Original Research Article

Effect of exogenous albumin replacement on plasma colloid osmotic pressure in severe preeclampsia. Cases and controls study.

ABSTRACT

Background: In preeclampsia, hypoalbuminemia reduces plasma colloid osmotic pressure (PCOP) and favors capillary leakage. Replacement with exogenous albumin is a therapeutic alternative.

Objective: to determine the effect of exogenous albumin replacement on PCOP in patients with severe preeclampsia (SP).

Methods: A case-control study was carried out in 76 pregnant patients with SP from the Intensive Care Unit (ICU). The case group (n=38) received 0.9% saline solution 1000 ml every 8 hours and 25% albumin 50 ml every 8 hours and the control group (n=38) only received 0.9% saline solution 1000 ml every 8 hours. Plasma albumin concentrations, PCOP, hemodynamic and laboratory data from admission (baseline measurement) vs discharge from the ICU (final measurement) of both groups were compared.

Statistical analysis: the data was analyzed with descriptive statistics, paired Student's t-test and Pearson's correlation coefficient with the statistical program SPSS® version 20. The p value <0.05 was significant.

Results: A significant decrease in plasma albumin was found (case group 2.72±0.44 vs 2.45±0.48 g/dL, p=0.0141; control group 3.06±0.33 vs 2.58±0.29 g/dL, p=0.0431). PCOP was also significantly reduced (case group 18.44±2.92 vs 16.82±2.70 mmHg, p=0.0210; control group 20.38±2.28 vs 17.46±1.96 mmHg, p=0.0763). The group of cases showed an increase in uresis (p=0.0326), but without changes in central venous pressure (p=0.3246) and serum creatinine (p=0.9515).

Conclusion: Exogenous albumin replacement therapy did not correct PCOP values.

Keywords: Human albumin; Plasma colloid osmotic pressure; Capillary leak; Severe preeclampsia; High risk pregnancy; Obstetric intensive care.

1. INTRODUCTION

The arteriolar and capillary endothelium is the first maternal organ to be affected in preeclampsia from the release into the bloodstream of one or more substances of placental origin with a direct toxic effect. Endothelial swelling and rupture of the basement membrane cause the loss of its function as a semi-permeable barrier and a state of capillary leakage of fluids, electrolytes and proteins (albumin) begins, altering the natural forces described by Starling that make possible the balance of the fluids in the tissues [1]. Albumin leakage into the interstitial space and urinary loss cause hypoalbuminemia and reduced plasma colloid osmotic pressure (PCOP) [2]. PCOP can be calculated using the following formula [3]:

PCOP = [albumin g/dL x 5.54] + [globulins g/dL x 1.43]

In normal pregnancy, PCOP decreases in the first and second trimesters, gradually increases in the third trimester, and a further decrease occurs in the postpartum period [4]. In patients with preeclampsia, hypoalbuminemia and reduction in PCOP present earlier with the same variations, but are more marked [5].

In Mexico it has been reported that in patients with preeclampsia the PCOP before delivery is 15 to 17 mmHg and in the immediate postpartum period 13 to 14 mmHg [6]. It has been proposed that the decrease in PCOP depends on the time of evolution and severity of preeclampsia, but also influences the type and volume of intravenous solutions used and the amount of intrapartum bleeding [2]. Hypoalbuminemia is a high maternal and fetal risk factor [7] and the reduction in PCOP has been related to the clinical appearance of extreme edema (anasarca) and the accumulation of fluid in the serous structures (pleurae, pericardium, peritoneum) that can increase the morbidity of the patients [8]. Hypoalbuminemia and reduced PCOP have also been associated with a higher frequency of cerebral edema and pulmonary edema, especially when intravascular hydrostatic pressure is increased simultaneously [2]. It has also been suggested that reduced PCOP

may be a predisposing factor for eclampsia, the most severe stage of the disease [9].

Exogenous albumin replacement may be a potentially useful therapeutic option to correct hypoalbuminemia, decreased PCOP, and capillary leak with its complications [2]. Albumin replacement therapy has provided benefits in selected patients with other serious disease states, [10-12] but in preeclampsia the results have not been entirely clear [13,14] In this context, the **objective** of the investigation was to determine the effect of replacement with exogenous albumin on PCOP in patients with severe preeclampsia (SP).

2. PATIENTS AND METHODS

A case-control study was carried out in a cohort of 76 pregnant patients with SP admitted to the Intensive Care Unit (ICU) of a High Specialty Medical Unit in Mexico City (Gynecology and Obstetrics Hospital No. 3, National Medical Center "La Raza". Mexican Institute of Social Security) between January 1 and December 31, 2022. The diagnosis of SP was compared with the criteria recommended by the American College of Obstetricians and Gynecologists (ACOG) in the year 2020 [15].

Patients of any age and parity, with termination of pregnancy and postpartum care during their ICU stay were included. Patients with a history of chronic liver failure, kidney disease with chronic proteinuria, or chronic malnutrition were excluded. All the records of the selected patients were available, so none of them was eliminated. All the patients in the study had been initially cared for in first and second level hospitals and were then sent to the hospital where this research was conducted for management in the ICU. None of them had received crystalloid solutions or exogenous albumin.

Two groups (cases and controls) were formed with the patients who met the selection criteria. The case group included 38 patients who received crystalloid fluids (0.9% sodium chloride solution) in a continuous intravenous infusion of 1,000 ml every 8 hours in addition to albumin in a 25% solution contained in a 50-ml bottle administered as a continuous infusion. intravenously for 30 minutes every 8 hours throughout his stay in the ICU. The control group was made up of 38

patients matched by maternal age and gestational weeks who received only crystalloid fluids (0.9% sodium chloride solution) as a continuous intravenous infusion of 1,000 ml every 8 hours during their entire stay in the ICU. The 76 patients underwent pharmacological management in the ICU as recommended by the institutional guidelines. **Table 1** The study began when the patients were admitted to the ICU and ended when they were discharged.

Table 1. Pharmacological management for pregnant patients with severe preeclampsia in the Intensive Care Unit

Drug	Dose
Magnesium sulphate *	4 g initial intravenous dose in 30 min., later 1 g x hour continuous intravenous infusion dose, dose-response
Dexamethasone **	10 mg intravenous dose every 12 hours
Sodium phenytoin *	15 mg x K weight / initial intravenous dose in 30 min, later 125 mg dose intravenous every 8 hours
Omeprazole	40 mg intravenous dose every 24 hours
Methyldopa	500 mg intravenous dose every 8 hours
Hydralazine	50 mg oral dose every 8 hours
Metoprolol	100 mg oral dose every 8 hours
Management of hypertensive crises	Nifedipine 10 mg sublingual dose every 30 min. for up to 4 doses Hydralazine 10 mg intravenous bolus dose every 30 min. for up to 4 doses Nimodipina 1 to 2 mg / hour continuous intravenous infusion dose, dose-response
Management of hyperglycemia	Rapid insulin, intravenous dose every 6 hours according to capillary glycemia

* It is indicated in cases with imminent eclampsia or eclampsia.
** It is indicated in cases with class I and II of the HELLP syndrome, Mississippi classification.

The records were consulted to know the general characteristics, the hemodynamic data and the results of the clinical laboratory. For the purposes of the investigation,

the PCOP of their admission (baseline measurement) was compared with that of discharge from the ICU (final measurement). PCOP was calculated using the following formula: [3] PCOP = [plasma albumin g/dL x 5.54] + [plasma globulins g/dL x 1.43]. Similarly, hemodynamic data (blood pressure, central venous pressure, uresis), clinical laboratory results (blood concentrations of creatinine (Cr), uric acid, albumin, globulins), length of stay in the ICU and mortality. Proteinuria was not studied because the results were not available in most of the patients due to the restriction of reagents in 2022 caused by the COVID-19 pandemic.

2.1 STATISTIC ANALYSIS

Data were analyzed using measures of descriptive statistics (mean, median, standard deviation, range) and inferential statistics (chi-square test, Student's t-test for paired samples, Pearson's correlation coefficient (r)) with the statistical program SPSS® version 20. The p value <0.05 was significant.

3. RESULTS

Table 2 shows the general data of all the patients and the comparison by groups. As can be seen, the maternal age was found to be around 30 years, with parity 2, a high percentage of prematurity, a body mass index with a borderline difference, a similar number of cases with HELLP syndrome, and the termination of pregnancy more frequently through cesarean section, the amount of intrapartum bleeding was similar for both groups. Systolic blood pressure was adequately reduced in both the case group (p=0.0489) and the control group (p=0.0368). Diastolic blood pressure also showed a significant reduction in the case group (p=0.0270) and in the control group (p=0.0178). The mean central venous pressure was similar. When intergroup baseline uresis was compared, a significant difference (p=0.0002) was found in favor of the control group, but the comparison of the final values of both groups showed only borderline significance (p=0.0503). Specifically, the uresis of the case group increased in the final measurement (p=0.0326), but not that of the control group (p=0.3681). The stay in the ICU was longer in the case group than in the control group (p=0.0056).

Table 2. General data

Parameters	All patients n=76	Case group n=38	Control group n=38	p value
Maternal age yr	30.77±6.67	30.92±6.69	30.63±6.74	0.8515
Parity median (limits)	2 (1 a 4)	2 (1 a 4)	2 (1 a 4)	-----
Weeks pregnant	32.73±4.50	31.84±4.24	33.63±4.62	0.0832
Prematurity <37 weeks % (n)	80.26 (61)	43.42 (33)	36.84 (28)	0.1540
Term pregnancy ≥37 weeks % (n)	19.74 (15)	9.22 (7)	10.52 (8)	0.4268
Body mass index	33.16±5.83	31.75±5.72	34.36±3.01	0.0598
HELLP syndrome % (n)	27.63 (21)	13.16 (10)	14.47 (11)	-----
Delivery % (n)				
Caesarean-section	90.79 (69)	47.37 (36)	43.42 (33)	-----
Vaginal delivery	9.21 (7)	2.63 (2)	6.58 (5)	-----
Intrapartum bleeding ml	1600±225	1800±600	1000±115	0.0811
Systolic blood pressure mmHg				
Baseline *	151.42±19.16	149.26±22.14	153.57±15.64	0.3296
Final **	125.65±15.95	123.71±17.68	127.60±13.98	0.2903
p value	0.0647	0.0489	0.0368	-----
Diastolic blood pressure mmHg				
Baseline *	94.69±11.01	89.48±17.87	97.07±9.96	0.0249
Final **	74.75±9.18	76.71±7.47	74.02±10.03	0.1901
p value	0.0178	0.0270	0.0178	-----
Central venous pressure cm water				
Baseline *	9.73±5.64	9.01±4.77	10.82±6.72	0.2351
Final **	10.09±3.48	10.03±3.71	10.19±3.18	0.8613
p value	0.6864	0.3246	0.6864	-----
Uresis ml/hour				
Baseline *	1.14±0.91	0.77±0.62	1.54±1.01	0.0002
Final**	1.80±0.86	1.86±1.01	1.73±0.66	0.0503
p value	0.3861	0.0326	0.3681	-----
ICU stay hours	49.47±34.11	62.34±20.37	27.65±10.91	0.0056

* ICU admission
** ICU discharge

Table 3 shows the data from the clinical laboratory of all the patients and the comparison by groups. As can be seen, the creatinine concentration of the case group was higher than that of the control group in the baseline (p=0.2435) and final (p=0.0488) measurements. The average values of creatinine in the case group did

not change (p=0.9515) and in the control group a significant reduction was documented at the end of the study (p=0.0139). Uric acid concentration was reduced in both groups without reaching a statistically significant change. The lowest values of albumin, globulins and PCOP of the basal measurement corresponded to the group of cases, in this group the comparison with the final measurement showed a significant reduction of albumin (p=0.0141) and PCOP (p=0.0210). A significant reduction in albumin (p=0.0431) and PCOP was also found in the control group, but to a lesser extent (p=0.0763). **Figures 1 and 2** The globulin concentration was significantly reduced only in the case group (p=0.0331), the downward change also occurred in the control group, but it did not reach a statistically significant value (p=0.6621).

Table 3. Clinical laboratory data

Parameters	**All patients n=76**	**Case group n=38**	**Control group n=38**	**p value**
Creatinine mg/dL				
Baseline *	0.77±0.39	0.83±0.52	0.72±0.17	0.2435
Final **	0.72±0.42	0.82±0.56	0.63±0.14	0.0488
p value	0.4506	0.9515	0.0139	-----
Uric acid mg/dL				
Baseline *	5.04±1.33	5.20±1.53	4.88±1.09	0.3092
Final **	4.73±1.39	4.92±1.48	4.54±1.30	0.2367
p value	0.1633	0.4272	0.2153	-----
Albumin g/dL				
Baseline *	2.89±0.42	2.72±0.44	3.06±0.33	0.0003
Final **	2.52±0.40	2.45±0.48	2.58±0.29	0.1654
p value	0.1217	0.0141	0.0431	-----
Globulins g/dL				
Baseline *	2.26±0.58	2.25±0.68	2.27±0.44	0.8954
Final **	2.09±0.47	1.97±0.41	2.22±0.51	0.0272
p value	0.0553	0.0331	0.6621	-----
PCOP *** mmHg				
Baseline *	19.46±2.76	18.44±2.92	20.38±2.28	0.0023
Final **	17.16±2.35	16.82±2.70	17.46±1.96	0.2535
p value	0.0288	0.0210	0.0763	-----

* ICU admission

** ICU discharge

*** PCOP= Plasma colloid osmotic pressure, calculated with the formula

(albumin g/dL x 5.54) + (globulins g/dL x 1.43)

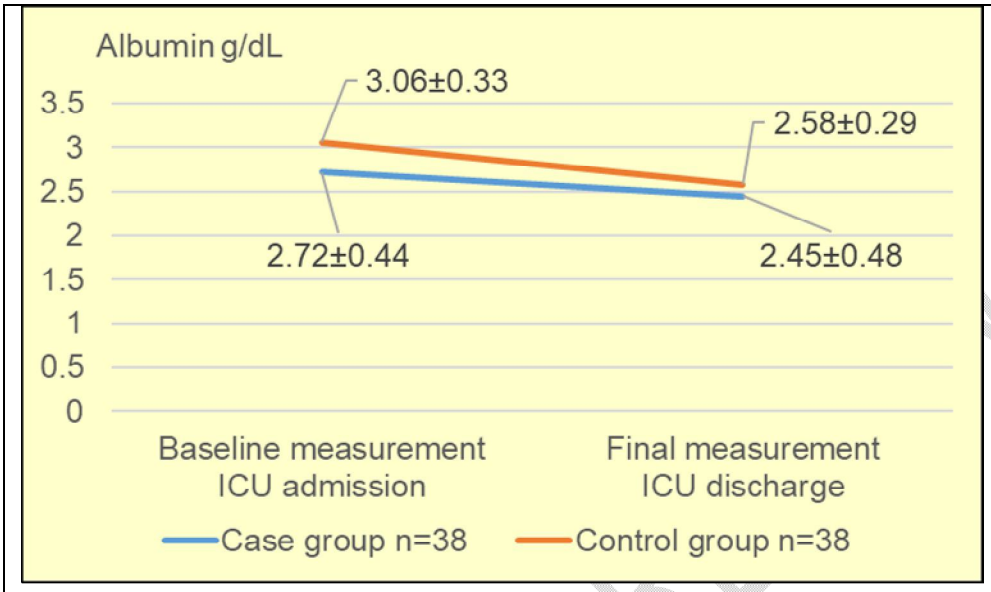

Figure 1. Comparison of plasma albumin concentration. Case group (p=0.0141) and control group (p=0.0431).
ICU: Intensive Care Unit

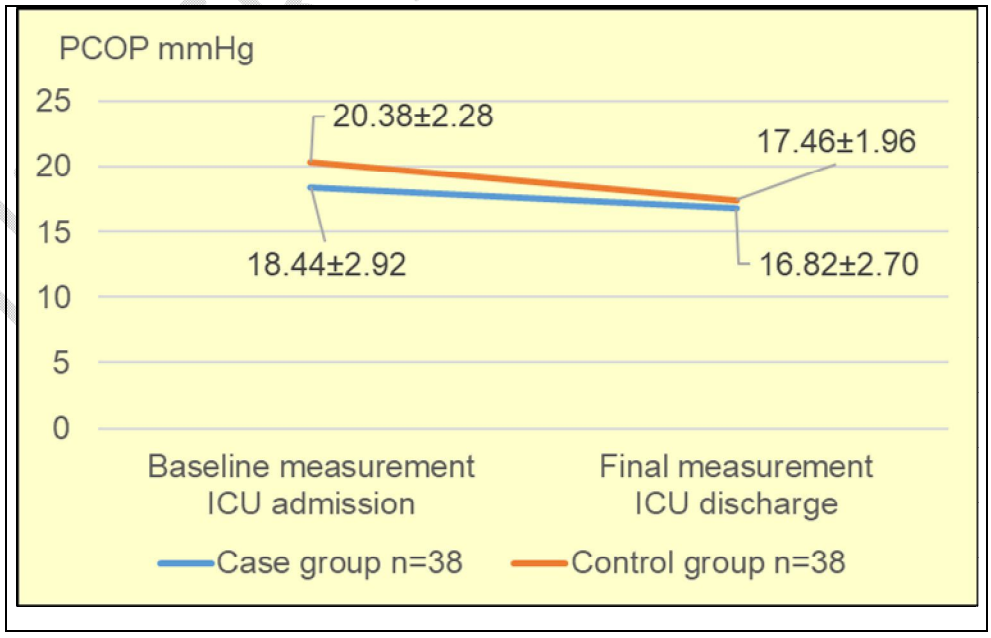

Figure 2. Comparison of plasma colloid osmotic pressure (PCOP). Case group (p=0.0210) and control group (p=0.0763). ICU: Intensive Care Unit

Table 4 shows the frequency and distribution of complications during the investigation period of all the patients and the comparison by groups. As can be seen, the frequency of acute kidney injury (AKI, defined as a creatinine value ≥1.1 mg/dL) at the beginning of the study was 7.89%, with a predominance in the case group (6.57%) over the control group (1.32%), the relative frequency was 4.97:1. The percentage of patients with AKI in the case group did not decrease in the final measurement (6.57%). No cases requiring dialysis were recorded. Regarding serous effusion (pleurae, pericardium, peritoneum, ascites) the frequency was 15.78% (12 cases), the distribution was similar in both groups; there was no possibility of statistical analysis due to the small number of patients. No complications due to fluid accumulation were recorded. Patients complicated with acute pulmonary edema 3.97% (3 cases) and obstetric hemorrhage (defined as loss >1000 ml) 5.26% (4 cases) were distributed in both groups in a similar way. No patients with eclampsia were recorded and mortality was 0%.

Table 4. Complications during the ICU stay

Complications	**All patients n=76**	**Case group n=38**	**Control group n=38**
Acute Kidney Injury n (%) (Cr ≥ 1.1 mg/dL)			
Baseline *	6 (7.89)	5 (6.57)	1 (1.32)
Final **	5 (6.57)	5 (6.57)	0
Serous effusion n (%)	12 (15.78)	7 (9.21)	5 (6.57)
pleurae	2	1	1
pericardium	2	1	1
peritoneum ascites <500 ml	8	5	3
Acute pulmonary edema n (%)	3 (3.94)	1 (1.31)	2 (2.63)
Obstetric hemorrhage n (%) (>1000 ml)	4 (5.26)	2 (2.63)	2 (2.63)
Eclampsia n (%)	0	-----	-----
Mortality n (%)	0	-----	-----

ICU: Intensive Care Unit

Cr: serum creatinine
* ICU admission
** ICU discharge

When the correlation of the final uresis with the final values of creatinine and the stay in the ICU of the group of cases was calculated, non-significant data were found (uresis vs creatinine r= -0.050, uresis vs stay in the ICU r= -0.083).

4. DISCUSSION

Exogenous albumin replacement therapy has shown encouraging results in selected critically ill patients, in patients with tissue destruction from extensive burns, septic shock, acute respiratory distress syndrome, nephrotic syndrome, pancreatic insufficiency, liver disease with ascites, and in patients undergoing extensive surgery [10,12]. In preeclampsia, previous research has documented that albumin-containing solutions slow the postpartum decline of PCOP, but do not correct it or modify maternal and fetal outcomes [13,14].

Jones et al. [13] reported in 1986 the results of a clinical study carried out to compare the effect of the infusion of crystalloid solutions (1,000 ml), Plasma-Lyte A solution (2,000 ml) and a 5% albumin solution (1,000 ml) on the Peripartum PCOP. Forty-five patients received one of the three types of solutions before elective caesarean section. The lowest PCOP (16.6±1.1 mmHg, $p<0.05$) occurred in the infusion group with 2,000 mL crystalloid solutions after 8 to 16 hours postpartum. Although PCOP fell in all groups, the reduction was significantly less ($p < 0.05$) in the 5% albumin infusion group. The authors concluded that the only advantage of the infusion of 5% albumin solutions would be to attenuate the reduction of the hydrostatic pressure gradient to avoid the possibility of acute pulmonary edema in selected patients.

Ganzevoort et al. [14] conducted a randomized clinical trial in two university hospitals in Amsterdam, the Netherlands. They included 216 patients with pregnancy between 24 and 34 weeks with PS and HELLP syndrome or with severe fetal growth restriction who were admitted between April 1, 2000 and May 31, 2003. The treatment group (volume expansion plasma with 200 ml of 6% Starch (Hydroxy Ethil Starch) infused for 4 hours every 12 hours) was formed with 111

patients and the control group (intravenous fluid restriction) included 105 cases. The authors found that plasma volume expansion did not improve maternal or fetal outcome.

In the present investigation, the case group (0.9% sodium chloride solution and exogenous albumin) and the control group (0.9% sodium chloride solution) showed similar data regarding the general characteristics of the patients, drop in blood pressure, termination of pregnancy and intrapartum bleeding. **Table 1** The severity of preeclampsia was greater in the control group because higher Cr values were documented, a higher number of patients with AKI in the two study measurements (relative frequency 4.97:1) and longer ICU stay. **Tables 1, 2 and 3**

Patients in the case group showed lower concentrations of albumin and PCOP at baseline than the control group. **Table 2** After replacement therapy with exogenous albumin, neither albumin nor PCOP values were corrected. **Figures 1 and 2**

Albumin infusion did not prevent the postpartum decline in both parameters, a situation that has already been identified by Jones et al. [13] The rule was the drop in albumin and PCOP to a greater or lesser extent regardless of the therapeutic intervention.

No evidence of an expanding effect on circulating volume was found in the patients in the case group because the basal central venous pressure did not increase, but uresis was higher than that of the control group at the final measurement of the study (p=0.0503). However, increased uresis in the group of cases was not correlated with better renal function (r= -0.050), the number of patients with AKI was not reduced, and it was not associated with a shorter ICU stay (r= - 0.083).

Two situations must be taken into account to explain the findings. It is possible that exogenous albumin did not correct the basal values of plasma albumin concentration and PCOP because its short half-life does not allow it to reach normal blood values or the time necessary to exert a prolonged pharmacological effect of susceptible vascular expansion measurement with central venous pressure [10,11,16,17]. The other scenario is that the presence of exogenous albumin in the bloodstream and its expanding effect have been fleeting due to persistent capillary leak and proteinuria. Bathia et al. [2] reported in 1987 the

results of an investigation about the mechanisms for the reduction of PCOP in preeclampsia. The authors studied 32 preeclampsia patients and 32 control patients and found a more marked reduction in PCOP and greater proteinuria in the preeclampsia group. The correlation of PCOP was very high with elevated Fibronectin levels suggesting that endothelial injury is the main mechanism for PCOP reduction, rather than proteinuria. Recovery from endothelial injury does not start automatically after termination of pregnancy, but rather takes time. Remuzzi et al. [18] have proposed a period of up to 37 days postpartum as a cut-off point for the disappearance of pathological proteinuria as evidence that indirectly translates endothelial recovery. In the present investigation, we did not have access to serial measurements of capillary leak or proteinuria because the study period was limited only to the length of stay in the ICU of the patients in both groups.

Exogenous albumin replacement therapy to improve PCOP has not been accepted as part of the pharmacological management of patients with preeclampsia in the North American region [15,19-21] because sufficient supporting scientific evidence has not been generated. In addition, the increase in uresis after replacement with exogenous albumin is a known pharmacological effect [10,11,16,17] and the administration of furosemide after albumin infusion to potentiate the diuretic effect has shown a benefit in selected patients with other conditions, but not in preeclampsia [10-12]. With this evidence and because the data from the present study showed that exogenous albumin does not correct or normalize albumin and PCOP values, the recommendation is that its use in patients with preeclampsia should be reserved for the experience of the medical team.

5. CONCLUSIONS

Exogenous albumin replacement therapy did not correct the PCOP values or the blood albumin concentration. Exogenous albumin infusion increased uresis, but did not show an expanding effect on circulating volume and did not modify renal function or the clinical course of the patients.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The study was previously approved by the local health research committee no. 3504 and Ethics in Health committee of the host hospital (Registration: R-2023-3504-4).

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