ORIGINAL ARTICLE

Comparison between ringerfundin (B Braun) and ringer lactate administration towards Interleukin-6 (IL-6) levels in sepsis and septic shock patients at Haji Adam Malik Hospital, Medan-Indonesia

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ABSTRACT

Background: Sepsis is the second leading cause of death in intensive care unit and one of the top 10 cause of deaths worldwide. In sepsis, an inflammation response occurs that leads to the tissue destruction. According to the Survival Sepsis Campaign in 2012, early management in septic patients with 30 ml/kg of crystalloid fluids will have better outcomes.

Objective: This study aimed to determine the optimal crystalloid fluid in the resuscitation of septic patients.

Method: This double-blinded study was held from March 2017-May 2017 in Haji Adam Malik General Hospital. A total of 40 patients who passed the inclusion and exclusion criteria were assessed for interleukin-6 changes before and after treatment with ringer acetate malate and ringer lactate.

Results and Discussion: From 40 Patients who passed the criteria, we compared the administration of Ringer's acetate and Ringer's lactate malate in septic patients. The mean systolic and diastolic blood pressure were increased in both study groups (p <0.05) and a significant decrease in pulse rate was also present in both groups (p <0.001). In both groups, there was a significant decrease in interleukin-6 levels (p <0.001). Administration of ringer acetate malate leads to a stronger decrease of interleukin-6 compared to ringer lactate administration (p <0.001).

Conclusion: Ringer's acetate malate in EGDT of septic patients is superior in decreasing interleukin-6 Compared with Ringer lactate.

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INTRODUCTION

Sepsis is still the leading cause of death in critical cases around the world.[1] The high incidence of infections and problems are usually associated with the state of the developing countries or less hygienic locations, but it is not entirely true. Data from the Centre for Disease Control (CDC) showed that the incidence of sepsis increased ± 8.7% per year, from 164000 cases (83 per 100000 population) in 1979 become 660000 cases (240 cases per 100000 population) in 2000. Sepsis is the 11th highest cause of death in all death cases.[1] In USA and developing countries, septic deaths incidence reached 70000 people annually. Approximately 500000 newly admitted cases have sepsis with mortality rate reached 35%.[2] Incidence of sepsis in Indonesia ranges from 1.5 to 3.72% at some referral hospitals in Indonesia such as Cipto Mangunkusumo Hospital, while the mortality rate ranged from 37.09 to 80%.[3]

Sepsis consists of an inflammatory response which can cause tissue damage. The inflammatory response begins with the emergence of recognition receptors such as toll-like receptors (TLR) that are found on the surface of macrophages, neutrophils, epithelial, endothelial, B cells, and T cells. Toll-like receptors recognize peptidoglycans or lipopolysaccharides in the bacteria and will stimulate an intracellular signalling that causes the activation of nuclear factor k regulatory protein B (NFkB) so that the proinflammatory cytokines such as Tumor Necrosis Factor-α (TNF-α), interleukin (IL) -1, IL-6, IL-12 and interferon-γ (IFN-γ) will increase.[4,5]

Surviving Sepsis Campaign (SSC) in 2012 recommends the initial fluid administration in patients with sepsis-induced tissue hypo perfusion with suspicion of hypovolemia with a minimum of 30 ml/kg of crystalloids (some of this may be equivalent with albumin). Faster administration and greater amounts of fluid may be needed in some patients.[6,7] Based on a meta-analysis study on sepsis resuscitation, early intervention prior to the occurrence of organ dysfunction may lead to better outcomes. New studies involving emergency room patients with severe sepsis or septic shock

to compare hemodynamic resuscitation until the achievement of physiological parameters with early treatment based on targets (EGDT- Early Goal Directed Therapy) showed a significant reduction in mortality (16.5%).[8]

EGDT is an algorithmic approach for optimization aimed at restoring a balance between the preparation and the oxygen requirement in cases of severe sepsis or septic shock in the first 6 hours of emergency care. This strategy aims to achieve adequate oxygenation through optimization of intravascular volume (preload) by monitoring central venous pressure (CVP), adequate blood pressure (afterload) by monitoring mean arterial pressure (MAP), adequate contractility by monitoring heart rate to avoid tachycardia and balance recovery between systemic oxygen delivery and oxygen demand (guided by SCVO2 measurements) to prevent global tissue hypoxia. EGDT components are derived from the recommendations made by the Society of Critical Care Medicine for hemodynamic support in sepsis.[7,9,10] According to all the description above, the aim of this study was to determine which crystalloid fluids give optimal results in the resuscitation of septic patients.

METHOD

This study was approved by Department of Anaesthesiology and Intensive Therapy, Medical Faculty, North Sumatra University and the Training Department of RSUP Haji Adam Malik Hospital. After obtaining informed consent and approved by the health research ethics committee of Medical School, North Sumatra University. A total of 36 adult patients suffering from sepsis and passed the inclusion criteria who agreed to participate in the study and has quick Sequential Organ Failure Assessment (Q SOFA) score >2 were recruited and then randomized. Samples are divided into two groups; ringer lactate and ringer acetate malate groups. IL-6 levels of both groups were measured. Group 1 received 30 ml/kg of ringer acetate malate, and group 2 received 30 ml/kg of ringer lactate. Three hours after fluid resuscitation, IL-6 levels were measured.

Fluids were prepared by volunteers who did the randomization, and researchers do not know the composition of the given drug. The IL-6 examination was performed after administration of either ringer lactate or Ringer acetate malate, and 3 ml of venous blood was collected and inserted into the SST tube. The tube is turned back slowly until the blood becomes homogeneous. Samples were sent to the Clinical Laboratory of RSUP HAM to be centrifuged at 1000 g (about 3000 rpm) for 15 minutes.

The serum is separated and inserted into 3 sample tubes of 0.5 ml each. Each was labeled with identity, name, date, and type of examination. Sample tubes were frozen and stored at a temperature of -20ºC. Examinations involve vital signs and laboratory tests to determine the levels of IL-6. After the sample analysis was done by the Clinical Laboratory of RSUP HAM, the result of both groups was statistically analyzed. The study was discontinued when the study subjects refused to participate further or due to the life-threatening emergency airway, heart, lung, or brain conditions. The study was conducted from March 2017 until June 2017 at RSUP H. Adam Malik Medan.

Data analysis

Once the necessary data has been collected, the data is processed using SPSS software. Data is deemed to be normally distributed if the value of $p > 0.05$ after Shapiro-Wilk test. Comparison of the mean difference value between the 2 groups was performed with T-test if data were normally distributed, or Mann-Whitney if the data were not normally distributed. Mean difference before and after treatment were determined using paired t-test if data were normally distributed, or Wilcoxon test if data were not normally distributed. Significance was determined by a value of $p < 0.05$ with 95% confidence interval.

RESULTS

This study followed by 40 septic patients who were divided into two equal groups, each of which amounted to 20 people. There were 10 male subjects in the ringer acetate malate group (50%) and 9 male subjects in the ringer lactate group (45%). Mean age of subjects were 42.85 years and 42.5 years respectively. The subjects are dominated by Bataknese both in the ringer acetate malate (50%) and ringer lactate groups (8 people (40%)). Most of the subjects were Muslims, with 12 people (60%) in the

Table 1   Inclusion and Exclusion Criteria

Inclusion Criteria
Adult septic patients with a Q SOFA score >2
Exclusion Criteria
No consent from patient or relatives
Patients with renal disorders
Patient with functional heart disorders
Immunological disorders
Patients with a history of cancer
Patients receiving immunosuppressants

Table 2 Characteristics of Study Subjects

Characteristics	Ringer Acetate Malate (n=20)	Ringer Lactate (n=20)	p
Gender, n (%)			
Male	10 (50)	9 (45)	1.000[a]
Female	10 (50)	11 (55)	
Age, mean (SD), years	42.85 (9.86)	42.5 (8.65)	0.906[b]
Race, n (%)			
Bataknese	10 (50)	8 (40)	0.539[c]
Javanese	5 (25)	7 (35)	
Karo	3 (15)	5 (25)	
Melayu	1 (5)	4 (20)	
Minang	1 (5)	1 (5)	
Religion, n (%)			
Islam	12 (60)	14 (70)	0.507[c]
Christian	8 (40)	6 (30)	

[a] Fisher's Exact, [b] T Independent, [c] Chi Square

Table 3 Hemodynamic Parameters between Ringer Acetate Malate and Ringer Lactate Groups Pre-and Post-Intervention

Hemodynamic Parameters	Ringer Acetate Malate (n=20)	Ringer Lactate (n=20)	P
Systolic blood pressure, mean (SD), mmHg			
Pre-intervention	94.95 (10.49)	97.50 (7.71)	0.339[a]
Post-intervention	106.55 (8.03)	106.65 (9.10)	0.387[a]
Diastolic blood pressure, mean (SD), mmHg			
Pre-intervention	57.35 (5.46)	56.30 (5.33)	0.462[b]
Post-intervention	65.80 (5.14)	63.10 (5.44)	0.159[b]
Pulse rate, mean (SD), x/m			
Pre-intervention	108.20 (15.16)	104.50 (12.12)	0.524[b]
Post-intervention	92.75 (12.50)	93.55 (11.92)	0.674[b]

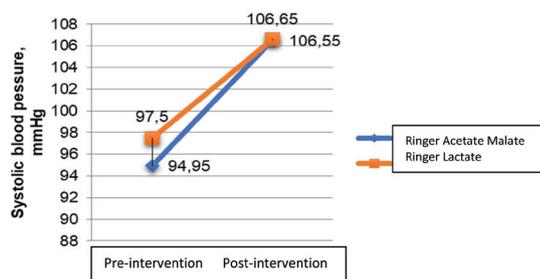[a] T Independent, [b] Mann Whitney

Figure 1 Mean Systolic Blood Pressure Difference Before and After Fluid Therapy
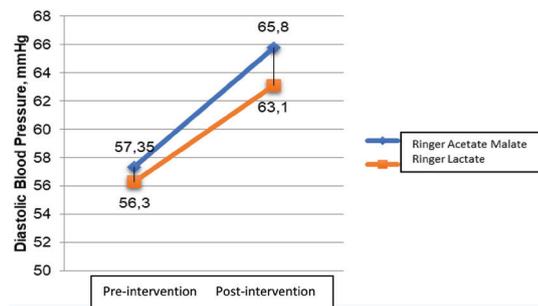

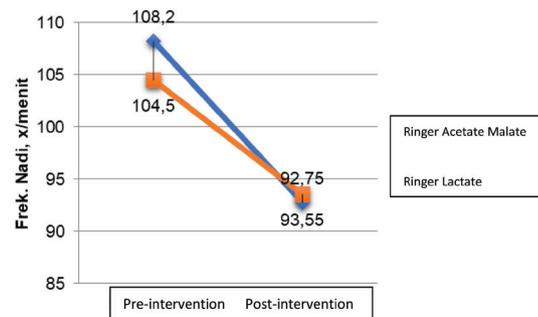**Figure 2** Mean Diastolic Blood Pressure Difference Before and After Fluid Therapy

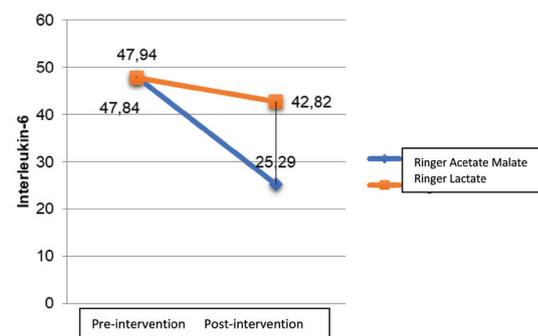**Figure 3** Mean Pulse Rate Difference Before and After Fluid Therapy

Figure 4 Mean IL-6 Levels Difference Before and After Fluid Therapy

ringer acetate malate group and 14 people (70%) in the ringer lactate group.

Table 3 shows the hemodynamic parameters before and after fluid therapy. No significant difference was found for all hemodynamic parameters between the two study groups (p> 0.05).

The mean systolic and diastolic blood pressure increased significantly in the two study groups (p <0.05). The mean systolic blood pressure in the ringer acetate malate group prior to therapy was 94.95 mmHg. After therapy, it increased to 106.55 mmHg. In the ringer lactate group, systolic blood pressure increased from 97.50 mmHg before therapy to 106.65 mmHg after therapy. Although, the increase in systolic blood

Table 4 Comparison of Hemodynamic Parameters between Ringer Acetate Malate and Ringer Lactate Groups Pre- and Post-Interventions

Hemodynamic Parameters	Ringer Acetate Malate (n=20)	p	Ringer Lactate (n=20)	p
Systolic blood pressure, mean, (SD), mmHg				
Pre-intervention	94.95 (10.49)	<0.001[a]	97.50 (7.71)	<0.001[a]
Post-intervention	106.55 (8.03)		106.65 (9.10)	
Systolic delta, mean, (SD), mmHg	11.60 (6.30)		9.15 (6.35)	0.106[c]
Diastolic blood pressure, mean (SD), mmHg				
Pre-intervention	57.35 (5.46)	<0.001[b]	56.30 (5.33)	<0.001[b]
Post-intervention	65.80 (5.14)		63.10 (5.44)	
Diastolic delta, mean (SD), mmHg	8.45 (3.68)		6.80 (5.12)	0.095[c]
Pulse rate, mean(SD), x/m				
Pre-intervention	108.20 (15.16)	<0.001[b]	104.50 (12.12)	<0.001[b]
Post-intervention	92.75 (12.50)		93.55 (11.92)	
Pulse rate delta, mean (SD), mmHg	15.45(10.22)		10.95 (6.18)	0.173[c]

[a] T Dependent, [b] Wilcoxon, Mann Whitney [c]

Table 5 Differences of IL-6 Levels between Ringer Acetate Malate and Ringer Lactate Groups Pre- and Post-Intervention

Interleukin 6 Level	Ringer Acetate Malate (n=20)	Ringer Lactate (n=20)	p*
Pre-intervention	47.94 (86.63)	47.84 (97.96)	0.499
Post-intervention	25.29 (56.86)	42.82 (89.68)	0.005

* Mann Whitney

Table 6 Comparison of IL- 6 Levels between Ringer Acetate Malate and Ringer Lactate Groups Pre- and Post- Intervention

IL-6 Levels	Ringer Acetat Malate (n=20)	P	Ringer Lactate (n=20)	p*
Pre-intervention	47.94 (86.63)	<0.001[a]	47.84 (97.96)	<0.001[a]
Post-intervention	25.29 (56.86)		42.82 (89.68)	
IL-6 level delta	22.65 (31.78)		5.02 (8.72)	<0.001[b]

[A] Wilcoxon, Mann Whitney [b]

pressure in the ringer acetate malate group was higher with a mean increase of 11.60 mmHg and the ringer lactate only had a mean increase of 9.15 mmHg, Mann Whitney analysis showed no significant difference between the two results (p = 0.106).

The mean diastolic blood pressure in the ringer acetate malate group prior to therapy was 57.35 mmHg. After therapy, it increased to 65.80 mmHg. In the ringer lactate group, diastolic blood pressure increased from 56.30 mmHg before therapy to 63.10 mmHg after therapy. Although the increase in diastolic blood pressure in the ringer acetate malate group was higher than the ringer lactate group, Mann Whitney analysis showed no significant difference between the two results (p=0.095).

There was a significant decrease in pulse rate in the two groups (p <0.001) with the greatest decrease occurring in the ringer acetate malate group. However, the magnitude of pulse rate changes did not differ in the two groups (p = 0.173).

The mean IL-6 levels before intervention was 47.94 (SD = 86.63) in ringer acetate malate group and 47.84 (SD = 97.76) in the ringer lactate group. Mann Whitney analysis showed no significant difference of IL-6 levels between ringer acetate and ringer lactate group before treatment (p> 0.499).

The result of Mann Whitney analysis showed a significant difference of mean interleukin 6 levels between ringer acetate malate and ringer lactate groups (p <0.001). The mean IL-6 level before administration of ringer acetate malate was 47.94 (SD = 86.63) and after administration it decreased to 25.29 (56.86). Analysis using Wilcoxon test showed a significant difference of mean IL-6 level before and after ringer acetate malate administration (p <0.001). In the ringer lactate group, a decrease of interleukin levels was also observed. Before ringer lactate administration, the mean IL-6 level was 47.84 (97.96). After administration, it decreased to 42.82 (89.68).

The decrease of IL-6 in the ringer acetate malate group was 22.65 (31.78) greater than the decrease in IL-6 levels in the ringer lactate group; the latter only had a decrease of 5.02 (8.72). Mann Whitney analysis showed a significant difference of mean IL-6 levels between the ringer acetate malate and ringer lactate groups (p <0.001).

DISCUSSION

In patients with sepsis, tissue hypoperfusion and release of inflammatory mediators occur. Patients with this condition must be managed with 30 cc/kg BW fluids in accordance with the Surviving Sepsis Campaign in 2016. The recommended fluid to use is crystalloids. This study focuses on the crystalloids ringer lactate and ringer acetate malate.[6,7]

In this study which was conducted from March 2017 to May 2017, 40 patients were divided into two equal groups. Group A received resuscitation with ringer acetate malate and group B received resuscitation with ringer lactate. The mean age of the subjects in groups A and B was 42.85 and 42.5. The characteristics of the subject showed that majority are Bataknese in both groups; 50% in group A and 40% in group B. A majority of the subject are Muslims, with 12 (60%) and 14 Muslims (70%) respectively in group A and B.

The mean systolic and diastolic blood pressure increased significantly in the two study groups (p <0.05). The mean systolic blood pressure in the ringer acetate malate group prior to therapy was 94.95 mmHg. After therapy, it increased became 106.55 mmHg. In the ringer lactate group, systolic blood pressure increased from 97.50 mmHg before therapy to 106.65 mmHg after therapy. Although, the increase in systolic blood pressure in the ringer acetate malate group was higher than ringer lactate group (only had a mean increase of 9.15 mmHg), Mann Whitney analysis showed no significant difference between these two results (p = 0.106). This result is consistent with a previous study by Rochwerg (2015), who stated crystalloids is the primary choice in treating sepsis that may reduce mortality.[11]

The mean diastolic blood pressure in the ringer acetate malate group prior to therapy was 57.35 mmHg. After therapy, it increased to 65.80 mmHg. In the ringer lactate group, diastolic blood pressure increased from 56.30 mmHg before therapy to 63.10 mmHg after therapy. Although the increasing in diastolic blood pressure in the ringer acetate malate group was higher than the ringer lactate group, Mann Whitney analysis showed no significant difference between the two results (p = 0.095). This result is consistent with a previous study by Rochwerg (2015).[11]

There was a significant decrease in pulse rate in the two groups (p <0.001) with the greatest decrease occurring in the ringer acetate malate group. However, the magnitude of pulse rate changes did not differ in the two groups (p = 0.173).

The result of Mann Whitney analysis showed a significant difference of mean IL-6 levels between ringer acetate malate and ringer lactate groups (p <0.001). The mean IL-6 level before administration of ringer acetate malate was 47.94 (SD = 86.63) and after administration, it decreased to 25.29 (SD= 56.86). Analysis using Wilcoxon test showed a significant difference of mean IL-6 level before and after ringer acetate malate administration (p <0.001). In the ringer lactate group, a decrease of interleukin levels was also observed. Before ringer lactate administration, the mean IL-6 level was 47.84 (97.96). After administration, it decreased to to 42.82 (89.68). The decrease of IL-6 in the ringer acetate malate group was 22.65 (31.78) greater than the decrease in IL-6 levels in the ringer lactate group; the latter only had a decrease of 5.02 (8.72). This result is consistent with the study by Wei Dong (2015), who found that ringer sodium pyruvate may significantly reduce IL-6 levels. Wei Dong also stated that the use of crystalloid fluids would reduce mortality, due to hemodynamic changes after resuscitation.[12]

The result of the analysis showed that there was a significant correlation between ringer acetate malate and ringer lactate administration with changes of hemodynamic and IL-6 parameters, though their effects vary. From this study, ringer acetate malate has a significantly greater impact towards the decrease in IL-6 level compared to ringer lactate.

CONCLUSION

The results of this study which compared ringer acetate malate and ringer lactate administration in septic patients found a decrease in IL-6 levels after administration of ringer acetate malate and ringer lactate, either separately or in combination, in septic patients at RSUP HAM. A stronger decrease of IL-6 was observed in ringer acetate malate fluid administration compared to ringer lactate in septic patients at RSUP HAM.

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