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THE IMPACT OF ZINC SUPLEMENTATION ON THE EVENT OF LAPAROTOMIC WOUND DEHISCENCE IN PERITONITIS: AN ANIMAL STUDY OF NEW ZEALAND RABBIT

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Abstract: *Patients with peritonitis have a high risk of wound dehiscence. Wound healing disorders, often occur in peritonitis conditions, could result from a relative zinc deficiency in peritonitis conditions. Zinc concentrations in the blood of septic subjects were often found to be low due to peripheral redistribution of zinc to the liver. This research was a randomized experimental research. A total of 36 male rabbits were induced to peritonitis by injecting 4ml/KgBW 10% autologous faecal solution and after six hours underwent exploratory laparotomy. The treatment group was then given zinc syrup supplementation of 10ml/KgBW per day for up to 5 days postoperatively. Wound healing was observed using wound dehiscence gradation system from World Union of Wound Healing Societies. However, there was no difference between the two group as there were no wound dehiscence observed in both group.*

Keywords: **zinc, peritonitis, wound dehiscence.**

I. INTRODUCTION

Postoperative wound dehiscence has a significant impact on patients such as increased mortality, delayed discharge of patients, follow-up surgery, delayed administration of adjuvant drugs (in cancer patients), non-optimal wound cosmetics, and impaired psychosocial well-being of patients. An analysis of research data in America showed that patients with wound dehiscence experienced an increase in mortality by 9.6%, an additional length of hospitalization up to 9.4 days, and an additional bill of care up to USD 40,000 greater than controls (1)**. This wound dehiscence, although significant, is often underreported. According to the World Union of Wound Healing Societies 2018, the incidence of wound dehiscence in laparotomy surgery is 0.4%-3.8% but increases to 88% in contaminated and dirty operating conditions** (1)**. The level of wound dehiscence in laparotomy surgery in the Pediatric Surgery Division of RSUD Dr. Soetomo reached 74 cases out of 1070 laparotomy operations (6.9%) in the 2014-2020 period.**

The causes of wound dehiscence could be categorized into three: a) technical problems related to incision closure – eg. detachment of suture knot; b) mechanical stress – eg. coughing can cause suture breakage or rupture of a healing incision after suture removal; c) impaired healing process – for example due to comorbid factors or medications that interfere with healing, or as a result of surgical site infection. Macronutrients and micronutrients were needed in sufficient quantities to prevent disruption of the wound healing process. The micronutrient needed at almost every stage of wound healing was zinc.

The objectives in this study was to prove that the healing of the laparotomic wound in the sepsis condition would be better with zinc supplementation rather than without zinc supplementation.

II. Material and Methods

A total of 36 male Newzealand white rabbits aged 6-9 months with a weight of 2-3 kilograms were randomized into two treatments with 18 rabbits each, then adapted for seven days. Each rabbit was placed in a separate cage, with a 12/12 hour lighting cycle. Feeding and drinking during the adaptation period and ad libitum treatment.

After being adapted for seven days, the rabbits were made peritonitis by introducing 10% autologous feces solution, ie 2 grams of feces collected from each rabbit and dissolved in 20 ml of 0.9% NaCl, an amount of 4 ml/kgBW into the intra-abdominal cavity. After 6 hours from the injection, a laparotomy was performed under general anesthesia using ketamine 20-40 mg/kg body weight intramuscularly. During the induction of anesthesia, the therapeutic antibiotics Ceftriaxone 25 mg/kgBW and Metronidazole 10 mg/kgBW were also given (2). Each rabbit was shaved on the stomach, then disinfected with 10% povidone iodine and the operating field was narrowed with a sterile drape. A longitudinal longitudinal incision in the midline of the abdomen is 4 centimeters long, deepened to reach the peritoneum. Then the abdominal cavity was washed with a 0.9% NaCl solution of 300 ml/kgBW until clean. The laparotomy wound is then sutured. The layers of the peritoneum, fascia, and muscle were sutured simply with absorbable multifilament sutures (Polyglycolic Acid 4.0), while the skin was sutured continuously with non-absorbable monifalmen (Nylon 4.0) and the wound was closed with gauze.

Postoperatively, all rabbits were given a combination of advanced therapeutic antibiotics Ceftriaxone 25 mg/kgBW every 12 hours and Metronidazole 10 mg/kgBW every 8 hours, as well as analgesic Paracetamol at a dose of 10 mg/kgBW every 8 hours. Daily zinc supplementation was given to the treatment group at a dose of 10 mg/kgBW/day started after surgery and continued for 5 days. The rabbits were observed on day 6, at which time the rabbits were terminated to take the abdominal wall tissue from the laparotomy scar. If the rabbit dies before 6 days, it is considered a drop out.

Postoperative day 6, wounds were observed using wound dehiscence gradation system from World Union of Wound Healing Societies (1).

Comparisons between treatment and control group specimens were performed using the Mann-Whitney U non-parametric test. All statistical analyses were carried out using the SPSS version 13.0 data analysis system. p-Values < 0.05 were considered to be statistically significant for all comparisons.

III. Results

Four rabbits were dropped out because of death. Two rabbits, each from control and treatment group, died at two hours and three hours after peritonitis induction (before laparotomy). A rabbit from the control group died on the second post-operative day and a rabbit from the treatment group died on the fourth post-operative day. All rabbits that died after the procedure were evaluated for their intra-abdominal conditions and all of them found that their gastrointestinal organs were intact and there were no leaks. Their deaths were probably due to sepsis as a result of peritonitis. On the 5th post-laparotomy day, specimens were harvested from the laparotomic scar and sent for histopathological examination.

Of all rabbits, in the control and treatment groups, the weight range was between 2100-3100 grams with an average weight of the control group 2500+278.01 grams and the zinc group 2487.50+305.23 grams. Based on statistical calculations, it was found that the distribution of weight data was normally distributed, and the homogeneity test of the subjects with the parametric T-Test test of two independent samples obtained p value = 0.904 and = 0.05. While the age range in this study was 6-9 months with an average age of the control group 7.13 1.09 months and the zinc group 6.94+1.06 months. From the results of the normality test, it was found that the age distribution in this study was not normally distributed, and the results of the homogeneity test with the Mann-Whitney U non-parametric test obtained p values = 0.606 and = 0.05. Based on statistical calculations of the two groups, there were no significant differences in weight and age (table 3.1).

Table 3.1. Sample Characteristics Statics

Group		Zinc	Control	p-value*
Age .	**N**	**16**	**16**	**.606**
	Minimum	**6**	**6**	
	Maximum	**9**	**9**	
	Mean	**6.94**	**7.13**	
	Median	**7.00**	**7.00**	
.	**Std. Deviation**	**1.063**	**1.088**	
	Normality Saphiro-Wilk (Significance)	**.014**	**.04**	
Weight	**N**	**16**	**16**	**.904**
	Minimum	**2100**	**2100**	
	Maximum	**3100**	**3100**	
	Mean	**2487.50**	**2500.00**	
	Median	**2450.00**	**2500.00**	
	Std. Deviation	**305.232**	**278.089**	
	Normality Saphiro-Wilk (Significance)	**.377**	**.297**	

***Homogen when p-value > 0,05**

3.1 Analysis of Wound Dehiscence in Zinc Group Compared to Control

Table 3.2 displayed the results obtained in this study. It turned out that there were no wound dehiscence at all in either the control group or the Zinc group. Using the Mann-Whitney test, we get the p value = .98404, so it could be concluded statistically that there were no significant differences between the two group.

Table 3.2 Wound Dehiscence Results of Control and Zinc Group

	Grade	Control	Zinc	p-value
Wound Dehiscence	0	16	16	.98404
	1	0	0	
	2	0	0	
	3	0	0	
	4	0	0	

* the test using Mann Whitney and considered to be significant/meaningful if the p-value <0.05

IV. DISCUSSION

In the process of wound healing, macronutrients and micronutrients are needed in sufficient quantities to prevent disruption of the wound healing process. The micronutrient needed in almost every stage of wound healing is zinc(3). In the hemostasis phase, zinc plays a role in increasing platelet activity and aggregation which is regulated through Protein kinase C-mediated phosphorylation of platelet protein tyrosine (4). In the inflammatory phase, zinc plays a role in the recruitment and activation of non-specific immune cells to the wound site by inducing the release of alpha-granule platelets which contain a number of pro-inflammatory enzymes so as to initiate the inflammatory phase of wound healing (4). Zinc also affects the activity of several nonspecific immune cells such as neutrophils, monocytes, macrophages, in the process of eliminating bacteria and damaged tissue, cytotoxicity, and apoptosis.

The adaptive immune system that participates in the wound healing process is also influenced by zinc . In the proliferative phase, zinc plays a role in the migration of fibroblasts and keratinocytes to the wound tissue and increases angiogenesis and stem cell activation. In the remodeling phase, zinc plays a role in extracellular matrix remodeling and scar tissue formation (3).

Septic conditions, such as in patients with peritonitis, are known to reduce serum zinc levels by redistributing zinc into the liver (5). While increasing the need for zinc in the peritoneum (6). While in wound healing the need for zinc in the peripheral wound edges increases (3). The relative condition of peripheral zinc deficiency in this condition of peritonitis can interfere with the wound healing process. From previous studies, zinc supplementation in experimental animals with zinc deficiency can accelerate the wound healing process (7).

Oral zinc preparations were preferred over topical considering that the subjects in the study were in peritonitis conditions, the systemic zinc administrations were expected to improve the overall condition of the subjects simultaneously. Although the toxicity of zinc is said to be quite low, from a study it is known that the effect of zinc supplementation depends on the dose of zinc given. Doses above 30 mg/kgbB were said to have a pro-inflammatory effect (8). It could prolong wound healing. In this study, we used a dose of 10 mg/kgBW to avoid the proinflammatory effect of zinc.(4)

In this study, a peritonitis model was used in rabbits that were given zinc supplementation in the treatment group and then performed a comparative analysis of the incidence of wound dehiscence. Four rabbits died in this study. From the examination of the rabbits that died after laparotomy, there was no intestinal perforation in the abdominal cavity. So that the death of the rabbits was most likely due to the sepsis condition they experienced.

There was no difference in the incidence of wound dehiscence between the two groups. Meanwhile, from previous studies (9), zinc was found to play a role in helping wound healing. In that study, zinc was thought to act as a cofactor in activating anti-inflammatory enzymes so as to help wound healing.

Our study failed to demonstrate the role of zinc in lowering the incidence of wound dehiscence. This could be because zinc was not a major factor in the incidence of wound dehiscence. Zinc played a role in wound healing, but in a smaller portion, as a cofactor. Wound dehiscence, that were the extreme point of impaired wound healing, had other factors that were more influential. To better understand the role of zinc in wound healing, further research needed.

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