

1. Paterson RL, Webster NR. Sepsis and the Systemic inflammatory Response Syndrome. *R. Coll. Surg. Edinb* 2000;178-182.
2. Hotchkiss SR, Karl EI. The Pathophysiology and Treatment of Sepsis. *2003;348:138-50.*
3. Karl IE. Pathogenesis of sepsis and multiorgan dysfunction. *J Cell Biochem* 1992;267:10931-44.
4. Oberholzer C, Oberholzer A, Clare-salzler M, Moldawer LL. Apoptosis in sepsis: a new target for therapeutic exploration. *The FASEB Journal* 2001;15:879-892.
5. Moncada S, Higgs A. The L-Arginine-Nitric oxide pathway. *NEJM* 1993;329:2002-12.
6. Moncada S, Palmer JMR, Higgs AE. Nitric Oxide: Physiology, Pathophysiology and Pharmacology. *The American Society for Pharmacology and Experimental Therapeutics* 1991;43(2):109-34.
7. Obelhozer. Vernooy JHJ, Mieke A. Dentener, Suylen RJ, Wim A. Buurman, Wouters EFM. Intratracheal Instillation of Lipopolysaccharide in Mice Induces Apoptosis in Bronchial Epithelial Cells .No Role for Tumor Necrosis Factor- α and Infiltrating Neutrophils. *Am. J. Respir. Cell Mol. Biol* 2001;24(5):569-76.

8. Arnold S, Kristof, Peter G, Victor L, Sabah AH. Role of Inducible Nitric Oxide Synthase in Endotoxin-induced Acute Lung Injury. *Am. J. Respir. Crit. Care Med* 1998;158(6):1883-89.
9. Recovery of activity endothelial nitric oxide synthase under condition of oxidative stress. 2003. Available from: URL.: <http://www.cse.emory.edu>
10. Wright G, Singh IS, Hasday JD, Farrance1 IK, Hall G, Cross AS, and Rogers TB. Endotoxin stress-responsse in cardiomyocytes: NF- κ B activation and tumor necrosis factor- α expression. *Am J Physiol Heart Circ Physiol* 2002;282:872-79.
11. Szabo C, Thiemermann C, Wu CC, Peretti M, Vane RJ. Attenuation of the induction of nitric oxide synthase by endogenous glucocorticoids accounts for endotoxin tolerance in vivo. *National Academy of Science* 1994;91:271-275.
12. Adam S. The antioxidant vitamins. Available from: URL,;: <http://www.i2k.~suzanne/vitamineandc.htm#c>.
13. Fisher AEO, Noughton DP. Iron supplements: the quick fix with longterm consequences. *Nutrition Journal* 2004; 3:2. Online at: <http://www.nutritionj.com>
14. Tjokprawiro A. Radikal Bebas. Aspek Klinik dan Kemungkinan Aplikasi Terapi. Dalam: Simposium Oksidan dan Antioksidan Peranannya Dalam Mencegah Progresivitas Kelainan Pembuluh Darah. Surabaya. 1993; 11-33.

15. Helen F.G, Michael J.D and Nigel R.W. Ascorbyl radical formation in patients with sepsis: Effect of ascorbate loading. Available from: URL.: <http://www.pubmed.gov>
16. Long C.L, Maull K.I, Krishnan R.S and Louis H.L. Ascorbic acid dynamics in the seriously ill and injured. Available from: URL.: <http://www.pubmed.gov>
17. Jameson, Shiji, Rajarajeswani, Chitikinemi, Helena. Oxidative stress in sepsis in children. Available from: URL.: <http://www.IndianJournal.gov>
18. Francis S, Bucher B, Schott C, Andre A, Schaeffer JG, Stoclet CJ. Effect of bacterial lipopolysaccharide on function of rat small femoral arteries. The American Physiological Society 1994;191-98.
19. Natanson_C, Hoffman_DW, Suffredini_FA, Eichacker_QP, Danner LR. Selected Treatment Strategies for Septic Shock Based on Proposed Mechanisms of Pathogenesis. The American College of Phycisian 1994;120(9):771-83.
20. Witzendichler B, Westermann D, Kneuppel S, Schultheiss HP, Tschope C. Protective Role of Angiopoietin-1 in Endotoxic Shock. Circulation 2005;111:97-105.
21. Lorente AJ, Landin L, Esteban A. Nitric Oxide in Critical Illness.In: Shoemaker, Ayres, Grenvik, Holbrook. Textbook of Critical Care. 4th Ed. Philadelphia: WB Saunders; 2000: 630-39

22. Szabo C, Cuzzocrea S, Zingarelli B, O'Connor M, Salzman LA. Endothelial Dysfunction in Rat Model of Endotoxic Shock. *Journal of Clinical Investigation* 1997;100(3):723-35.
23. Schoonover LL, Stewart SA, Clifton DG. Hemodynamic and Cardiovascular Effects of Nitric Oxide Modulation in the Therapy of Septic Shock. *Pharmacotherapy Publications* 2000;20(10):1184-97.
24. Balligand LJ, Cannon JP. Nitric Oxide Synthases and Cardiac Muscle. *American Heart Association, Inc* 1997;17:1846-58.
25. Vallance P, Collier J. Fortnightly Review Biology and Clinical Relevance of Nitric Oxide. *BMJ* 1994;309:453-57.
26. Landry WD, Oliver AJ. The Pathogenesis of Vasodilatory Shock. *NEJM* 2001; 345:588-95.
27. National Academy of Sciences. Vitamin C. In : Dietary reference intakes for vitamin c, vitamin e, selenium and carotenoids. Washington DC: National Academy Press: 2000. 95 – 131.
28. FAO / WHO. Vitamin and mineral requirements in human nutrition. 2nd ed. China: Sun Fung; 2004. 130 – 58
29. Wiryatmadi B. Mengatasi gangguan nutrisi dan kelainan metabolisme akibat kemoterapi pada karsinoma gastrointestinal. Dalam : PIB XIX Proyek Trigonum Plus; 17-20 November 2005.

30. Goodman S. Vit C the master nutrien. Positivehealth Publication. Available in [http:// www.positivehealth.com](http://www.positivehealth.com). Diakses tanggal 29 juni 2007
31. Levine M, Conry-Cantilena C, Wang YH, Welch RW, Washko PW, Dhariwal KR, et all. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. PNAS. April 1996. vol 93. 3704 – 9.
32. Padayatty SJ, Levine M. New insight into the physiology and pharmacology of vitamin C. CMAJ, Feb. 6.2001:164(3); p. 353-5
33. Washko PW, Wang Y, Levine M. Ascorbic acid recycling in human neutrophils. J Biol Chem 268:15531-5, 1993
34. Tsao CS, Miyashita K. Effects of high intake of ascorbic acid on plasma levels of amino acids. IRCS med Sci 1984; 12: 1052-3
35. Tsao CS, Miyashita K. effects of large intake of ascorbic acids on urinary excretion of amino acids and related compaounds. ICRS Med Sci 1985; 13: 855-6
36. Padayatty SJ, Sun H, Wang Y, Riordan HD, Hewitt SM, Katz A, Wesley RA, Levine M. vitamin C pharmacokinetics: implication for oral and intravenous use. Ann Intern Med 2004; 140: 533 – 7
37. Herlambang N, Kustiowati E, Kusmiyati. Pengaruh Penambahan Vitamin E pada Terapi Standar Stroke Iskemik Akut terhadap Perbaikan Status Neurologi. Media Medika Indonesiana. 2006:41(3);146-54.

38. Soemantri. Peran Radikal Bebas pada Penyakit Jantung Koroner. Dalam: Simposium Oksidan dan Antioksidan Peranannya Dalam Mencegah Progresivitas Kelainan Pembuluh Darah. Surabaya. 1993; 51-59
39. Favier AE, Cadet J, Karyawarman. Analysis of Free Radicals in Biological Systems. Berlin. 1995; 185-200.
40. Hogg N. Pro-oxidant and Antioxidant Effect of Nitric Oxide. In: Favier EA, Cadet J, Kalyanaraman B, Fontecave M, Pierre LJ. Analysis of Free Radicals in Biological Systems. Switzerland; 2001:37-49
41. Dietert RR, Hotchkiss JH, Austic RE, Sung Y. Production of Reactive Nitrogens Intermediates by Macrophages. In: Methods in Immunotoxicology vol 2, editor: Burleson GR, Dean JH, Munson AE. New York: A John Wilye Liss & sons Inc Publ, 1995; 99-117.

Lampiran 1. Data dan Hasil Analisa

Data hasil kadar *nitric oxide*

Kelompok		NO(uMol/liter)
P1	0.2625	19.226875
P1	0.196	18.2726
P1	0.165	17.82775
P1	0.166	17.8421
P1	0.268	19.3058
P2	0.0155	15.682425
P2	0.013	15.64655
P2	0.012	15.6322
P2	0.012	15.6322
P2	0.014	15.6609
P3	0.005	15.53175
P3	0.0055	15.538925
P3	0.0065	15.553275
P3	0.003	15.50305
P3	0.0035	15.510225
P4	0.0005	15.467575
P4	0.0015	15.481525
P4	0	15.46
P4	0.0015	15.481525
P4	0.001	15.47435

Explore

Sampel

Descriptives

Sampel				Statistic	Std. Error
Hasil	K	Mean		18.49502	.325115
		95% Confidence Interval for Mean	Lower Bound	17.59236	
			Upper Bound	19.39769	
		5% Trimmed Mean		18.48705	
		Median		18.27260	
		Variance		.529	
		Std. Deviation		.726980	
		Minimum		17.828	
		Maximum		19.306	
		Range		1.478	
		Interquartile Range		1.431	
		Skewness		.367	.913
		Kurtosis		-3.071	2.000
		P1		Mean	
95% Confidence Interval for Mean	Lower Bound			15.62443	
	Upper Bound			15.67728	
5% Trimmed Mean				15.65014	
Median				15.64655	
Variance				.000	
Std. Deviation				.021284	
Minimum				15.632	
Maximum				15.682	
Range				.050	
Interquartile Range				.039	
Skewness				.839	.913
Kurtosis				-4.411	2.000
P2				Mean	
		95% Confidence Interval for Mean	Lower Bound	15.50178	
			Upper Bound	15.55311	
		5% Trimmed Mean		15.52737	
		Median		15.53175	
		Variance		.000	
		Std. Deviation		.020671	
		Minimum		15.503	
		Maximum		15.553	
		Range		.050	
		Interquartile Range		.039	
		Skewness		-.038	.913
		Kurtosis		-1.804	2.000
		P3		Mean	
95% Confidence Interval for Mean	Lower Bound			15.46130	
	Upper Bound			15.48453	
5% Trimmed Mean				15.47315	
Median				15.47435	
Variance				.000	
Std. Deviation				.009355	
Minimum				15.460	
Maximum				15.482	
Range				.022	
Interquartile Range				.018	
Skewness				-.541	.913
Kurtosis				-1.488	2.000

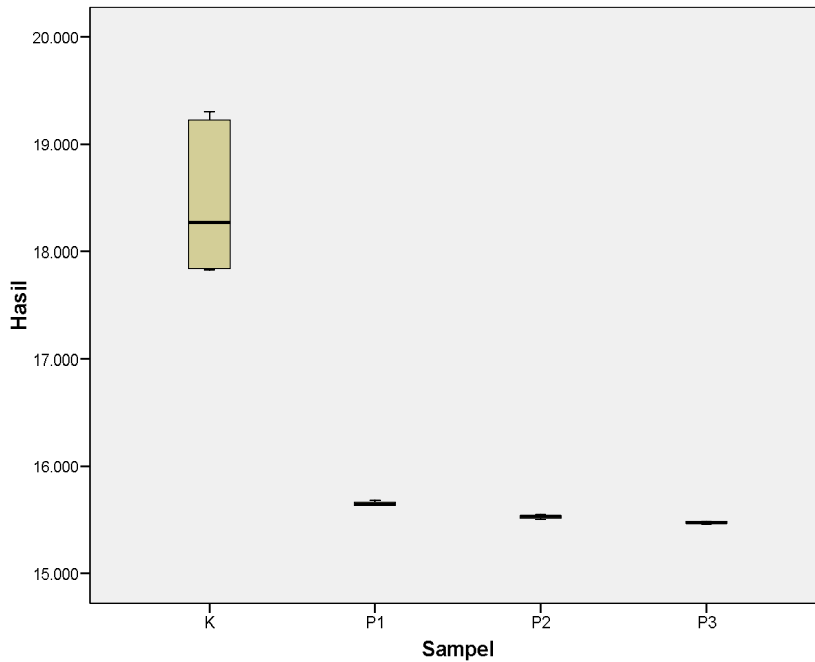
Tests of Normality

Sampel	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Hasil K	.243	5	.200*	.820	5	.117
P1	.210	5	.200*	.897	5	.391
P2	.198	5	.200*	.951	5	.742
P3	.221	5	.200*	.902	5	.421

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Hasil



Test of Homogeneity of Variances

Hasil			
Levene Statistic	df1	df2	Sig.
34.514	3	16	.000

NPar Tests

Kruskal-Wallis Test

Ranks

	Sampel	N	Mean Rank
Hasil	K	5	18.00
	P1	5	13.00
	P2	5	8.00
	P3	5	3.00
	Total	20	

Test Statistics^{a,b}

	Hasil
Chi-Square	17.884
df	3
Asymp. Sig.	.000

a. Kruskal Wallis Test

b. Grouping Variable: Sampel

NPar Tests

Mann-Whitney Test

Ranks

	Sampel	N	Mean Rank	Sum of Ranks
Hasil	K	5	8.00	40.00
	P1	5	3.00	15.00
	Total	10		

Test Statistics^b

	Hasil
Mann-Whitney U	.000
Wilcoxon W	15.000
Z	-2.619
Asymp. Sig. (2-tailed)	.009
Exact Sig. [2*(1-tailed Sig.)]	.008 ^a

a. Not corrected for ties.

b. Grouping Variable: Sampel

NPar Tests

Mann-Whitney Test

Ranks

	Sampel	N	Mean Rank	Sum of Ranks
Hasil	K	5	8.00	40.00
	P2	5	3.00	15.00
	Total	10		

Test Statistics^b

	Hasil
Mann-Whitney U	.000
Wilcoxon W	15.000
Z	-2.611
Asymp. Sig. (2-tailed)	.009
Exact Sig. [2*(1-tailed Sig.)]	.008 ^a

a. Not corrected for ties.

b. Grouping Variable: Sampel

NPar Tests

Mann-Whitney Test

Ranks

	Sampel	N	Mean Rank	Sum of Ranks
Hasil	K	5	8.00	40.00
	P3	5	3.00	15.00
	Total	10		

Test Statistics^b

	Hasil
Mann-Whitney U	.000
Wilcoxon W	15.000
Z	-2.619
Asymp. Sig. (2-tailed)	.009
Exact Sig. [2*(1-tailed Sig.)]	.008 ^a

a. Not corrected for ties.

b. Grouping Variable: Sampel

NPar Tests

Mann-Whitney Test

Ranks

	Sampel	N	Mean Rank	Sum of Ranks
Hasil	P1	5	8.00	40.00
	P2	5	3.00	15.00
	Total	10		

Test Statistics^b

	Hasil
Mann-Whitney U	.000
Wilcoxon W	15.000
Z	-2.619
Asymp. Sig. (2-tailed)	.009
Exact Sig. [2*(1-tailed Sig.)]	.008 ^a

a. Not corrected for ties.

b. Grouping Variable: Sampel

NPar Tests

Mann-Whitney Test

Ranks

	Sampel	N	Mean Rank	Sum of Ranks
Hasil	P1	5	8.00	40.00
	P3	5	3.00	15.00
	Total	10		

Test Statistics^b

	Hasil
Mann-Whitney U	.000
Wilcoxon W	15.000
Z	-2.627
Asymp. Sig. (2-tailed)	.009
Exact Sig. [2*(1-tailed Sig.)]	.008 ^a

a. Not corrected for ties.

b. Grouping Variable: Sampel

NPar Tests

Mann-Whitney Test

Ranks

	Sampel	N	Mean Rank	Sum of Ranks
Hasil	P2	5	8.00	40.00
	P3	5	3.00	15.00
	Total	10		

Test Statistics^b

	Hasil
Mann-Whitney U	.000
Wilcoxon W	15.000
Z	-2.619
Asymp. Sig. (2-tailed)	.009
Exact Sig. [2*(1-tailed Sig.)]	.008 ^a

a. Not corrected for ties.

b. Grouping Variable: Sampel

Lampiran 2. Hasil uji beda kadar *Nitric Oxide* makrofag intraperitoneal

	P2 Vitamin C 0,52 mg	P3 Vitamin C 1,04 mg	P4 Vitamin C 2,6mg
P1 Kontrol	$P=0,009$	$P=0,009$	$P=0,009$
P2 Vitamin C 0,52 mg		$P = 0,009$	$P = 0,009$
P3 Vitamin C 1,04 mg			$P = 0,009$

Lampiran 3.

CARA PEMELIHARAAN DAN DEKAPITASI HEWAN COBA

A. Cara pemeliharaan

Mencit yang dipilih adalah yang berumur kurang lebih 8 minggu. Mencit dipelihara dalam kandang selama 7 hari. Masing-masing kandang berisi 6 ekor mencit. Mencit diberi makanan dan minuman yang sama.

B. Cara memegang mencit

Untuk memegang mencit yang akan diperlakukan (baik pemberian obat maupun pengambilan darah) maka diperlukan cara-cara yang khusus sehingga mempermudah cara perlakuannya. Secara alamiah mencit cenderung menggigit bila mendapat sedikit perlakuan kasar. Pengambilan mencit dari kandang dilakukan dengan mengambil ekornya kemudian mencit ditaruh pada kawat kasa dan ekornya sedikit ditarik. Cubit kulit bagian belakang kepala dan jepit ekornya.

C. Cara penyuntikan

Mencit dimasukkan dalam alat pemegang mencit, sehingga mencit lebih mudah dikendalikan. Tarik ekornya dan kemudian penyuntikan dilakukan pada bagian lateral ekor, yang sebelumnya diusap kapas yang dibasahi dengan air hangat agar vena tampak lebih jelas. Dimasukkan obat injeksi sebanyak 0,2 cc.

D. Euthanasia

Mencit dibunuh dengan cara melakukan dislokasi pada tulang leher. Dengan cara menaruh mencit di permukaan rata kemudian sebuah pensil

diletakkan di kuduk mencit. Sambil menekan pensil, ekor ditarik kuat-kuat dan diarahkan ke atas kepala mencit

Mengetahui
Laboratorium Biokimia FK UNDIP

Lampiran 4. *Ethical Clearance*