar , March 19, 2004, Tokyo.

2) Senior Food Research Specialist , Corporate Research & Development, PT Indofood Sukses Makmur, Jakarta.
email : endangs.sunaryo@indofood.co.id.

3) Director of Student Affairs. Bogor Agriculture University.Bogor
email : rimbawan62@yahoo.com.

The importance of Complementary Food (CF) as a foundation for healthy development of infants is underestimated. In case of Indonesia, the fact that growth faltering start from 3 mo infant when breast milk is no more exclusive and inappropriate CF is started. In addition, they are often receiving in insufficient amounts and they displace breast milk. Poor quality of sanitation and hygiene also care giving behaviour affect infant growth and development (Sukirman, 2000).

Since sufficient quantity of published researches information on glutamine, these fascinated results have opened possibility to incorporate glutamine in CF. Lacey et al (1996) conducted study on 44 premature infants using TPN and the result showed no difference between groups, but TPN group less time to full feeds, less time on ventilator. While Neu et al (1997) studied 68 low birth weight neonates and result showed sepsis less (OR 0,38) and better tolerant for enteral nutrition.

The objective of this paper is to provide information on how the Enriched L-Glutamine CF could influence cellular immunity and further reduce morbidity score of 6 mo underweight infants during 3 mo intervention program. It is also in keeping with evidence that Enriched L-Glutamine CF reduced the prevalence of Iron Deficiency Anemia in the group.

Enriched L-Glutamine CF and Mucosal Protection

Growth faltering is widely prevalent in the developing world including Indonesia. The prevalence of mild and moderate Protein Energy Malnutrition (PEM) vary among regions but overall reaching more than 20 % in case of infants and U2Y. Faltering in weight begins at about 3 mo and continues rapidly until 12 mo. Thereafter, it continues to decline at a slower pace until 18 – 19 mo with a subsequent catch-up pattern (Lutter & Rivera, 2003). Maternal malnutrition and inappropriate breast milk and complementary feeding represent huge risk to ill health, and ill health causes further deterioration in nutritional status. These evidences are common observed in infants and U2Y.

Inappropriate feeding practices are a major cause of the onset of PEM. Infant and children who are not breast fed appropriately have repeated infections, suffer the risk of disability or grow less well and likely to die. In 2002, more than 50 % of the burden of ARI (Acute Respiratory Infections), diarrhoea, dengue, measles and other high fever was attributable to PEM (UNU, 2003).

complementary feeding. Access to adequate CF is a necessary condition for improved nutritional status. Adequate CF and appropriate feeding guidance including care giving practices are the best approach in nutrition intervention particularly to prevent growth faltering. Inappropriate breast feeding and CF may lead insufficient protein, energy as well as micronutrient and further influence infant immune system. Repeated infections and diseases reduce appetite and increase the risk of PEM (UNU, 2003).

Table 1. CF Profile

Parameter	MPG	MPK	MPP
Energy Density (Cal/g)	1.1	0.8	1.0
Protein quality :			
1. Deficit Amino Acid (compare to WHO,1985)			
Methionine (%)	142	90	131
Tryptophan (%)	111	74	100
2. PER	3.2 ± 0.3	1.9 ± 0.2	3.4 ± 0.4
Fatty Acid Profile :			
1. SFA/MUFA	1.59	2.75	1.67
2. SFA/ PUFA	2.32	1.92	2.88
3. Omega3/Omega6	0.11	0.09	0.11

Note: MPG : Enriched L-Glutamine CF
MPK : Control CF
MPP : No Enriched L-Glutamine CF

Enriched L-Glutamine CF made of cereals, milk protein, mungbean, milk fat and mixture of vegetable oil, finally enriched with 0.3 g/kg body weight or 2.5 g/25 g CF. The desired CF (Table 1) provided energy density, protein quality and fatty acids profile. The CF at least should fulfil proposed nutrient composition for fortified processed CF which is presented by Lutter and Dewey (2003) or in principle, Codex Stan 74-1981which regulated CF formulation.

Since the work of Windmueller and Spaeth in 1974, continued research works have been demonstrated the importance of glutamine to support the intestinal mucosal metabolic function (Windmueller, 1982 ; Van der Hulst et al, 1993 ; Firmansyah , 1992; Van der Hulst et al, 1997; Reeds & Burrin, 2001). They demonstrated that glutamine has an important metabolic role in the maintenance of mucosal structure (Firmansyah, 1992; Panigrahi et al, 1997). Also glutamine has played a critical role in intestinal mucin synthesis (Khan et al, 1999).

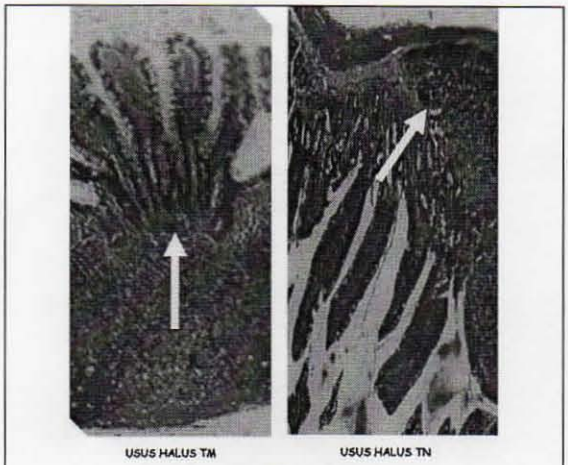
Enriched L-Glutamine CF in animal rat experimental supported earlier finding that the presence of glutamine is important for maintenance of mucosal health (Firmansyah,1992; Panigrahi et al, 1997; Neu et al, 2000). Glutamine improved

pyrimidine and amino sugar synthesis. Proliferation of enterocytes of the mucosal in Enriched L-Glutamine CF group of rats provided better protection of *E. coli* infections (negative *E.coli* at day 10 th after infections versus positive *E.coli* day 13 th in control as presented in Table 2). Proliferation of lymphoid of the Enriched L-Glutamine CF group of rats is presented in **Fig.1.**

Table 2. *E.coli* and Non *E.coli* in rat feces

Observation	CF	*E.coli* (Col/g feces)		Non *E. coli* (Col/g feces)	
		TM	TN	TM	TN
Day 1- 3 (10^{10}/1ml)	MPG	$3,5 \times 10^2$	$5,8 \times 10^3$	$2,6 \times 10^2$	$1,8 \times 10^3$
	MPK	neg	neg	$7,5 \times 10^3$	$1,4 \times 10^3$
	MPP	$1,2 \times 10^2$	$2,5 \times 10^2$	$7,3 \times 10^4$	$3,2 \times 10^3$
Day 8	MPG	$5,1 \times 10^3$	$3,8 \times 10^3$	$2,8 \times 10^3$	$2,4 \times 10^4$
	MPK	$6,4 \times 10^3$	$1,7 \times 10^3$	$2,2 \times 10^4$	$1,7 \times 10^4$
	MPP	$1,4 \times 10^5$	$1,7 \times 10^4$	$7,4 \times 10^4$	$1,8 \times 10^4$
Day 9	MPG	$4,8 \times 10^3$	$1,2 \times 10^3$	$4,3 \times 10^4$	$3,4 \times 10^4$
	MPK	$4,2 \times 10^4$	$1,8 \times 10^4$	$2,2 \times 10^4$	$9,7 \times 10^3$
	MPP	$6,4 \times 10^4$	$8,8 \times 10^3$	$1,5 \times 10^4$	$4,7 \times 10^4$
Day 10	MPG	neg	neg	$1,8 \times 10^3$	$3,0 \times 10^3$
	MPK	$2,0 \times 10^3$	$8,8 \times 10^2$	$1,2 \times 10^3$	$4,2 \times 10^3$
	MPP	$4,0 \times 10^3$	$1,8 \times 10^3$	$4,8 \times 10^3$	$2,6 \times 10^3$
Day 11	MPG	neg	neg	$2,4 \times 10^2$	$1,3 \times 10^3$
	MPK	$2,4 \times 10^3$	$3,2 \times 10^2$	$1,4 \times 10^3$	$9,6 \times 10^2$
	MPP	$3,6 \times 10^3$	$9,2 \times 10^2$	$1,1 \times 10^3$	$7,8 \times 10^2$
Day 12	MPG	,neg	neg	$1,6 \times 10^3$	$1,4 \times 10^2$
	MPK	$3,4 \times 10^2$	$6,2 \times 10^2$	$7,3 \times 10^2$	$5,6 \times 10^2$
	MPP	neg	neg	$1,3 \times 10^3$	$7,2 \times 10^2$
Day 13	MPG	neg	neg	$8,6 \times 10^3$	$7,5 \times 10^2$
	MPK	$2,2 \times 10^2$	$1,2 \times 10^2$	$9,5 \times 10^2$	$7,2 \times 10^2$
	MPP	neg	neg	$8,6 \times 10^2$	$7,5 \times 10^2$

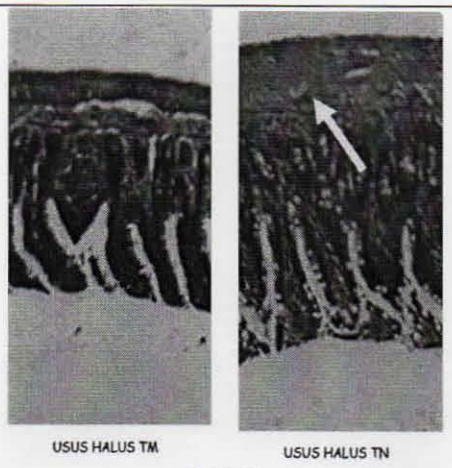
Note : Neg = negative



MPG

Note:
TM = Malnutration rat
TN = Normal rat

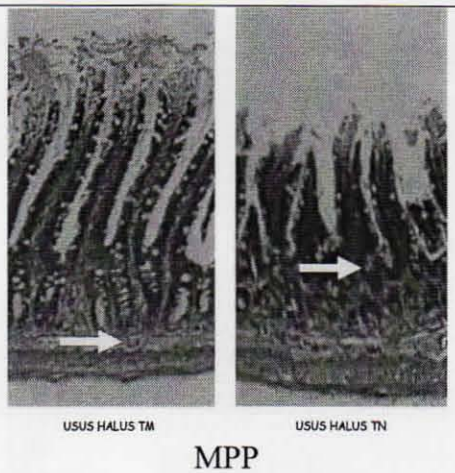
1) Normal observation
2) Proliferation of lymphoid very responsive (+++)



MPK

Note :
TM = Malnutrition rat
TN = Normal Rat

1) Normal observation
2) Proliferation of lymphoid (+)



MPP

Note :
TM = Malnutrition rat
TN = Normal rat

1) Normal observation
2) Proliferation of lymphoid responsive (++)

Figure 1. Histopathologie of Small intestine in rats of différent group of CF

Glutamine and Cellular Immunity Profile

To investigate the effect of Enriched L-Glutamine CF on the cellular immunity, blood profile and morbidity score, the experimental study using double blind randomized trial was conducted in 19 villages. The study was supervised by medical doctors of 6 community health centres in 4 sub districts of Bogor, West Java. Three groups of totally 143 infants of 6 months ± 1 week were involved in the study. The respective infants were healthy infants with slightly underweight. Each group were assigned to receive different intervention during 3 mo i.e MPG (Enriched L-Glutamine CF), MPK (Control CF) and MPP (No Enriched L-Glutamine CF). The CF was given daily after reconstituted with boiled water, 7 days a week, 2 packs @ 25g CF per day for 12 weeks (3 mo duration).

Glutamine have provided evidence to become conditional amino acid during stress or inflammatory conditions such as infection and injury. Under appropriate conditions, glutamine is essential for cell proliferation, it can act as a respiratory fuel and it can enhance the function of stimulated immune cells (Newsholme, 2001). Granulocytes, lymphocytes and monocytes play important roles in he immune and inflammatory response. Granulocytes have cytoplasmic granule containing active biologic substances like proteolytic enzymes and Reactive Oxigen Substances (ROS) which act as an essential stimulated immune cells by lymphocytes to overcome inflammatory and allergy (Ganong, 1995).

Mature lymphocytes recirculation via blood and lymph through lymphoid tissues and effective to a bacterial or viral infection. T-lymphocytes are required in vivo to proliferate in response to antigenic stimuli, to produce cytokines essentials to the propagation of the immune response and to up-regulate specific cytokine receptor on the T cell surface, which further enhance rates of proliferation (Newsholme, 2001). Enriched L-Glutamine CF improved total T-lymphocytes, T helper land T supressor (Table3).

B-lymphocytes activities mainly via production of regulatory cytokines. B-lymphocytes produce and secrete antibodies in response to antigenic stimuli particularly bacterial infections. The activities is glutamine dependent. No dought from our study, there is an evidence that B-lymphocytes of Enriched L-Glutamine CF group showed improvement by decreasing percentage of B-lymphocytes.

Table 3. Infants Cellular Immunity Profile during CF Intervention

Immunity Profile %	MPG n = 47		MPK n = 52		MPP n = 44		Standard
	mean	sd	mean	sd	mean	sd	
Lymphocytes							
Begin	56,1	10,5	58,1	12,8	61,4	7,5	20 – 40
End	56,1	6,8	51,8	11,8	57,3	9,1	
Difference	0,1	11,5	(6,3)	14,4	(4,1)	10,1	
Total T Lymph.							
Begin	56,9	9,4	59,5	10,4	61,1	11,9	59,4 – 84,6
End	59,3	9,4	60,1	16,6	56,3	9,3	
Difference	2,4	10,5	0,6	16,3	(4,8)	12,1	
T helper							
Begin	31,0	12	33,4	8,2	35,6	11,8	28,5 – 60,5
End	34,8	7,4	34,6	11,6	29,9	8,5	
Difference	3,8	14,2	1,3	12,2	(5,7)	8,3	
T suppressor							
Begin	18,2	9,2	21,4	8,7	25,9	8,4	11,1 – 38,3
End	23,0	6,8	25,1	11,2	23,2	7,4	
Difference	4,8	8,5	3,8	12,3	(2,8)	9,1	
Total T lymph.							
Begin	26,8	7,6	23,9	10,7	21,2	10,9	6,4 – 22,6
End	23,6	7,0	20,6	5,5	23,3	5,5	
Difference	(3,2)	6,3	(3,2)	9,9	2,1	12,8	
Natural Killer							
Begin	9,6	4,8	7,0	3,7	10,1	4,4	5,6 – 30,9
End	11,9	5,4	11,8	7,1	10,8	4,3	
Difference	2,4	6,3	4,8	7,3	0,8	5,6	

Note: Cellular Immunity Profile analyzed by Flow cytometric method

Macrophages are terminally differentiated and cells in which the ability to proliferate is gradually lost. They originate in the bone marrow and enter the blood as immature macrophages, named monocytes. Monocytes enter the tissues and serious cavities of the body where they mature into macrophages or Natural Killer and subsequently phagocytose foreign material and appoptosing host cells. They present antigen at the cell surface in association with MHC and secrete inflammatory cytokines and ROS (Newsholme, 2001). All CF when consume in sufficient amount (recommended by Proposed Nutrient Composition of CF 40 g/day) can influence the Natural Killer of the Cellular Immunity Profile(Table 3).

Neu (2001) stated glutamine, glutamate and their metabolites play critical role in numerous cell processes. Their designation as condentionally essential nutrients downplays their importance in rapidly growing fetus and premature infant particularly for mucosal integrity and immune response.

From Table 3, total lymphocytes of 3 groups indicated higher than standard 20

due to poor condition of the environment and inappropriate care giving practices, bacterial and viral infections still dominant.

IDA and Enriched L-Glutamine CF

During 3 mo intervention, Enriched L-Glutamine CF provided significant role in reduction of Iron Deficiency Anemia (IDA). Using cut-off less than 11 g/dL for Hb and less than 4.2 x 10^6 cell/ μL at the beginning of intervention, prevalence of IDA within the range of 57.1 % to 85.7 %. By end of intervention, reduction of IDA prevalence is 42.8 % in MPG group ; 14.2 % in MPP and none in MPK.

Table 4. Infants Blood Profile during CF Intervention

Blood Profile	MPG n = 47		MPK n = 52		MPP n = 44		standard
	mean	sd	mean	sd	mean	sd	
Leucocytes (X 10^3 sel/μL)							
Begin	10,7	2,3	10,5	2,9	10,2	4,1	4,3 – 10,8
End	10,6	2,2	12,8	3,1	10,1	2,4	
Difference	(0,1)	2,3	2,3	4,0	(0,1)	3,7	
Erythrocytes (X 10^6 sel/μL)							
Begin	4,35	0,35	4,46	0,27	4,49	0,48	4,2 – 5,5
End	4,67	0,25	4,65	0,36	4,77	0,50	
Difference	0,32	0,25	0,19	0,34	0,29	0,22	
Hb (g/dL)							
Begin	10,5	0,8	10,8	1,1	10,7	0,8	> 10,5
End	10,9	0,7	10,8	0,9	11,1	0,9	
Difference	0,4	0,8	(0,1)	0,7	0,4	1,0	
Ht (%)							
Begin	32,2	2,8	32,7	2,7	32,6	2,6	> 30
End	33,8	2,1	33,3	2,0	34,1	2,8	
Difference	1,6	2,8	0,6	2,1	1,5	2,6	
MCH (pg)							
Begin	24,3	2,3	24,2	1,8	23,9	1,9	> 27
End	23,3	1,8	23,1	2,2	23,1	2,0	
Difference	(1,0)	1,2	(1,2)	0,8	(0,8)	0,8	

Note : Blood Profile analysed by Sysmec method

Milk protein in CF play important role as building block for improving erythrocytes and hemoglobin's (Hb) both in MPG as well as in MPP group. From Table

5) indicated correlation between erythrocytes with leucocytes, hemoglobin, hematocrit and mean corpuscular hemoglobin. Although blood cells development is regulated by erythropoietin, Enriched L-Glutamine CF enhanced better result particularly in case of IDA

Milk protein, Iron, vitamin B6, Folic acid and vitamin C have beneficial in improving erythrocytes and Hb. Enriched L-Glutamine CF have opportunity in accelerating erythrocytes and Hb. Postulated this theory, glutamine in the presence of siutable condition of protein could donate the amide nitrogen of glutamine to support synthesis of purine and pyrimidine or nucleotides for DNA. In fact, Enriched L-Glutamine CF also have direct beneficial in nutrition utilization. Therefore improvement of erythrocytes enhance leucocytes development or vies versa.

Table 5. Pearson Analysis between erythrocytes and infant blood profile

	SDP	Hb	Ht	MHC
Erythrocytes				
Coef. Pearson	0,257	0,318	0,577	0,312
Sig. (2 tailed)	0,130	0,059	0,001	0,064
N	36	36	36	36

Morbidity Score and Enriched L-Glutamine CF

Morbidity score has been calculated using portfolio approach by multiplying risk of diseases based on severenity with duration of the disease in each respondent. To indicate degree of the risk is done by survey on several medical doctors and the scoring system are as follows 10 for the least severe disease such as dermatitis, scurvy ; 50 for ARI, Bronchitis ; 70 for measles and 80 for diarrhea, cholera or the most severe disease which lead to death.

Enriched L-Glutamine CF provided least score of morbidity i.e 239 $\pm$ 302 lower than MPK (345 + 468) and MPP (314 + 357), The most frequent disease are ARI 68.5 %, high fever 60.8 %, diarrhea 36.4 %, dermatitis 23.8 % and the rest due to others. This evidence supported HKI and Unicef findings in 2001 which stated ARI and diarrhea as the most determinant causes of infant mortality. Enriched L-Glutamine CF provided strong evidence in reducing morbidity score (4.3 times better than control). It is postulated glutamine in infant increased glutamine pool, enhanced lymphocytes proliferation thus improve intestinal protection (Windmueller,1982 ; Firmansyah,1992 ;

particularly T-lymphocytes and B-lymphocytes could protect infant against bacterial and viral infections. This evidence supported earlier result and infact strengthen clinical evidence that glutamine supplementation through enteral nutrition is save at lower dosage. The role of glutamine in improving mucosal tissues and enhance leucocytes development especially lymphocytes could be taken into consideration for improving and maintaining infant immune system particularly in Indonesia.

From our study, morbidity score also influenced by care giving behavior (OR 0.46) and mother education (OR 0.43), further it influenced intake of CF (OR 0.30).. Pelto et al (2003) stated care giving behavior playing as determinant factor and it is influenced by mother educations. If mothers aware to prioritize appropriate feeding to their infants, possible to find positive defiant and prevent the growth faltering (Zeitlin,1996 ; Saadah et al,1999 ; LIPI & Unicef,2000 ; Pelto et al,2003)

Conclusions

Enriched L-Glutamine CF containing cereals, milk protein, mungbean, milk fat and mixture of vegetable oils with additional 0.3 g/kg body weight or 2.5 g/25 g CF. Incorporation glutamine in CF during 3 mo intervention provided beneficial :

- In improving T-lymphocytes and B-lymphocytes in which further improve infant immune system (leucocytes)
- Reducing morbidity score
- Improving erythrocytes and haemoglobines, thus reduce incidence of IDA

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