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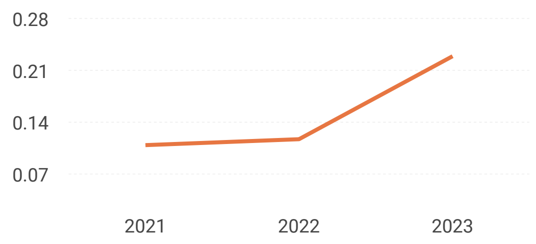

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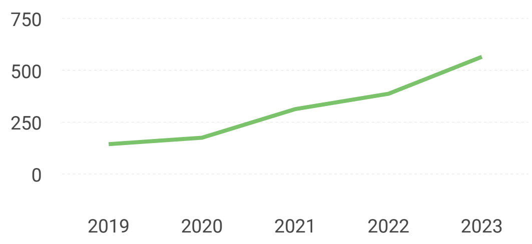

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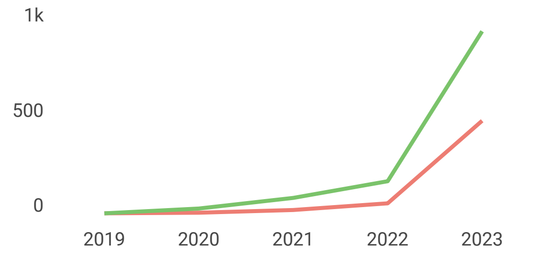

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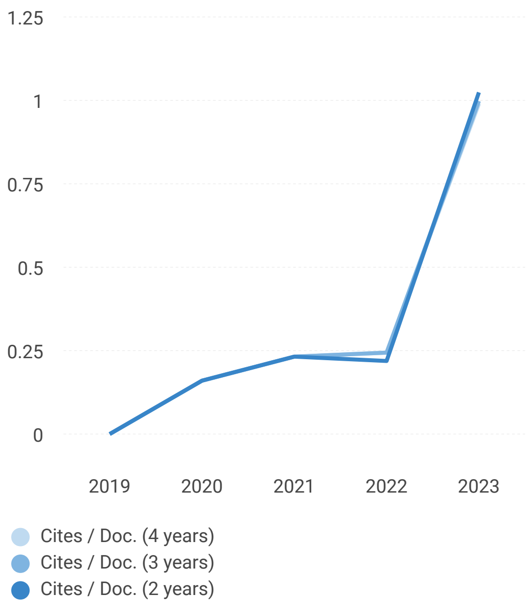

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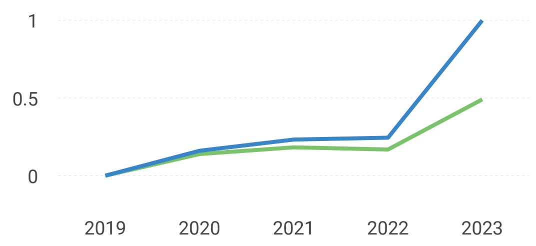

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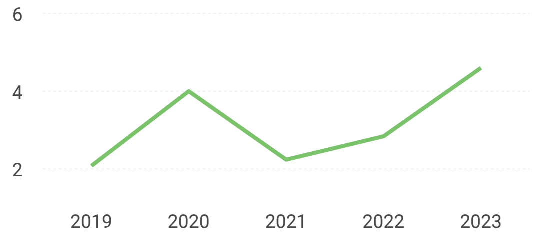

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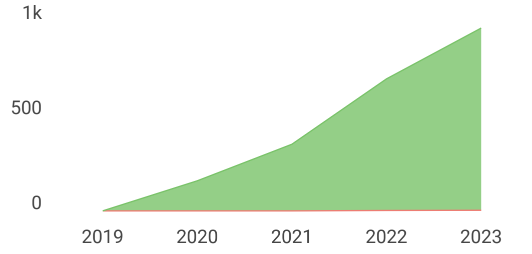

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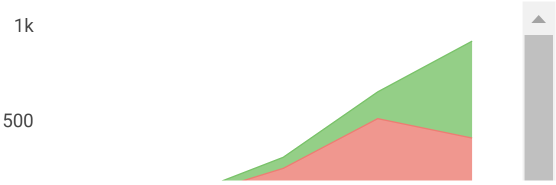

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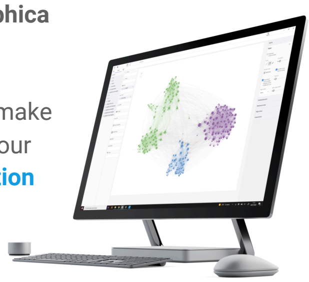

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The role of transdermal carbon dioxide on changes in malondialdehyde levels as a marker of ischemia-reperfusion injury in patients with placenta accreta spectrum underwent temporary abdominal aortic cross-clamping as an adjunct procedure during cesarean hysterectomy

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ABSTRACT

Background: Temporary abdominal aortic cross-clamping is often applied as an adjunct procedure to control bleeding in patients with placenta accreta spectrum during cesarean hysterectomy. It is claimed to reduce the blood loss need for transfusion and improve visualization of the operating field. After the cross-clamp is removed, the tissue distal to the occlusion, which was initially in an ischemic state, gets a sudden blood flow causing ischemia-reperfusion injury due to the release of ROS. Transdermal administration of carbon dioxide is expected to reduce the release of ROS through the Bohr Effect to protect against ischemia-reperfusion injury, which can be seen from the level of malondialdehyde.

Method: This experimental study recruited all patients with placenta accreta spectrum who underwent temporary abdominal aortic cross-clamping during cesarean hysterectomy from January to June 2022. Subjects were divided into control groups and treatment groups. The treatment group was given transdermal CO_2 immediately after the aortic cross-clamp was removed. The plasma MDA levels were examined before and after aortic cross-clamping.

Results: The number of subjects in each group was 7 subjects. There was an increase in MDA levels from 19.779$\pm$0.870nmol/ml to 21.104$\pm$1.053nmol/ml after cross-clamp in all groups, with an average increase of 1.325$\pm$0.801nmol/ml (p=0.00). The treatment group that received transdermal CO_2 had a lower tendency to increase MDA levels, 1.063$\pm$0.803nmol/ml, compared to the control group at 1.586$\pm$0.766nmol/ml.

Conclusion: There was an increase in MDA levels as a predictor of ischemia-reperfusion injury in patients undergoing temporary abdominal aortic cross-clamping. The administration of transdermal CO_2 tends to suppress ischemia-reperfusion injury.

Keywords: malondialdehyde, placenta accreta spectrum, temporary abdominal aortic cross-clamping, transdermal carbon dioxide.

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INTRODUCTION

The placenta accreta spectrum is defined as the abnormal invasion of trophoblast on one part or all parts of the placenta into the myometrial layer of the uterine wall, which results in a placenta that is morbidly adherent to the uterine wall. As a consequence of the morbidly adherent placenta, the risk of hemorrhage, which prompts blood transfusion and peripartum hysterectomy, increases.[1] According to a systematic review by Jauniaux et al, the prevalence of placenta accreta spectrum is 0,17% (95% CI, 0,14 – 0,19), with 0,5 (95% CI, 0,3 – 0,36) per 1000 birth and 0,3 (95% CI, 0,2 – 0,4) per 1000 birth as the prevalence for adherent grade and invasive grade, respectively. The incidence of hemorrhage requiring blood transfusion is 46,9% (95% CI, 34 – 66,4), whereas the incidence of peripartum hysterectomy is 52,2% (95% CI, 38,3 – 66,4). Estimated maternal mortality on placenta accreta spectrum is 0,05% (95% CI, 0,06 – 0,69).[2] In our center at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, placenta accreta spectrum disorder was increased in the last 6 years. The prevalence was 1% in 2015, 4% in 2017, and increased to 6% in 2019.[3,4] Extensive bleeding in the placenta accreta spectrum is hypothesized to be caused by the development of extensive intrapelvic vascular anastomosis by arteries to the gravid uterus.

A clear and dry surgical field is important to properly perform surgery and minimize operative blood loss. This can be achieved by reducing uteroplacental blood flow. Cross-clamping of the abdominal aorta is one of the techniques to reduce uteroplacental blood flow.[5] Temporary aortic cross-clamp is often applied as an adjunct procedure to control bleeding in patients with placenta accreta during cesarean hysterectomy. It is claimed to reduce the blood loss need for transfusion and improve visualization of the operating field. After the cross-clamp is removed, the tissue distal to the occlusion, which was initially in an ischemic state, gets a sudden blood flow causing ischemia-reperfusion injury due to the release of ROS.

Visceral ischemia and reperfusion injury are significant side effects of the aortic cross-clamp.[6] In a state of prolonged ischemia, tissue reperfusion can be accompanied by inflammation that results in tissue cell damage and death.[7] During aortic cross-clamping, an ischemic condition occurs. After the aortic cross-clamp is opened, the distal tissue from the occlusion, which was initially in an ischemic state, gets sudden blood flow (reperfusion), causing ischemia-reperfusion injury.

The most widely accepted molecular mechanism underlying the occurrence of ischemia-reperfusion injury is an increase in Reactive Oxygen Species (ROS).[8] Tissue damage that occurs due to reperfusion begins with the release of ROS. The imbalance between increased ROS and the ability to neutralize free radicals by antioxidant defense causes oxidative stress.[8] ROS will then affect lipid degradation, and this can be seen in the final product, such as the detection of Malondialdehyde.[9]

Malondialdehyde (MDA), a three-carbon chain with a low molecular weight aldehyde, is one of the end products of the peroxidation of polyunsaturated fatty acids in cells.[9-11] Malondialdehyde levels are generally recognized as markers of oxidative stress.[9] ROS causes cell damage by negatively affecting antioxidant defense mechanisms by reducing superoxide dismutase (SOD) levels and increasing MDA levels by inflammatory processes mediated by tumor necrosis factor-alpha (TNF-α).[12] The increase in free radicals leads to an overproduction of MDA.

Several studies have demonstrated a significant effect of using transdermal CO_2 on microcirculation.[13,14] Carbon dioxide therapy refers to the transdermal application of CO_2 for therapeutic purposes with the effect of increasing O_2 pressure in tissues, known as the 'Bohr effect'.[14,15] Following the 'Bohr Effect,' there is an increase in oxygen delivery to the tissues due to CO_2 and Hydrogen, which shifts the Oxygen-Hemoglobin dissociation curve, thus forcing O_2 to be released from hemoglobin and consequently increasing the amount of O_2 in the tissues.[16] CO_2 is believed to be a strong inhibitor of ROS through inhibition of the activity of NADPH-oxidase.[17] Transdermal administration of CO_2 is expected to reduce ROS production through the Bohr Effect so that there is protection against the incidence of ischemia-reperfusion injury, which can be seen from MDA levels.

The purpose of this study was to determine changes in MDA levels as a predictor of ischemia-reperfusion injury in patients undergoing temporary abdominal aortic cross-clamping and to determine the effect of transdermal administration of CO_2 as a protective factor for ischemia-reperfusion injury.

METHOD

Study design

This is a clinical trial study of patients with placenta accreta spectrum who underwent temporary abdominal aortic cross-clamping. Subjects were divided into control groups and treatment groups. The treatment group was given transdermal CO_2 immediately after the aortic cross-clamp was removed. Randomization is done by order. Blinding is performed on the patient and the outcome assessor. The patient did not know the treatment received. MDA levels were checked by laboratory staff who did not know the treatment group. The ethical clearance was approved by Ethics Committee in Health Research Dr. Soetomo Academic General Hospital number 0319/KEPK/XII/2021 on December 1st, 2021.

Subject

This study recruited all patients with placenta accreta spectrum who underwent temporary abdominal aortic cross-clamp during cesarean hysterectomy from January 2022 to June 2022 at Dr.Soetomo General Academic Hospital Surabaya, Indonesia. The inclusion criteria were patients with placenta accreta who were diagnosed with placental accreta index (PAI) based on the results of ultrasonography performed by obstetrics and gynecology specialists at Dr. Hospital. Soetomo Surabaya underwent temporary abdominal aortic cross-clamping as an adjunct procedure during a cesarean hysterectomy. Patients with severe comorbid disorders such as chronic kidney disease, heart disease, patients with septic shock and sepsis, patients with peripheral artery disease, and patients with pneumonia covid-19 were excluded.

Treatment Protocol

The patients were put under general anesthesia. The blood samples for MDA I (basal) were collected after anesthesia. The surgical approach was obtained by median laparotomy. A midline or transversal fundal incision is performed to deliver the baby. The umbilical cord was clamped and ligated at the placenta end, and the hysterotomy wound was clamped with forceps. The obstetrician then evaluated the segment involved by the abnormality accreta to determine whether to perform a hysterectomy or a uterine conservative resection surgery. The temporary abdominal aortic cross-clamping was performed by a cardiovascular surgeon if a hysterectomy was planned.

The retroperitoneum between the inferior mesenteric artery and aortic bifurcation was opened. The uterus was pushed downward for a better surgical field. The intestine was retracted by a Deaver retractor and big gauze to expose retroperitoneal fascia. After dissecting the tissue surrounding the aorta, a right-angled was used to place a vessel loop under the aorta avoiding injury to lumbar vessels. Unfractionated heparin 2500 I.U. was administered through the peripheral intravenous line. The vessel loop was used to lift the aorta. The aorta was clamped with a professional atraumatic flexible cardiovascular clamp.

After completion of the hysterectomy procedure, the aortic cross-clamp was removed, and bleeding was evaluated. Transdermal CO_2 is immediately given to the thumb with a D'Oxyva device at a dose of 16g for 2-5 minutes. Then a second MDA II blood sample (reperfusion) was collected after 60 minutes after reperfusion.

Laboratory test

The blood was collected preoperative (basal) and 60 minutes after abdominal aortic cross-clamp off, and the plasma MDA levels were measured. Blood samples were centrifugated to separate the serum from the blood. The separated serum was then stored at -70oC for later examination of MDA using the thiobarbituric acid method. The MDA concentration was measured by the spectrophotometric method for the reaction with thiobarbituric acid reactive substances (TBARS).

Data collection and analysis

The data were presented in mean and standard deviation (S.D.) and then tested using the Kolmogorov-Smirnov normality test to assess the normality of the data. Paired t-test was used to determine the differences in MDA level before and after the temporary aortic cross-clamp. Independent t-test (2-tailed) was used for data with normal distribution, and Mann-Whitney (2-tailed) was used for data with non-normal distribution to compare the difference between the control and treatment groups. All data analysis was carried out in SPSS v23.

RESULT

From January to June 2022, there were 38 patients diagnosed with placenta accreta based on preoperative ultrasonography, and 15 patients (39,4%) underwent temporary abdominal aortic cross-clamping as an adjunct procedure for bleeding control during cesarean hysterectomy. One patient was excluded because of comorbid pneumonia covid-19. The number of subjects who were successfully recruited was 14 patients. The number of subjects who were successfully recruited was 14 patients. The demographic characteristics of the patients are presented in Table 1. It can be seen that both control and treatment groups have comparable characteristics, so it can be concluded that both groups have the same prognostic and confounding factors.

Based on the surgical variables in Table 2, it appears that both control and treatment groups also have comparable characteristics, so it can be concluded that both groups have the same prognostic and confounding factors. The vascular control with temporary abdominal aortic cross-clamping was mostly used in percreta

Table 1. Patient Characteristic.

Demographic	Treatment group (n=7) Mean (S.D.)	Control group (n=7) Mean (S.D.)
Age	31.57 (3.55) years	36.14 (3.34) years
Weight	69.00 (5.77) kg	66.14 (7.22) kg
Height	154.29 (3.15) cm	155.71 (2.56) cm
Number of Pregnancy	4.0 (1.73) times	4.14 (1.46) times
History of cesarean delivery	1.71 (0.76) times	1.71 (0.49) times

Table 2. Operative Variable.

Operative Variable	Treatment group (n=7)	Control group (n=7)
Placenta invasion type*		
Accreta	0	0
Increta	2 (28.57%)	2 (28.57%)
Percreta	5 (71.43%)	5 (71.43%)
FIGO grading*		
Grade 1	1 (14.29%)	0
Grade 2	1 (14.29%)	0
Grade 3A	2 (28.57%)	2 (28.57%)
Grade 3B	2 (28.57%)	4 (57.14%)
Grade 3C	1 (14.29%)	1 (14.29%)
PAS staging*		
PAS 1	2 (28.57%)	1 (14.29%)
PAS 2	1 (14.29%)	2 (28.57%)
PAS 3	4 (57.14%)	4 (57.14%)
Segment involved*		
Segment 1	2 (28.57%)	2 (28.57%)
Segment 2	5 (71.43%)	5 (71.43%)
Aortic Cross-Clamp duration**	61.43 (15.74) minutes	70.71 (28.79) minutes
Estimated Blood Loss**	2,435.71 (1,367.70) ml	2,807.14 (1,241.78) ml

***n(%)**
****mean(SD)**

Table 3. Malondialdehyde level in all group.

n=14	Mean	SD	P
MDA 1 (basal), nmol/ml	19.779	0.870	0.00*
MDA 2 (reperfusion), nmol/ml	21.104	1.053	

***Paired-T test (2-tailed)**

Table 4. Malondialdehyde level between group.

	Treatment group (n=7) Mean(S.D.)	Control group (n=7) Mean(S.D.)	P
MDA 1 (basal), nmol/ml	20.220 (0.543)	19.377 (0.943)	0.053*
MDA 2 (reperfusion), nmol/ml	21.283 (1.034)	20.923 (1.121)	0.544*
ΔMDA, nmol/ml	1.063 (0.803)	1.586 (0.766)	0.402**

***Independent-T test (2-tailed)**
****Mann-Whitney (2-tailed)**

Table 5. Secondary outcome.

	Treatment group (n=7) Mean(S.D.)	Control group (n=7) Mean(S.D.)	P
Intubation time, hours	14.82 (8.42)	17.89 (19.65)	0.803**
Hospital length of stay, days	7.86 (3.13)	6.71 (2.14)	0.531**
Mortality	0	0	-
Hemoglobin, gram/dL	9.46 (1.13)	8.04 (1.83)	0.685**
Haematocrit, %	29.04 (3.61)	25.30 (6.42)	0.779**
White Blood Cell count, 10^3/uL	17,695 (6,138)	14,641 (7,588)	0.424*
Platelet count, 10^3/uL	173,000 (81,973)	145,428 (108,669)	0.602*
Albumin, gram/dL	2.86 (0.28)	2.64 (0.37)	0.224*

**Independent-T test (2-tailed)*

***Mann – Whitney (2-tailed)*

invasion type, high FIGO grade, and PAS 3 stage, with most in segment 2 involved. The mean estimated blood loss (EBL) was 2,435.71±1,367.70 mL in treatment group and 2,807.14±1,241.78) mL in control group. The aortic cross-clamp duration was 61.43±15.74 minutes in the treatment group and 70.71±28.79 minutes in the control group.

In all groups, it is shown that there was an increase in MDA levels from 19.779±0.870nmol/ml to 21.104±1.053nmol/ml after cross-clamp with an average increase of 1.325±0.801nmol/ml (p=0.00) (Table 3). It was concluded that there was an increase in MDA levels as a predictor of ischemia-reperfusion injury in patients who underwent temporary abdominal aortic cross-clamping.

Based on the results shown in Table 4, the treatment group that received transdermal CO_2 had a lower tendency to increase MDA levels, 1.063+0.803nmol/ml, compared to the control group at 1.586+0.766nmol/ml. However, based on statistical tests, the results were not significant. Changes in MDA levels between groups can be seen in Figure 1 until Figure 3.

Table 5 shows the mean intubation time and length of stay in the hospital. There were no statistical differences in the length of intubation and hospitalization in the two groups. There were no patients who died during the study period. Based on the results of routine postoperative laboratory examinations, there were no differences in hemoglobin levels, white blood cell counts, platelets, and albumin levels.

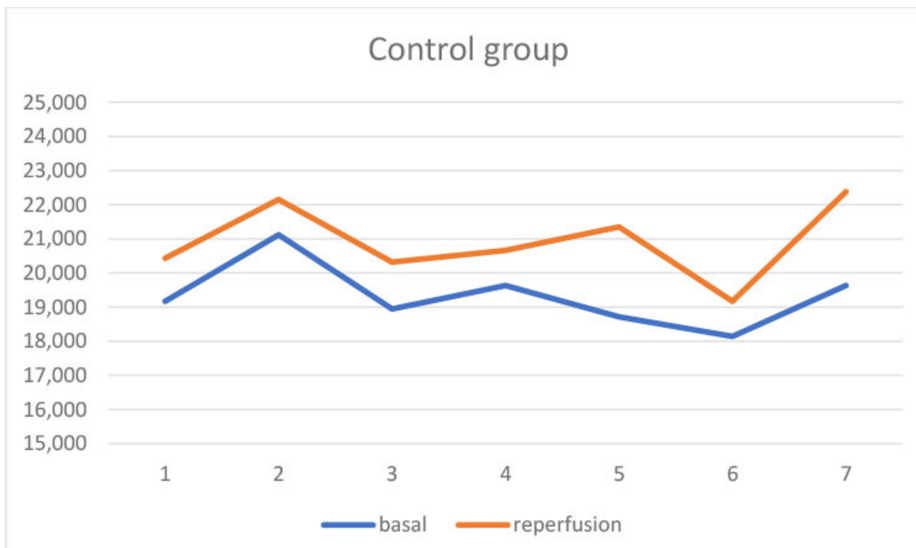

Figure 1. MDA level in the control group.

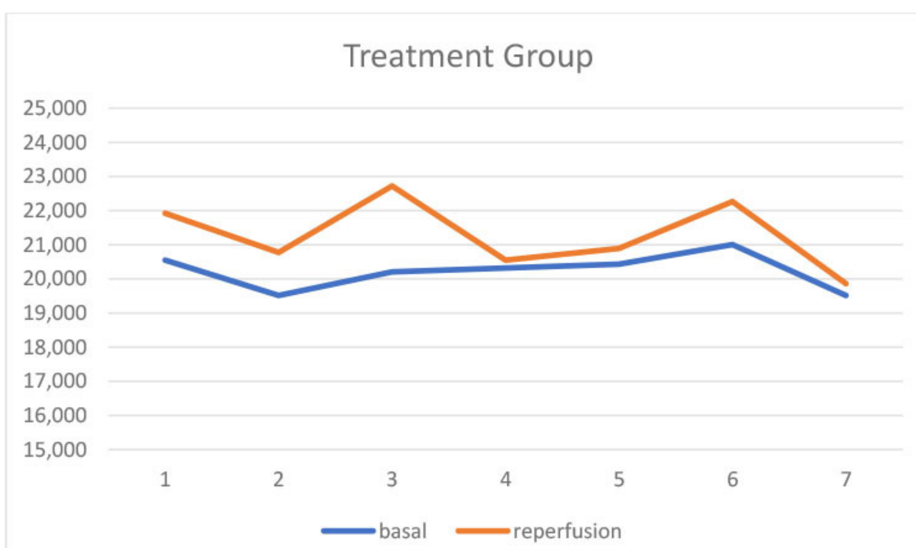

Figure 2. MDA level in the treatment group.

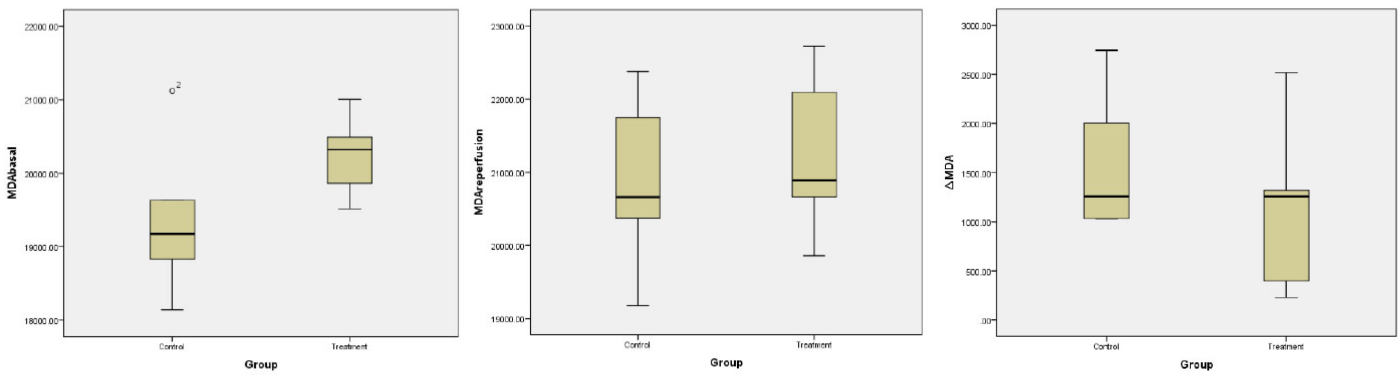

Figure 3. Boxplot of MDA level between the control and the treatment groups on basal and reperfusion examination (top), and boxplot of change in MDA level in control and treatment groups (bottom).

DISCUSSION

Abdominal aortic occlusion has been performed to control severe hemorrhage in patients with the placenta accreta spectrum. This can be achieved via a direct external approach and endovascular approach.[5,18,19] Temporary cross-clamping of the abdominal aorta is one of the methods to control severe hemorrhage.[20] Implementation of abdominal aortic cross-clamping to control operative blood loss was first described in a case report by Chou et al. The technique starts with the separation of the inferior abdominal aorta (IAA) from the inferior vena cava between the fourth lumbar and aortic bifurcation. It was also emphasized that the procedures were performed by a team consisting of one cardiovascular surgeon and two obstetricians.[5] Yoshida et al. emphasized that temporary clamping of the abdominal aorta should be done as close to the renal artery as possible.[21]

Based on the results of this study, it was found that there was an increase in MDA levels before and after the abdominal aortic temporary cross-clamping was performed. It can be concluded that MDA can be used as a predictor of ischemia-reperfusion injury after temporary abdominal aortic cross-clamping. The ischemia-reperfusion injury occurs when the blood supply to an organ is disrupted (ischemia) and then restored (reperfusion), which causes the release of Reactive Oxygen Species (ROS) from the mitochondria.[22] Reperfusion after ischemia produces ROS, mitochondrial failure, endothelial dysfunction, and sterile inflammation. Under physiological conditions, mitochondria produce small amounts of ROS through electron leakage.[23] Cells that are ischemic have lower antioxidants.[7] When exposed to ischemia, the mitochondrial complex is damaged, resulting in excessive ROS generation beyond the antioxidant restoring capacity after reperfusion. ROS, in turn, causes damage to membrane lipids, proteins, and nucleic acids that can lead to cell death.[23]

ROS is not very stable, so the measurement is carried out indirectly by the release of MDA as a result of ROS reactions to lipids degradation that is found in cell membranes. Malondialdehyde levels are generally recognized as a marker of oxidative stress.[9] Plasma MDA levels increased significantly within 1 hour after the onset of reperfusion in all patients who had successful revascularization. MDA levels then slowly decreased to near basal values after 4 hours of revascularization.[8,24]

In the condition of ischemia-reperfusion injury, there is an increase in NADPH-oxidase activity and a decrease in antioxidants.[7,22] NADPH-oxidase will cause the conversion of O_2 to O_2^-. O_2^- will be converted into H_2O_2 by Superoxide dismutase (SOD) and then into H2O by Catalase or Glutathione peroxidase (GPX). The most important radicals or pro-oxidant molecules involved in the disease process are superoxide (O_2^-), hydroxyl radicals (H.O.$^-$), and $^1O_2$.[7,10] The imbalance between increased ROS and the ability to neutralize free radicals by antioxidant defenses causes oxidative stress with the result of increased ROS.[8] ROS is not very stable at the time of examination. So that the examination is carried out indirectly, namely the formation of MDA as a result of ROS reactions to cell lipids that are abundant in cell membranes. Malondialdehyde levels are generally recognized as markers of oxidative stress.[9]

Efforts are currently being made to reduce the incidence of ischemia-reperfusion injury. one of them is by giving transdermal CO_2. Several studies have demonstrated a significant effect of using transdermal CO_2 on microcirculation.[15] Finzgar *et al.* found that transdermal CO_2 had a significant effect on skin microcirculation, as seen from the increase in laser Doppler flux.[14] The use of transdermal CO_2 in patients with intermittent claudication significantly increased walking distance, peripheral systolic pressure, and pO_2.[13] In patients with Diabetic Foot Ulcers, the use of transdermal CO_2 showed an increase in dermal microcirculation based on perfusion index and tissue oxygenation, therefore helping in the wound healing process.[25] Damanik & Puruhito found that administration of transdermal CO_2 significantly increased $TcPCO_2$ and increased tissue perfusion index 5.6 times in patient with placenta accreta spectrum underwent temporary abdominal aortic cross-clamping without the presence of adverse events or complications.[26] Following the 'Bohr Effect', there is an increase in oxygen delivery to tissues due to CO_2 and Hydrogen which shifts the Oxygen-Hemoglobin dissociation curve so that O_2 is released from hemoglobin and consequently increases the amount of O_2 in the tissues.[15,16] CO_2 is believed to be a strong inhibitor of ROS through inhibition of the activity of NADPH-oxidase.[17] Based on the results of this study, transdermal CO_2 administration tends to reduce the incidence of ischemia-reperfusion injury after temporary abdominal aortic cross-clamping seen from the less change of malondialdehyde in the treatment group than in the control group. However, it is not statistically significant.

The population of this study was patients with placenta accreta spectrum who underwent aorta abdominal temporary cross-clamping during cesarean hysterectomy. The non-significant MDA concentration in the two groups may also be due to lipid peroxidation during abdominal aortic temporary clamping surgery in addition to the distal ischemia of the clamp, also due to high oxidative stress conditions in pregnant patients. Research by Khan *et al.* showed that pregnant women experienced an increase in oxidative stress and a decrease in antioxidants, with the mean MDA levels found to be significantly higher in pregnant women compared to non-pregnant women.[27] Antioxidant activities such as SOD and Catalase was found to be significantly lower in pregnant women compared to non-pregnant women.[27,28] Oxidative stress in pregnancy may be a result of increased oxygen consumption and metabolism due to energy and oxygen requirements for fetal growth and development.[27,28]

The limitations obtained during this study were that the research subjects were limited and carried out during the pandemic era. Further research needs to be done with a larger sample size to obtain greater statistical significance.

CONCLUSION

This study concluded that there was an increase in MDA levels as a predictor of ischemia-reperfusion injury in patients undergoing temporary abdominal aortic cross-clamping. The administration of transdermal CO_2 tends to suppress ischemia-reperfusion injury. Suggestions for further research are: further research needs to be done with a larger sample size to get greater statistical significance. It is necessary to conduct another research to determine the effect of transdermal CO_2 administration on other subjects who are not pregnant or under conditions of oxidative stress.

ETHICAL CLEARANCE

The ethical clearance of this study was approved by Ethics Committee in Health Research Dr. Soetomo Academic General Hospital number 0319/KEPK/XII/2021 on December 1st, 2021.

CONFLICT OF INTEREST

There is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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AUTHOR CONTRIBUTION

All authors contributed equally to the manuscript. All authors read and approved the final version of the manuscript.

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