Very Low Carbohydrate Diet Effect on Modified Glasgow Prognostic Score: A Randomized Controlled Trial on Stage-IV Colorectal Adenocarcinoma Patients

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ABSTRACT

Background: The stage-IV Colorectal adenocarcinoma patients who cannot be treated with any conventional cancer treatment (surgery, chemotherapy, or radiotherapy) belong to the best supportive care group. Very low carbohydrate diet reduces the glucose supply to the cancer cells through the specific metabolic pathway called the Warburg effect. The cancer cell may “starve” and limit the growth that can be measured by the reduction of the systemic inflammation reaction using modified Glasgow Prognostic Score (mGPS). This study aimed to prove that a very low carbohydrate diet may reduce the systemic inflammation score in adenocarcinoma patients with best supportive care.

Methods: Randomized controlled trial of two groups, 12 participants in one group were given the diet of very low carbohydrate for three weeks, and the other 12 participants in control group were given normal diet. All of the participants were given a diet with the amount of calorie according to their respective needs. We measured serum albumin and C Reactive Protein (mGPS) before and after the intervention.

Results: We found statistically significant reduction of modified Glasgow Prognostic Score in the intervention group.

Conclusion: The growth of the stage-IV colorectal adenocarcinoma measured by the systemic inflammation indicators was reduced by giving very low carbohydrate diet.

Key words: best supportive care, stage IV colorectal adenocarcinoma, systemic inflammation, very low carbohydrate diet

INTRODUCTION

There are specific metabolic pathways on cancer cell in utilizing substrate to produce energy, which is known as the Warburg effect. Warburg effect is an aerobic glycolysis in which the cancer cells convert glucose to ATP without Krebs cycle, so the energy product is inefficient. These cancer cells must use more glucose to produce the same amount of energy as normal cells do. Furthermore,

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cancer cells can only use glucose as the source of energy and cannot use other substrates, such as ketone bodies to produce ATP. Many studies have shown that cancer cells have an upregulation of glucose receptors and because of it, almost exclusively dependent on glucose as the source of energy. The shift of the source of energy from glucose to ketone bodies can be tolerated by normal cells but not by cancer cells (1,2,3). Reducing glucose intake and switching caloric source to other nutrients may limit the growth of cancer cells (4,5,6,7).

Very low carbohydrate diet is defined as isocaloric diet with most of the calories based on fat, and normal intake of protein. Most studies use the 1:4 ratio, in which the contribution of carbohydrate was one-fifth of the total caloric requirement. The cells are then forced to use ketone bodies as the main fuel because glucose supply is reduced and ketone bodies are readily available (3,8,9). We can clinically find ketone bodies excreted in the urine. This diet will reduce glucose supply to the cancer cells and prevent the cancer cells from being metabolically active. The reduction of glucose intake will decrease the systemic inflammatory response triggered by the cancer growth (10,11,12). A preliminary study by Schmidt et al showed that the diet is safe without severe side effects and can also improve the quality of life of advanced stage cancer patients who no longer receive conventional therapy (13).

Inflammation can be induced by carcinogenesis by the stimulation of proinflammatory mediators such as TNF alpha, IL-6, and IL-10. Modified Glasgow Prognostic Score has been validated as a measurement of systemic inflammation. This score is also correlated well with the overall survival of many cancers, including gastric, prostate, and colorectal adenocarcinoma (14-19). It is easy to utilize only two laboratory measurements, which are the serum level of albumin and C Reactive Protein. We use this measurement as an indicator of systemic inflammation and as a prognostic factor of survival.

METHODS

Design

This was a randomized controlled trial (RCT) without blinding conducted on the patients with colorectal adenocarcinoma with the best supportive care.

Time and location

The research was conducted at Dr. Soetomo General Hospital Surabaya from March to October 2017.

Sampling and sample size

We recruited 24 stage-IV colorectal adenocarcinoma patients with the best supportive care consecutively at Dr. Soetomo Hospital between March and October 2017 who met our inclusion and exclusion criteria and randomly divided into the treatment group and the control group.

The inclusion criteria are as follows

Diagnosed pathologically as stage-IV adenocarcinoma of the colon or rectum, the decision made by the attending physician (digestive surgery consultant) that the patient belonged to the best supportive care group, aged more than 17 years and be able to give consent, Karnofsky score > 50% or ECOG performance status ≤ 2, no clinical signs of infection based on one or more of criteria: fever, leucocytosis and local infection on clinically observable body region, AST (SGOT) less than 2 times normal limit, ALT (SGPT) less than 2 times normal limit, Creatinine serum less than 1.5 normal limit, for women not pregnant, able and willing to sign informed consent document.

The exclusion criteria are as follows

Diabetes Mellitus, Fat intolerance, Chronic corticosteroid use, severely malnourished patients or patients with cancer cachexia, patients with significant comorbid such as symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, psychosis or other mental problems hindering the ability to obey the study protocol.

The sample size was determined using Iceberg Sim version 4.0.3 Beta Clinical Trial Simulator with the parameter in *fig. 1*. The result was 24 samples, 12 in the control group and the other 12 in the intervention group, with power 80% and alpha 1,4%.

Study protocol

The samples (Serum Albumin and C Reactive Protein) were taken on the 1st and the 21st day. The calorie requirement for the two groups was calculated according to the weight of the patient and the daily composition of the diet was determined by the qualified hospital dietitian. The composition of the diet on the Very Low Carbohydrate Diet group was 1:4 ratio, in which the contribution of carbohydrate was one-fifth and protein plus fat was four-fifth from the total calorie

Figure 1 - Output from Iceberg Sim version 4.0.3 Beta

requirement. While on the control group the calorie and composition of the diet were measured in the same way as those of the common patients in the hospital. As long as the patients were included in the study, the patients were isolated in the hospital to ensure that the patients complied with the diet protocol (fig. 2).

Data analysis

We analyze the data using paired t-test on SPSS.

RESULTS

Our sample includes 14 females (58%) and 10 males (42%) divided into intervention and control groups. In the intervention group, there were 5 women and 7 men, and in the control group, there were 9 females and 3 males (table 1). Based on age, most samples were between 40-65 years old (79,2%) (table 2).

Secondary variables distribution before intervention

We measured the secondary variables to evaluate

the impact on very low carbohydrate diet in liver, renal, and hematologic variables (table 3). Most variables were within normal limit, and all samples met the inclusion criteria.

Primary variables (CRP and Albumin) before intervention

The CRP of the control group was higher than that of

Table 1 - Sample sex distribution

Sex	Intervention	Control	Total	%
Male	7	3	10	42
Female	5	9	14	58
	12	12	24	100

Table 2 - Sample age distribution

	Intervention	Control	Total	%
<40 Years	0	2	2	8,3
40-65 Years	11	8	19	79,2
>65 Years	1	2	3	12,5
	12	12	24	100

Figure 2 - Study protocols

the intervention group, while the mean of albumin level of the control group was lower than the intervention group (table 4).

Secondary Variables Distribution after Intervention

We found a rise in mean SGPT level on the intervention group, while there was no change in the control group (table 5).

Primary variables (CRP and Albumin) after intervention

The mean CRP level in the intervention group was lower than that in the control group, while the albumin level in the intervention group was higher than that in the control group (table 6).

Modified Glasgow prognostic score before and after intervention

There was a reduction in mGPS after intervention in the intervention group, while in the control group, the score increased (table 7).

We tested the normality of mGPS distribution using Kolmogorov-Smirnov, and the test showed normal distribution. On the paired T-test, the result showed that there was a significant difference in the mean of mGPS in both groups (table 8).

Table 3 - Central tendency of secondary variables

Variable	Intervention			Control		
	Min	Max	Mean	Min	Max	Mean
Hb	8,9	13,5	11,7	9	12,4	10,9
Leukosit	4,62	19	9,3	7,5	19,1	12,3
SGPT	10	58	27	11	27	19
SGOT	16	66	30	18	66	28
BUN	6	20	12	7	30	17
Creatinine Serum	0.58	1.2	0.86	0.4	1.1	0,7

Table 4 - Central tendency of albumin and CRP before intervention

Variable	Intervention			Control		
	Min	Max	Mean	Min	Max	Mean
CRP	0,1	16	6,2	7,5	22	16,8
Albumin	3,2	4,5	3,7	2,1	3,9	3,0

Table 5 - Central tendency of secondary variables after intervention

Variable	Intervention			Control		
	Min	Max	Mean	Min	Max	Mean
CRP	0,1	16	6,2	7,5	22	16,8
Hb	8,9	14,4	11,2	8,8	12,5	11
Leukocyte	6,29	17,5	10,1	7,8	40	8,5
SGPT	12	125	37	14	23	19
SGOT	15	206	46	12	65	28
BUN	0.9	23	14,3	7	29	17,7
	0.5	1.1	0,8	0,3	1	0,69

Table 6 - Central tendency of albumin and CRP after intervention

Variable	Intervention			Control		
	Min	Max	Mean	Min	Max	Mean
CRP	0,1	9	4,17	9	26	18,2
Albumin	3,1	4,6	3,8	2,3	3,8	2,9

Table 8 - T-test results of mGPS in intervention and control group

Group	Pairs	t	df	p
Intervention	mGPS Pre and Post	1,820	11	0,043*
Control	mGPS Pre and Post	-1,915	11	0,04*

* significant in the level of 95%

Table 7 - mGPS before and after Intervention

	Intervention		Change	Control		Change
	Pre	Post		Pre	Post	
mGPS	0,58	0,17	-0,41	1,5	1,75	0,25

DISCUSSION

Very low carbohydrate diet is the diet that shifts the main source of energy from glucose to ketone (3, 8, 9). The diet is extensively used in pediatric epilepsy cases to reduce seizures, (3,20,21) and also beneficial to brain tumor cases (22, 23). Carcinogenesis and cancer growth are connected to local and systemic inflammation (24-26). The reduction in glucose consumption will also reduce systemic inflammation (10-12).

Our data showed that very low carbohydrate diet reduced systemic inflammation as measured with mGPS on colorectal adenocarcinoma patients with Best Supportive Care. This reduction did not happen in the control group but instead, there was an increase of the systemic inflammatory reaction. The best supportive care samples were recruited in this study because there was no other treatment such as surgery, chemotherapy, or radiotherapy given to the patient, so the changes in themGPS were mainly because of the intervention we gave. Pantano et al showed that in cancer patients with palliative care, higher mGPS score was related to more aggressive cancer and worse survival (27). Other studies also showed that mGPS predicted survival in colorectal cancer patients who underwent curative hepatectomy (28). mGPS also predicts earlier mortality in colorectal cancer with peritoneal carcinomatosis in cancer patients who undergo chemotherapy (29).

Our measurements of secondary variables which monitored the liver, renal, and hematologic function showed that the diet increased SGOT and SGPT, although the overall change was not statistically significant. Nevertheless, one patient showed more than twofold increase at the end of the study. Ballaban-Gil et al found that this diet increased liver function test, but a review by Lin et al after that study showed that liver toxicity happened because of concurrent drug given to the study population

(30,31). Ketonuria was measured to ensure that the patients in the treatment group had already been able to use ketone as the source of energy and all of them positive for ketonuria on the 3th and the 21st day. We cannot do this study for more than 21 days because we have found it impossible to isolate the patients in the hospital longer than that period.

Renal function did not show significant change before and after the diet. The other study in 317 children showed that this diet may increase the incidence of urinary tract stone, with the frequency of less than 5% (21).

CONCLUSION

From this study, it could be concluded that very low carbohydrate diet given for three weeks increased the albumin level and reduced CRP level in stage-IV colorectal adenocarcinoma patients with best supportive care. Very low carbohydrate diet also reduced Modified Glasgow Prognostic Score used as the indicator for systemic inflammation in these patients. Moreover, very low carbohydrate diet apparently did not cause significant effect in liver and renal function after three weeks in stage-IV colorectal adenocarcinoma patients with best supportive care.

Ethical clearance

This RCT is cleared ethically by the Ethics Committee of Dr. Soetomo Hospital Surabaya Indonesia with ethical clearance letter no. 293/Panke.KKE/IV/2017.

Conflict of interest

The authors declare that they have no conflict of interest.

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