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Effect of Preoperating Maltodextrin 12.5% Carbohydrate Drink on High Sensitive C Reactive Protein Levels Post-Brachytherapy

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ABSTRACT

Background: Brachytherapy is radiation therapy that will cause inflammation and tissue damage that leads to inflammation, characterized by the release of pro-inflammatory cytokines, including hs-CRP levels in the plasma. Preoperative administration of glucose solution is known to reduce the increase in cortisol, and is thought to reduce postoperative hs-CRP levels. So far there has been no research that specifically examines the effect of preoperative carbohydrate administration on hs-CRP values after brachytherapy. This study aims to determine the effect of preoperative carbohydrate administration on post-brachytherapy hs-CRP values.

Subjects and Method: This study was designed a double-blind randomized controlled trial was conducted at the Radiotherapy Unit of Dr. Moewardi General Hospital, Surakarta, from April to September 2022. Sixty-four cervical cancer patients with ASA physical status I or II undergoing brachytherapy under general anesthesia were recruited using consecutive sampling. Participants were randomly assigned into two groups: an intervention group receiving 12.5% maltodextrin solution and a control group receiving mineral water. The independent variable was preoperative carbohydrate administration, and the dependent variable was hs-CRP level measured 2 hours before and 4 hours after brachytherapy. Data were analyzed using paired t-test

Results: Post-brachytherapy hs-CRP levels were significantly lower in the treatment group (mean = 2.565 ± 2.0 mg/dL) compared to the control group (mean = 3.69 ± 2.58 mg/dL; $p = 0.019$). Both groups showed significant increases in hs-CRP from pre- to postoperative values ($p < 0.001$). The change in hs-CRP (Δhs-CRP) was also significantly lower in the treatment group ($p = 0.025$).

Conclusion: The administration of maltodextrin was able to significantly reduce post-brachytherapy hs-CRP levels compared to placebo.

Keywords: Carbohydrates, Brachytherapy, hs-CRP, Inflammation, Maltodextrin

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BACKGROUND

Brachytherapy is an internal radiation therapy involving the placement of radio-active sources close to malignant tissues (Tanderup et al., 2017). This method delivers a high dose of radiation with limited penetration to protect surrounding healthy tissue, resulting in relatively mild tissue damage compared to surgical procedures (Maranzano et al., 2019; Gabani et al., 2018). However, brachytherapy still causes tissue damage, leading to inflammation and

the release of proinflammatory cytokines, including elevated high-sensitive C-reactive protein (hs-CRP) levels in plasma (Reichstein, 2015; Zhou et al., 2024). Monitoring hs-CRP after brachytherapy is important for assessing the inflammatory response to the treatment.

C-reactive protein (CRP) is a classic acute-phase inflammatory protein with a homo-pentameric structure, whereas hs-CRP shares the same characteristics but has higher analytical sensitivity to detect even low CRP levels (Sproston et al., 2018). CRP is widely used as a biomarker of acute or chronic inflammation. CRP levels are known to rise significantly in response to infection, inflammation, and tissue injury, including surgery (Straatman et al., 2016; Zhou et al., 2024). Therefore, understanding factors that influence hs-CRP levels is critical in managing postoperative recovery after brachytherapy.

Preoperative carbohydrate intake has been shown to reduce inflammation associated with surgical injury and stabilize postoperative blood glucose levels compared to patients who fast preoperatively (Widnyana et al., 2017; Smith et al, 2014). Previous research demonstrates that carbohydrate supplementation before surgery can accelerate recovery and reduce metabolic stress caused by surgical trauma (Li et al., 2012). Given these benefits, preoperative carbohydrate drinks may positively affect the inflammatory response following brachytherapy.

Additionally, glucose regulation affects CRP levels; higher fasting or post-load glucose concentrations are associated with increased CRP, especially in diabetic patients (Doi et al., 2005). This suggests that managing blood glucose through appropriate carbohydrate administration may help modulate inflammation.

Based on explanation mentioned above, administration of preoperative carbohydrate drinks may accelerate recovery and improve the patient's condition post-brachytherapy by assessing levels of hs-CRP as one of inflammatory parameters. To our knowledge, there has been no research conducted to examine the effect of preoperative carbohydrate administration on post-brachytherapy hs-CRP levels. Thus, this study aims to determine the effect of preoperative carbohydrate administration on post-brachytherapy hs-CRP levels.

SUBJECTS METHOD

1. Study Design

This study design was double-blind randomized controlled trial and conducted between April 2022 to September 2022 in Radiotherapy Installation Dr. Moewardi General Hospital Surakarta, Indonesia.

2. Population and Sample

The target population of the study were patients with cervical cancer who would undergo brachytherapy using spinal anesthesia at the Radiotherapy Installation of Dr. Moewardi General Hospital Surakarta. Non-probability sampling with consecutive sampling technique was used to recruit study subjects who met the inclusion criteria for a certain period of time until the required number of subjects was met. Based on the calculation, minimum sample size of the study was 64 patients and will be randomly divided into two groups. The group that received maltodextrin is called the treatment group while the group that received a placebo is called the control group, consist of 32 subjects for each group. The inclusion criteria of this study were: (1) female patient undergoing brachytherapy; (2) patient aged 18–60 years; (3) BMI 18.5 - 24.9; (4) ASA I or ASA II physical status; (5) have no history of carbohydrate allergy or intolerance to any carbohydrate pro-

ducts; (6) willing to participate in the research and sign informed consent form. Smoker patient and patients with a history of diabetes mellitus, coronary heart disease, decreased kidney function were excluded from the study. Patients requiring intubation and patients who withdraw from the study were dropped out for further analysis.

3. Study Variables

The independent variable from this study was Maltodextrin administration and the dependent variables were hs-CRP levels pre and post-brachytherapy.

4. Operational Definition of Variables

Maltodextrin administration is administration of 400 mL Maltodextrin drink while placebo consist of 400 mL mineral water, packed in identical bottles.

hs-CRP level is acute phase protein and commonly used as sensitive biomarker of tissue damage and systemic inflammation. hs-CRP levels were measured 2 hours before and 4 hours after the brachytherapy.

5. Study Instruments

Study instruments consist of informed consent form, personal data form, 400 mL mineral water, 400 mL maltodextrin 12.5%, spinal anesthetic drugs (Levobupivacaine 15 mg and Fentanyl 25 mcg), and emergency drugs. The outcome measures included hs-CRP levels will be carried out from the venous blood samples then examined in the laboratory.

6. Data analysis

Observed and primary data were recorded on the form provided, then statisticaly analyzed. Data analysis was performed using IBM SPSS Statistics Ver.22 for Windows (IBM Corp., Armonk, NY, USA). Statistical analysis was used to measure the effectiveness of 12.5% Maltodextrin administration using paired t-test.

7. Research Ethics

Research ethical issues including informed consent, anonymity, and confidentiality, were addressed carefully during the study process. Ethical consideration of this study has been reviewed and approved by the Research Ethics Committee of Dr. Moewardi General Hospital/Faculty of Medicine Universitas Sebelas Maret, Surakarta, Indonesia with unique registration ID number 841/VI/HREC/2022.

RESULTS

1. Sample Characteristics

The normal distribution of the variables was evaluated using visual (histogram and probability graphs) and analytical (Kolmogorov-Smirnov test and Shapiro-Wilk test) methods. A descriptive analysis was performed using frequency tables for the categorical variables. Means and standard deviations were used to describe the normally distributed variables. Medians and inter quartil ranges (IQR) were used to describe the variables with a non-normal distribution. To assess differences between groups, the Mann-Whitney test for continous data were used in bivariate analysis.

Table 1. Sample characteristics (continous data)

Characteristics	Group		p
	Control group (n= 32)	Treatment (n= 32)	
Age	55±9.5[a] (47-62)	54.50±10.5[a] (46-62)	0.814
BMI	19.92±2.68[a] (18.2-22.76)	20.62±1.26[b] (18.3-22.98)	0.184

Over the study period, 64 subjects with cervical cancer who underwent brachytherapy with subarachnoid block anesthesia in Radiotherapy Installation Dr. Moewardi General Hospital were included in the study, leaving no subject into drop-out criteria. Median age of patients in the control group was 55; IQR= 9.5 years, and the median age in the treatment group was 54.50; IQR= 5.38 years; p= 0.814. The body mass index (BMI) of patients in the control group had a median of 19.92; IQR= 2.68 kg/m2 while the treatment group had an average BMI of 20.62; SD= 1.26 kg/m^2; p= 0.184. Based on the description above, subject characteristics based on age and BMI are not significantly different between the control and treatment groups, indicating the data is homogeneous and can be compared (Table 1).

2. Bivariate Analysis

Shapiro Wilk Test was used to assess normality of hs-CRP level in preoperative, postoperative, and the difference in hs-CRP level. Since the data did not pass the normality test, we used a non-parametric test (Mann-Whitney test) to compare the control group and the treatment group hs-CRP level. Wilcoxon test was performed to compare preoperative and postoperative hs-CRP level in each group (Table 2).

Table 2. Hs-CRP Difference Test Between Treatment and Control Groups

Variable	Group		p
	Control group (n= 32)	Treatment group (n= 32)	
Hs-CRP preoperative	1.615 (SD= 0.51)	1.52 (SD= 0.58)	0.846
Hs-CRP postoperative	3.69 (SD= 2.58)	2.57 (SD= 2.0)	0.019
Δ Hs-CRP	1.91 (SD= 1.63)	1.32 (SD= 2.08)	0.025

Preoperative hs-CRP (baseline) in the control group had a median of 1.615; IQR= 0.51 mg/dL, while those in the treatment group had a median of 1.52; IQR= 0.58 mg/dL; p= 0.846. Postoperative hs-CRP Mann-Whitney test shows a significant difference (p = 0.019) between the control group (median= 3.69; IQR= 2.58 mg/dL) and the treatment group (median= 2.565; IQR= 2.0 mg/dL), indicating statisticaly lower hs-CRP level in the group given preoperative maltodextrin 12.5%.

Hs-CRP scattered boxplot (Figure 1) showed that the baseline hs-CRP levels in the control and treatment groups was not different statistically (1.615 mg/dL vs 1.52 mg/dL), while postoperative hs-CRP level showed higher median differences between the control and treatment groups (3.69 mg/dL vs. 2.56 mg/dL). Wilcoxon test indicates that both the treatment group and the control group experienced a significant increase in hs-CRP level (p<0.001, respectively). However, subjects in the treatment group experienced a lower increase in hs-CRP compared to the control group (p= 0.019). Δ hs-CRP in treatment group were also lower (Median= 1.32; IQR= 2.08 mg/dL) compared to control group (Mean= 1.91; SD= 1.63 mg/dL; p= 0.025).

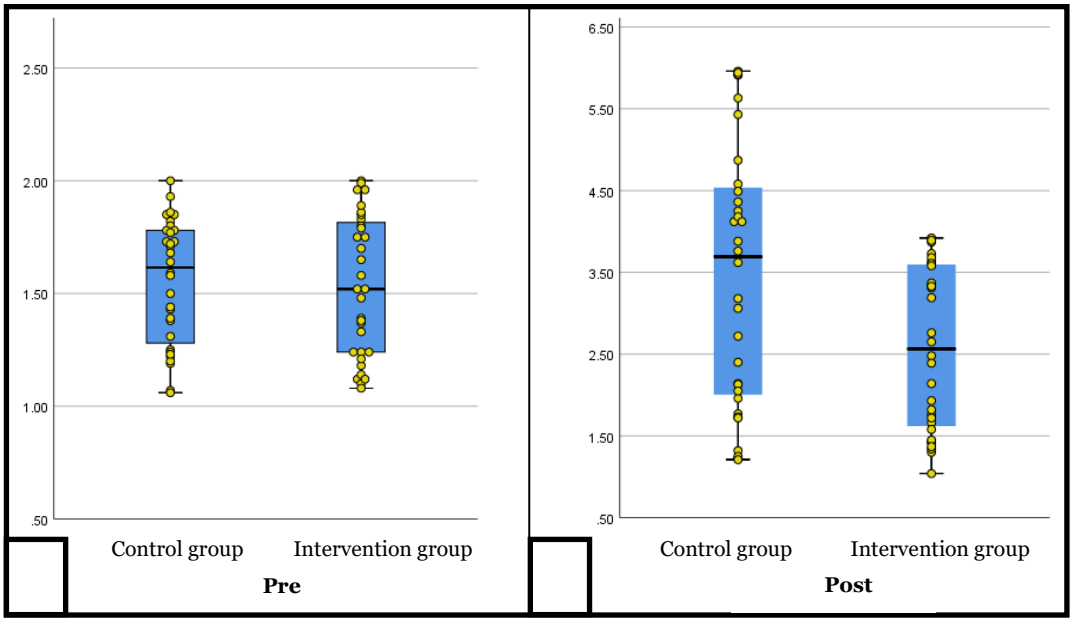

Figure 1. Hs-CRP Scattered Boxplot between Treatment and Control Group. Description: A) Baseline hs-CRP levels; B) Postoperative hs-CRP levels.

DISCUSSION

In this study, median age of control group was 55; IQR= 9.5 years, and the median age of the treatment group was 54.50; IQR= 5.38 years. Study by Han et al. (2013) in 4,669 female patients with cervical cancer who underwent brachytherapy procedures reported mean age of 54; SD= 14 years. This result share the same characteristic as data according to Cancer Research UK (2022) where the average age at diagnosis of cervical cancer is 50 years.

Hs-CRP level difference were significantly different between control group (Median= 1.32; IQR= 2.08 mg/dL) and treatment group (Median= 1.91; IQR= 1.63 mg/dL; p=0.025). The results were within the previously reported studies. A randomized pilot study showed that preoperative administration of maltodextrin 12.5% 2 hours preoperatively resulted higher CRP level in 4 hours post-operative compared to control group (Mean= 80.6; SD= 10.9) vs (Mean= 66.5; SD= 16.4 mg/L; p<0.01), with baseline CRP values were not significantly different between the two groups (Alito and de Aguilar-Nascimento, 2016). Study by Tavalee et al. (2022) regarding clinical outcomes and metabolic responses after preoperative dextrose administration on patients underwent laparoscopic cholecystectomy showed significant reduction in insulin resistance, CRP, CRP to albumin ratio, and cortisol levels while baseline CRP was not much different between the two groups (p<0.05). Preoperative maltodextrin administration were associated with lower length of hospital stay while control group were associated with higher hs-CRP/albumin ratio (p=0.04) (Pexe-Machado, 2013).

An RCT that examined the effect of preoperative carbohydrate administration supplemented with whey protein on the acute phase response and postoperative insulin resistance showed a significant decrease in CRP elevation and CRP to albumin ratio in the group receiving preoperative carbohydrate and whey protein (p<0.05). The proportion of patients show-

ing normal CRP to albumin ratio was significantly greater in the group receiving carbohydrates and whey protein (87.5%) than in the control group (33.3%) , p<0.05 (Perrone *et al.*, 2011). Besides, administration of preoperative carbohydrates and protein nutrition reduces postoperative thirst and hunger, resulted in increased albumin levels, decreased CRP concentrations, and blood glucose fluctuations (Deng *et al.*, 2020).

A meta-analysis showed that preoperative administration of carbohydrate drinks showed advantages in reducing PONV, reducing insulin resistance and increasing insulin sensitivity, decreasing CRP, and reducing postoperative hospital stay compared to fasting patients (Ricci *et al.*, 2022). Another RCT showed that patients who received preoperative carbohydrate nutrition supplemented with antioxidant vitamin C had lower postoperative CRP and IL-6 level, as well as higher albumin than the fasting group, p=0.01 (Rizvanovic, 2019).

However, there were some studies that share contrast results with this study as well as other literature. A study showed CRP levels measured at 2 hours preoperatively and 4, 6, 24 hours postoperatively were higher in intervention group who received maltodextrin. This can be affected by higher mean baseline CRP level 2 hours preoperatively in the intervention group compared to control group (Mean= 9.37; SD= 15.68 vs Mean= 3.11; SD= 3.12; p= 0.028) (Gumus and Aydin, 2020). This shows that it is important to compare the mean CRP baseline of the two groups to reduce bias. In our study, the two groups had almost the same baseline level (Median= 1.53; IQR= 0.31 vs Median= 1.55; IQR= 0.27; p=0.846).

The results of this study also showed a significant difference in hs-CRP level before and after brachytherapy procedure in both groups (p<0.001), indicating that brachytherapy is still able to induce an inflammatory response although minimally invasive. Another study also showed increased IL-6 serum level at 24 and 48 hours after the brachytherapy procedure. The increased level of these cytokines most likely reflect collateral damage of normal cervical epithelial cells in the brachytherapy procedure (Wickremesekera *et al.*, 2001). Instead of damage to normal tissue due to brachytherapy, increased hs-CRP level were also associated with absence of intake during perioperative fasting.

Preoperative fasting activated the inflammatory system, characterized by increased proinflammatory cytokines including IL-6, TNF-α, and hs-CRP. Administration of carbohydrates such as maltodextrin will change the patient's metabolic status from the fasting state to the fed state, resulted in reduction of the inflammatory system marked by lower level of pro-inflammatory cytokines compared to placebo group (Feng *et al.*, 2022).

This study has several limitations. First, only one dose of maltodextrin solution was used, with no addition of other metabolically beneficial substances to reduce post-brachytherapy hs-CRP level. Secondly, measurement of other proinflammatory cytokines was not carried out in this study and only performed once (4 hours after the procedure), causing measurement of the extended reduction effect of proinflammatory cytokines from maltodextrin administration was not completely followed. However, this study is the first study in Indonesia which compares the hs-CRP levels of post-brachytherapy patients between maltodextrin 12.5% group and control group.

In conclusion, in this study we found that preoperative administration of 12.5%

maltodextrin showed beneficial effects on post-brachytherapy patients, where the group given maltodextrin showed lower hs-CRP levels. These results can be taken into consideration as one of Enhanced Recovery After Surgery (ERAS) component before brachytherapy procedure in order to improve the patient's quality of life and outcome.

AUTHOR CONTRIBUTIONS

Purwoko raised the initial research question, planned study design, managed data collection, data analysis, manuscript revision and finalization. Ardana Tri Arianto refined research questions, planned study design, managed data collection, data analysis, manuscript revision and finalization. Eka Satrio Putra planned study design, managed data collection, planned and ran statistical analysis, interpreted results, drew tables and graphs, wrote up manuscript, manuscript revision and finalization. Frederick Johan Purnomo managed data collection, planned and ran statistical analysis, interpreted results, wrote up manuscript, manuscript revision and finalization.

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CONFLICT OF INTEREST

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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