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MAIN TEXT

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The effect of perioperative hemadsorption in patients operated for acute infective endocarditis—A randomized controlled study

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Abstract

Patients operated for infective endocarditis (IE) are at high risk of developing an excessive systemic hyperinflammatory state, resulting in systemic inflammatory response syndrome and septic shock. Hemoadsorption (HA) by cytokine adsorbers has been successfully applied to remove inflammatory mediators. This randomized controlled trial investigates the effect of perioperative HA therapy on inflammatory parameters and hemodynamic status in patients operated for IE. A total of 20 patients were randomly assigned to either HA therapy or the control group. HA therapy was initiated intraoperatively and continued for 24 hours postoperatively. Cytokine levels (IL-6, IL-1b, TNF-α), leukocytes, C-reactive protein (CRP), and Procalcitonin (PCT) as well as catecholamine support, and volume requirement were compared between both groups. Operative procedures included aortic (n = 7), mitral (n = 6), and multiple valve surgery (n = 7). All patients survived to discharge. No significant differences concerning median cytokine levels (IL-6 and TNF-α) were observed between both groups. CRP and PCT baseline levels were significantly higher in the HA group (59.5 vs. 26.3 mg/dL, $P = .029$ and 0.17 vs. 0.05 µg/L, $P = .015$) equalizing after surgery. Patients in the HA group required significantly higher doses of vasopressors (0.093 vs. 0.025 µg/kg/min norepinephrine, $P = .029$) at 12 hours postoperatively as well as significantly more overall volume replacement (7217 vs. 4185 mL at 12 hours, $P = .015$; 12 021 vs. 4850 mL at 48 hours, $P = .015$). HA therapy did neither result in a reduction of inflammatory parameters nor result in an improvement of hemodynamic parameters in patients operated for IE. For a more targeted use of HA therapy, appropriate selection criteria are required.

KEYWORDS

cytokines, endocarditis, hemadsorption, sepsis, SIRS

1 | INTRODUCTION

Infective endocarditis (IE) is a multiorgan disease caused by microbial infection of the endocardium. Streptococci and staphylococci are diagnosed in 80% of patients.[1] Native or prosthetic heart valves can both be affected, often resulting in valvular dysfunction due to leaflet destruction or vegetations as well as perivalvular or myocardial abscess

formation. Severe congestive heart failure may occur.[2] Even with the best available therapy, mortality rates are as high as 25%.[3] In addition to the appropriate antibiotic therapy, cardiac surgery is a key component in the management of IE which is associated with a significant reduction of in-hospital mortality.[1,4]

However, the surgical trauma and the use of cardiopulmonary bypass (CPB) cause an additional systemic inflammatory response.[5] In combination with the potential intraoperative bacterial spread, patients operated for IE are at a high risk of developing an excessive systemic hyperinflammatory state, resulting in systemic inflammatory response syndrome (SIRS) and septic shock.[2] The release of proinflammatory cytokines, for example, IL-6, IL-1b, and TNF-α, leads to increased capillary permeability and accumulation of interstitial fluid, causing hemodynamic depression and organ dysfunction.[6,7] This may result in higher rates of respiratory failure and acute kidney injury as well as a prolonged postoperative course.[5,8,9]

New therapeutic approaches addressing inflammatory reactions have shown to improve perioperative outcomes.[10] Among them, hemoadsorption (HA) by cytokine adsorbers, which has been successfully applied to remove inflammatory mediators and, thereby, preventing post-CPB SIRS and multiple organ dysfunction syndrome (MODS).[11,12] In patients with IE, the intraoperative application of cytokine adsorbers was assumed to be associated with a mitigated postoperative response of key cytokines and metabolic parameters (lactate level and base excess) and, subsequently, a positive effect on intra- and postoperative hemodynamic stability, associated with a decrease of vasopressor therapy.[2]

Based on these results, the aim of this study was to investigate the effect of intra- and postoperative HA therapy in patients operated for IE.

2 | METHODS

Patients with confirmed IE of any type (native or prosthetic valve) and localization (affected valve) undergoing cardiac surgery were included in this study and randomly assigned to either the HA group or the control group. Exclusion criteria were a lack of informed consent, noninfectious endocarditis, and pregnancy as well as contraindications for HA therapy (ie, heparin-induced thrombocytopenia [HIT], thrombocytopenia [<20 000/μL] and ongoing immunosuppressive therapy). All procedures described in this study were in accordance with the institutional ethics committee (application number: 21/4/18), national data safety regulations, and the Helsinki declaration and its last amendment in 2013. Patient selection is outlined in Figure 1.

Between November 2018 and March 2020, a total of 35 patients were assessed for eligibility. Among them, nine patients were excluded: 5 patients declined to participate and another 4 patients were unable to give informed consent due to sedation or major neurologic impairment. Thus, 26 patients were included in the study and randomly assigned to either the HA group or the control group (Figure 1). For randomization the urn design has been applied. Six patients were excluded from analysis for various reasons: in one patient, the diagnosis of IE was not confirmed, intraoperatively. In another patient, the operative procedure exceeded 12 hours due to technical difficulties. Therefore, the exchange of the cartridges was not performed as per protocol. In two patients, postoperative HA treatment was not completed, due to repeated clotting of the dialysis circuit. In two other patients, HA therapy was discontinued because of clinically relevant hypotension after initiation of dialysis. Neither the clotting of the circuits nor the hypotensive

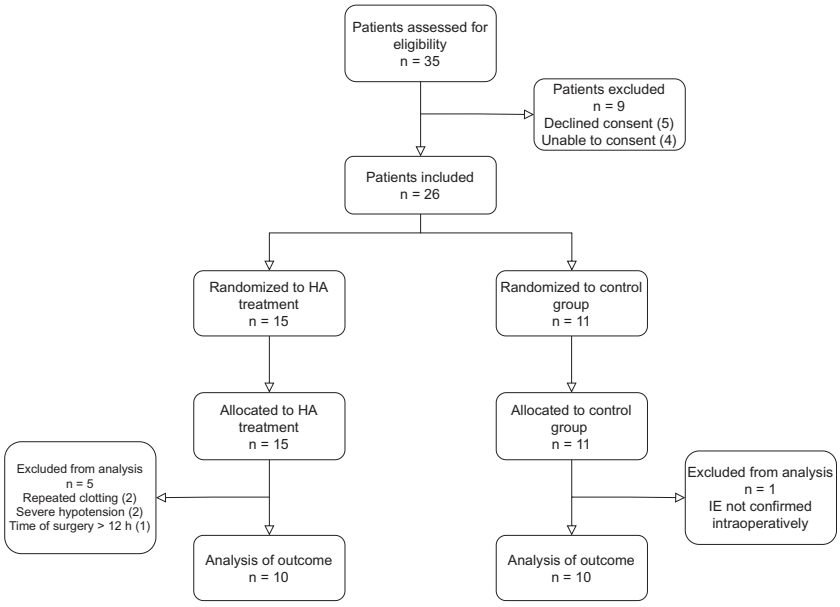

FIGURE 1 Patient enrollment

episodes did result in any serious health impairment of the investigated patients.

The primary endpoint of the study was the postoperative course of cytokine levels (IL-6, TNF-a, IL-1b) and infection parameters (CRP, PCT, leucocytes). Secondary endpoints were the development of the severity-of-the disease (estimated by the SOFA, SAPS II and APACHE II score), postoperative catecholamine and fluid requirement, the incidence of adverse events as well as in-hospital mortality.

Baseline characteristics as well as details of surgery and outcome were reported. The EuroSCORE II was calculated. General inflammatory markers (leucocytes, CRP, PCT) as well as serum cytokines (IL-6, IL-1b, TNF-α) were recorded.

The following immuno assays have been used for estimation of serum cytokines: Elecsys IL-6 test, cobas (IL-6), TNF-alpha and IL-1b Immulite Test for the Immulite 1000 System, Siemens (TNF-a, IL-1b).

Vasopressor and inotropic therapy, cumulative fluid replacement and transfusion requirements were recorded. Blood tests were performed on the day before surgery, on arrival on the intensive care unit (ICU) and on the 1st, 2nd, 3rd and 7th postoperative day (POD). ICU scores were performed at 6 hours (APACHE 2) and 24 hours (SOFA, SAPS II) after arrival on the ICU.

For direct whole blood hemadsorption the CytoSorb cytokine adsorber (CytoSorbents Europe GmbH, Berlin, Germany) was applied, which is approved to eliminate cytokines, toxins and other inflammatory mediators sizing between five and 60 kDa. Intraoperatively, the cytokine adsorber was integrated in the CPB circuit as a shunt returning the blood into the venous reservoir. Blood flow was regulated within the approved range. On ICU, HA therapy was continued for 24 hours, postoperatively, with the cartridge integrated in a hemodialysis circuit (multiFiltrate, Fresenius Medical Care AG & Co, Bad Homburg, Germany) placed in line after the blood pump and the dialysis filter. According to the estimated saturation time of 8 hours (product information) the cartridges were regularly exchanged after that time, resulting in a total of four cartridges (one intra- and three postoperatively) used in each patient. The application via dialysis circuit was preferred to a stand-alone circuit because of previous reports on an elevated risk of clotting. Apart from hemodialysis therapy all patients received the same intra- and postoperative standard care.

Data were analyzed using the IBM SPSS Statistics software version 26 (SPSS Inc, Chicago, IL, USA). Categorical variables were evaluated using Fisher's exact test and continuous variables were evaluated using the Mann–Whitney *U* test. Differences within groups over time were analyzed using the Friedman test. The null hypothesis was rejected and a significant difference was assumed for P values $\leq .05$. Results are presented as medians with interquartile ranges.

3 | RESULTS

3.1 | Baseline parameters and details of surgery

There were no significant differences between both groups. Median age was 65 years in the HA group versus 69 years in the control group (P = ns), 7 versus 9 patients were male (P = ns). Median estimated perioperative mortality according to the EuroSCORE II was 8.5 versus 3.6 (P = ns). The majority of patients suffered from single valve endocarditis. Four patients in each group had a history of septic embolism.

Intraoperative parameters were comparable, as well. Median operation time was 264 minutes in the HA group versus 277 minutes in the control group (P = ns) with a median time on cardiopulmonary bypass (CPB) of 126 versus 180 minutes (P = ns) and a median cross-clamp time of 90 versus 118 minutes (P = ns). Operative procedures included aortic (5 vs. 2 pts., P = ns) and mitral valve replacement (2 vs. 4 pts., P = ns) as well as multiple valve surgery (3 vs. 4 pts., P = ns). Detailed information is provided in Table 1.

3.2 | Postoperative adverse events and outcome

Outcome parameters are presented in Table 2. The incidence of postoperative adverse events was similar in both groups. One patient in the HA group required postoperative ECMO support. There was no significant difference regarding time on mechanical ventilation (21 vs. 14 hours, P = ns), however, there was a significantly prolonged stay on ICU in the HA group compared with the control group (10.5 vs. 4.5 days, $P = .023$). All patients survived to discharge. Postoperative "severity of disease" and "risk of mortality" scores on the ICU (SOFA, SAPS, and APACHE II) were comparable in both groups (P = ns).

3.3 | Inflammatory markers and infection parameters

Median cytokine levels (IL-6 and TNF-α) are depicted in Figure 2. There were no significant differences between both groups. Concerning IL-6, there was a significant increase in both groups immediately after surgery (25-255 pg/mL, $P = .001$ vs. 18-258 pg/mL, $P = .001$) with a subsequent

TABLE 1 Baseline parameters and details of surgery

	HA group	Control group	
	n = 10	n = 10	*P* value
Baseline parameters			
Age [years]	65 (53-70)	69 (56-81)	.315
Female gender [n]	3	1	.582
Body mass index [kg/m^2]	26.0 (21.5-30.6)	25.0 (20.7-31.8)	.853
LVEF [%]	50 (50-56)	60 (54-62)	.105
EuroSCORE II [%]	8.5 (2.7-16.4)	3.6 (2.6-11.8)	.393
Re-operation [n]	3	2	1.000
Emergency surgery [n]	2	1	1.000
Endocarditis-related parameters			
Single valve IE [n]	7	9	1.000
Multiple valves IE [n]	3	1	1.000
Septic embolism [n]	4	4	1.000
Cardiogenic shock [n]	1	0	1.000
Co-morbidities			
Arterial hypertension [n]	4	7	.370
Insulin-dependent diabetes [n]	1	3	.582
Peripheral artery disease [n]	2	0	.474
Renal replacement therapy [n]	1	1	1.000
COPD [n]	2	0	.474
Cardiac surgery			
AV surgery [n]	5	2	.350
MV surgery [n]	2	4	.628
AV and MV surgery [n]	2	3	1.000
MV and TV surgery [n]	1	1	1.000
Cross clamp time (minutes)	90 (65-150)	118 (60-148)	.888
CPB time (minutes)	126 (94-276)	180 (93-219)	.963
Operation time (minutes)	264 (187-372)	277 (171-345)	1.000

Note: Data are presented as medians (25th-75th percentiles) or absolute values.

Abbreviations: AV, aortic valve; COPD, chronic obstructive pulmonary disease; CPB, cardio-pulmonary bypass; LVEF, left ventricular ejection fraction; MV, mitral valve; TV, tricuspid valve.

decline. Regarding TNF-α, there were no significant differences between both groups during the perioperative course, with a considerably wider dispersion of preoperative TNF-α levels in the HA group. IL-1β was not considered for statistical analysis, because levels were below the detection limit in 16 of 20 pts.

Median CRP, PCT, and leukocyte levels are illustrated in Figure 3. A significantly higher baseline CRP was observed in the treatment group (60 vs. 26 mg/dL, $P = .029$). In both groups, CRP peaked on POD 2 (137 vs. 182 mg/dL, $P =$ ns). Until POD 7, CRP decreased in both groups, with a subsequent decline. With regard to PCT, the treatment group started with significantly higher levels (0.17 vs. 0.05 µg/L, $P = .015$). However, peak levels were comparable in both groups. Similarly, in the treatment group, there was a significantly elevated leukocyte count immediately after surgery (10.5 vs. 17.8 × 10^3/µL, $P = .001$) which equalized thereafter.

3.4 | Catecholamine and fluid therapy

Postoperative catecholamine and fluid therapy are presented in Figure 4. At 12 hours postoperatively, norepinephrine (NA) doses were significantly higher in the treatment group (0.093 vs. 0.025 µg/kg/min, $P = .029$) with a continuous decrease in both groups thereafter. Two patients required additional vasopressin therapy during the first 24 hours (one in each group). There was a trend toward higher doses of dobutamine in the treatment group early after surgery (3.012 vs. 2.285, $P =$ ns). Two patients (one in each group) received adrenaline instead of dobutamine. At 48 hours after surgery,

TABLE 2 Postoperative adverse events and outcome

	HA group n = 10	Control group n = 10	*P* value
Adverse events [n]			
Cerebrovascular event	2	0	.474
Postoperative delirium	2	2	1.000
Nosocomial pneumonia	4	1	.303
Renal replacement therapy (after POD3)	2	0	.474
Gastrointestinal bleeding	1	0	1.000
Pacemaker implantation	3	2	1.000
Reexplorative surgery	1	1	1.000
ECMO support	1	0	1.000
Outcome parameters			
Transfusion [n]			
Packed red blood cells	2 (1-4)	1 (0-1)	.631
Platelet concentrates	0 (0-0)	0 (0-0.8)	.796
Fresh frozen plasma	0 (0-3)	0 (0-0)	.529
Human albumin [mL]	200 (0-425)	0 (0-225)	.218
Mechanical ventilation [hours]	20.5 (9.8-609.5)	14.0 (10.3-26.0)	.315
Time on ICU [days]	10.5 (4.8-29.0)	4.5 (2.0-7.3)	.023
In hospital stay [days]	20.0 (10.8-31.0)	11.5 (10.8-23.0)	.579
Mortality [n]	0	0	1.000
Scores			
SOFA Score[a]	7 (5-10)	6 (3-8)	.353
SAPS II Score[a]	34 (25-43)	29 (23-35)	.393
APACHE II Score[b]	23 (20-24)	21 (18-25)	.631

Note: Data are presented as medians (25th-75th percentiles) or absolute values.

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

[a]On the second postoperative day.

[b]At 6 hours postoperatively.

the majority of patients did not require any further inotropic support (8 vs. 7 pts., P = ns). With regard to fluid therapy, patients in the treatment group required significantly more volume replacement compared with the control group (7217 vs. 4185 mL at 12 hours; 10 819 vs. 4934 mL at 24 hours, and 12 021 vs. 4850 mL at 48 hours, $P = .015$).

Neither base excess nor lactate levels differed significantly between both groups. There were no significant differences in the number of patients receiving hydrocortisone, methylene blue, calcium, or sodium bicarbonate during the first 48 hours after surgery, neither.

4 | DISCUSSION

According to the results of the presented study, HA therapy did neither result in a reduction of inflammatory parameters nor of catecholamine or fluid requirement in patients after cardiac surgery for IE. A beneficial effect can only be surmised based on the observation, which significantly higher preoperative CRP and PCT levels in the HA group equalized intra- and postoperatively (Figure 3).

Since its introduction into clinical practice in the early 2000s, HA therapy has been controversially discussed. Aiming to reduce the so-called "cytokine storm" and, thus, preventing SIRS, septic shock, and organ dysfunction as well as capillary leakage, the actual clinical effect of HA therapy has been shown to be highly variable.[2,5] On the one hand, there are a number of studies supporting the efficacy of this therapeutic approach. However, there are only six randomized controlled trials concerning SIRS in cardiac surgery. However, there are a variety of reports, which did not observe any effect of the HA therapy. As outlined below its efficacy seems to be dependent on the underlying disease of the treated patient population as well as on the onset and duration of therapy. However, distinct criteria for the identification of

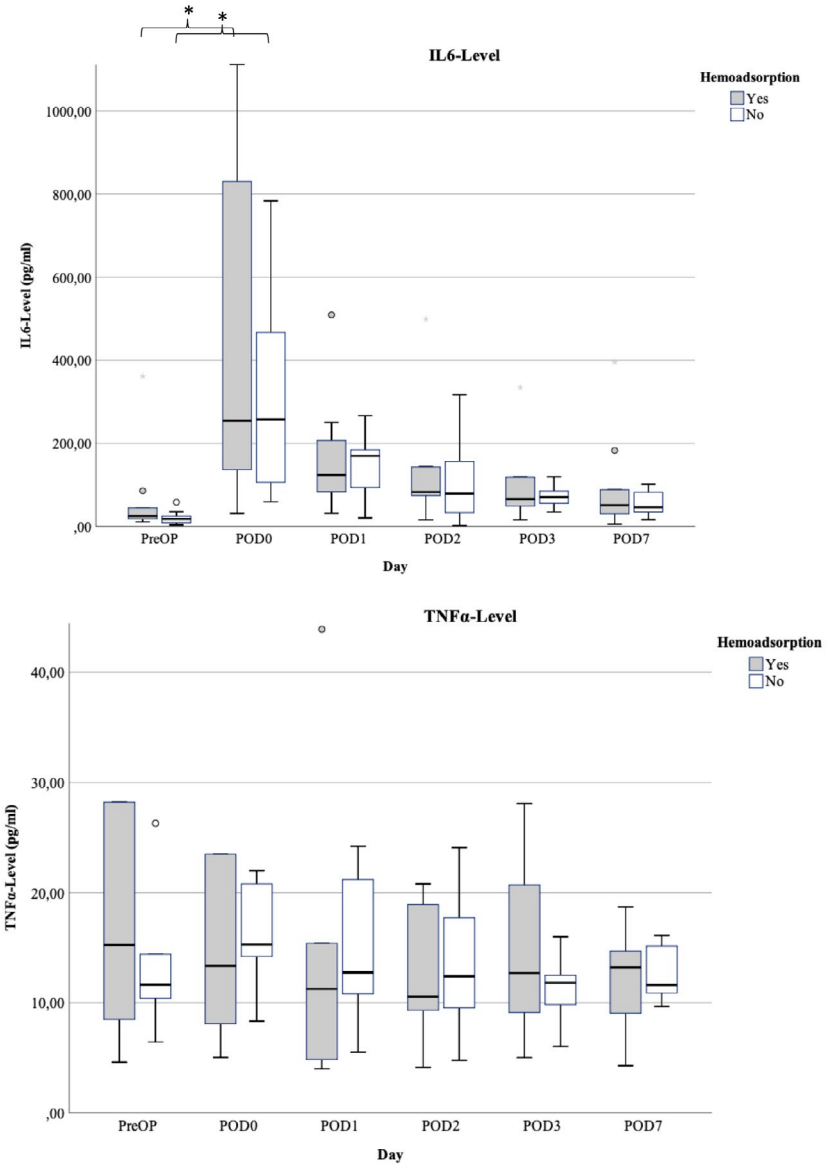

FIGURE 2 Development of cytokine levels (IL-6 and TNF-α). CPB, cardiopulmonary bypass; IL-6, interleukin 6; POD, postoperative day; TNF-α, tumor necrosis factor-α [Color figure can be viewed at wileyonlinelibrary.com]

those patients who might benefit from this therapeutic approach are still lacking.

In this context, the underlying pathomechanism has to be considered. The activation of the immune system by pathogen- or damage-associated molecular patterns (PAMPs or DAMPs) results in the release of inflammatory cytokines which are associated with the development of SIRS and sepsis, resulting in organ dysfunction and increased mortality.[5,13,14] Moreover, capillary leakage is induced by specific cytokines, such as IL-6, resulting in tissue edema, hypoxia, and necrosis.[5,15] It has been shown that an early start of HA therapy is crucial for the therapeutic effect in septic patients.[16] An introduction within the first 24 hours after the onset of septic shock has been reported to have a positive effect on patient survival.[5] Moreover, a sufficient duration (≥24 hours) of treatment seems to be essential. As previous studies revealed, neither an HA therapy for 5 hours on CPB in a porcine model, nor a clinical application with a mean treatment time of 191 ± 56 minutes on CPB had any effect on postoperative inflammatory parameters.[8,17] It has also been reported that peak interleukin levels after cardiac surgery occurred during CPB and 6 hours thereafter.[8,18] Therefore, in the presented study, HA therapy has not only been applied during CPB, but also continuously thereafter until 24 hours, postoperatively, however, without any significant therapeutic effect. On the contrary, catecholamine doses, fluid requirement and length of ICU stay were (significantly) less favorable in the HA group.

In accordance with our results, there are previous studies that found neither evidence for a reduction of proinflammatory cytokine levels in patients after cardiac surgery[8,19] nor any other therapeutic effect in critically ill patients with septic shock and multiorgan failure.[20] However, there are also encouraging reports, although mainly case series. Träger et al reported a cytokine reduction associated with an improved hemodynamic stability and organ function

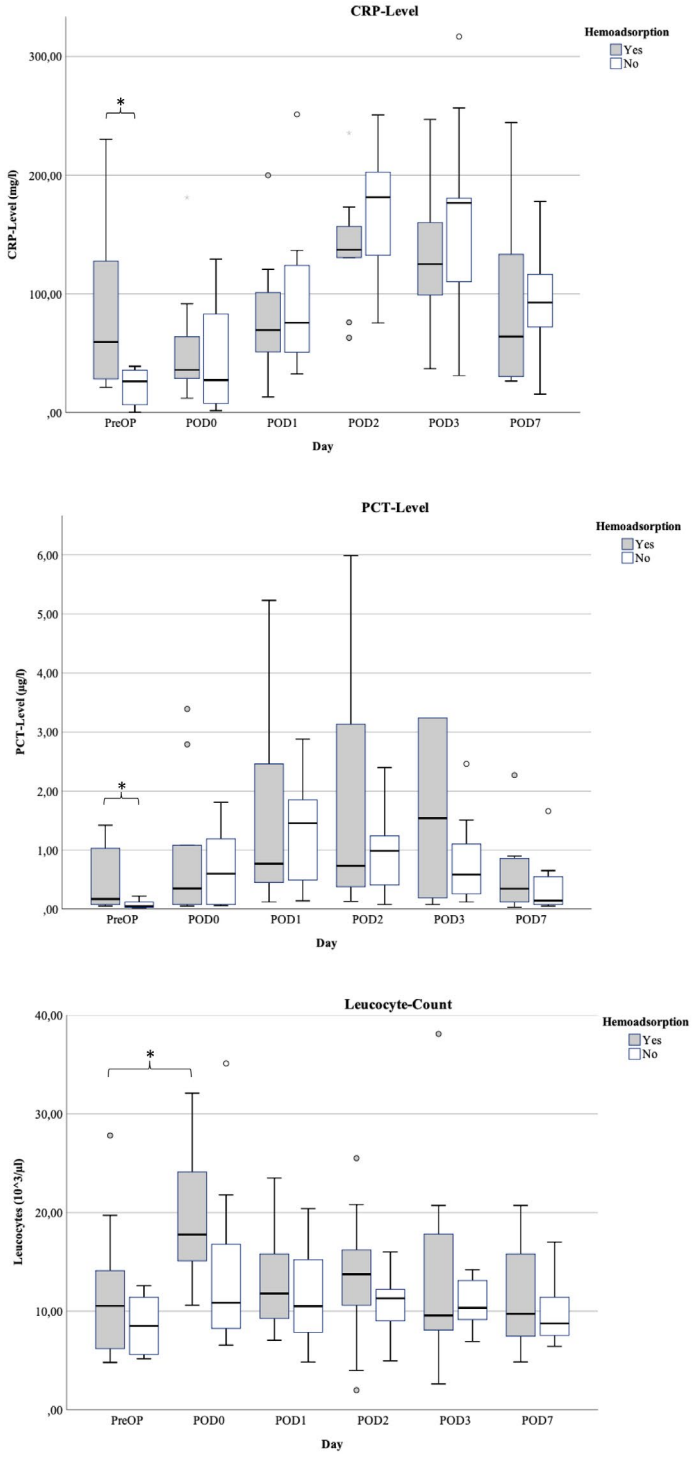

FIGURE 3 Development of infection parameters (CRP, PCT, and leukocytes). CPB, cardiopulmonary bypass; CRP, C-reactive protein; PCT, procalcitonin; POD, postoperative day [Color figure can be viewed at wileyonlinelibrary.com]

in patients with IE receiving intraoperative HA therapy.[2] Similar results have been achieved in patients developing postcardiopulmonary bypass SIRS treated with HA therapy.[12]

The explanation for the highly variable effect of HA therapy seems to be multifactorial depending on the particular study population. First, the activation of cytokines by CPB is associated with substantial inter-individual differences.[8] In the investigated patient cohort, overall cytokine levels were comparably low. As the removal of substances by HA therapy depends on its particular plasma concentration: cytokine plasma levels are reduced less effectively when peak concentrations are already low.[2] Therefore, repeated HA therapy does not result in a further decrease of already low cytokine levels.[12] This decreasing efficacy of HA therapy in low cytokine levels is an important safety aspect, as the immune system depends on a certain level of cytokines.[12] Second, according to the "cytokinetic theory" described by Honore et al, cytokine plasma levels may remain stable while being removed from the blood because of a cytokine shift from the interstitial into the blood compartment.[21]

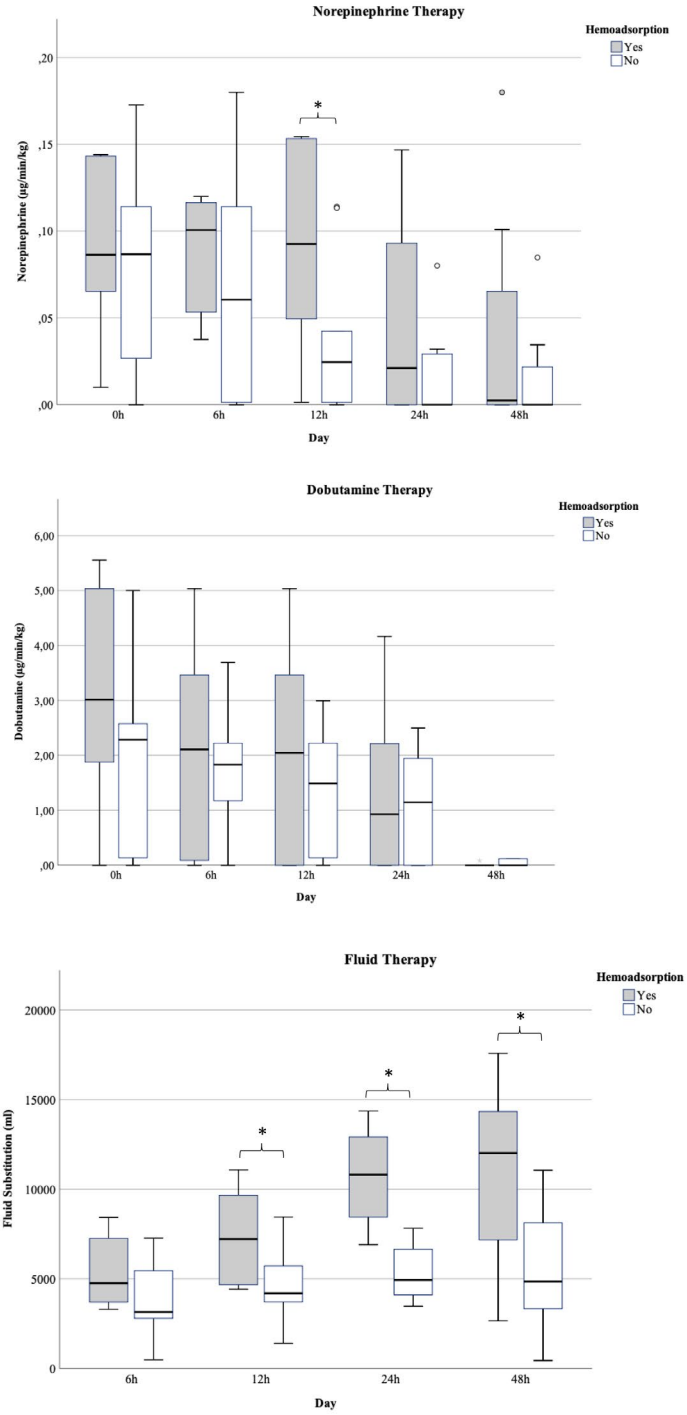

FIGURE 4 Postoperative catecholamine and fluid therapy. CPB, cardiopulmonary bypass; POD, postoperative day [Color figure can be viewed at wileyonlinelibrary.com]

This theory is supported by Schädler et al, reporting a substantial (up to 18%) elimination of Il-6 by HA therapy in septic patients, estimated by pre-filter compared to post-filter concentration, without any effect on systemic plasma levels.[20] Obviously, cytokine elimination can largely be compensated. Third, in the presented study, the significantly higher leukocyte count in the treatment group may have resulted in a more pronounced cytokine release masking the therapeutic effect of HA therapy. According to Schädler et al, a prolonged treatment (6 hours per day for several days) may be more effective in reducing IL-6 plasma levels in a comparable group of patients.[20] In sum, either an individualized therapeutic approach based on cytokine plasma levels or a prolonged HA therapy for several days or a combination of both might be the strategy of choice in future patients.

Concerning inotropic support and fluid therapy, no therapeutic effect of HA therapy was observed in the study population either. On the contrary, norepinephrine doses and fluid requirements were significantly higher in the HA group. These results correspond to the findings of previous studies. Bernardi et al investigated the effect of HA therapy during CPB surgery. They did not find any significant reduction of

catecholamine or postoperative fluid requirement nor was there any positive effect on the development of postoperative edema.[8] In our patient cohort, the relatively low severity of disease (Table 1) may be a possible explanation for the lack of a therapeutic effect of HA therapy. Compared with the study of Träger et al,[12] who observed a decrease of cytokine levels associated with hemodynamic stabilization and decreasing vasopressor support, baseline vasopressor doses were twice as high in their patients compared with our study population.

Based on the presented results, the diagnosis of IE per se is probably not an adequate indication for HA therapy. Accordingly, Diab et al reported that median cytokine levels after surgery for infective and noninfective valvular heart disease did not even differ in the postoperative period (>6 hours postoperatively),[22] indicating the necessity of an individually based treatment.

With a median EuroSCORE II of 4.6 the overall risk profile in the investigated patients was comparably low. According to Bernardi et al, patients with an intermediate to high operative risk (EuroSCORE II 16-31 or 31-97, respectively) should primarily be considered for HA therapy.[2,8] Moreover, patients with an excessive inflammatory response need to be identified.[8] Previous studies reported that higher postoperative cytokine levels (IL-6 up to 5000 pg/mL) were associated with a more effective HA treatment.[2,8,20] Therefore, preoperative, intraoperative, and postoperative estimation of inflammation parameters may be advisable and cutoff values have to be defined.

Finally, the onset of treatment seems to be crucial. In a case series of 26 critically ill patients with septic shock, patients were treated by a combined CVVHD (continuous veno-venous hemodialysis) and HA therapy.[16] All ICU and hospital survivors were treated early (<24 hours) after the onset of septic shock, whereas none of those patients, who were treated late (>48 hours), survived.[5,16] Therefore, HA therapy during and after cardiac surgery for IE seems to be indicated dependent on the severity of symptoms associated with SIRS or sepsis, whereas the treatment of all patients independent of disease severity (as in the investigated study population) does not seem to have a beneficial effect.

Due to the limitations of the study which are mainly based on the lack of informed consent in critically ill patients, a more expedient approach for future investigations will rather be observational than a randomized one. Meanwhile, hemoadsorption has become a standard therapy in cardiac surgery at many institutions although available data are limited and contradictory. Also at the authors institution, where HA is applied for a variety of indications, such as infective endocarditis, heart transplantation, as well as extended aortic surgery. Interestingly, a substantial number of surgeons, anesthetists, and intensivists are somehow convinced of this therapy usually based on positive "single-case observations."

5 | LIMITATIONS

The overall number of patients was low. Therefore, interindividual differences had a major impact on statistical results. As informed consent had been required by the local ethics committee, intubated and sedated patients were not available for inclusion, among them, several patients with advanced disease in a critical state. As a consequence, disease severity was comparably low in the investigated patient collective.

6 | CONCLUSION

In the investigated patient population, HA therapy did neither result in a reduction of inflammatory parameters nor result in an improvement of postoperative hemodynamic parameters. Therefore, cardiac surgery for IE per se, independent of the severity of SIRS or sepsis, does not seem to be an indication for HA therapy. For a more targeted use of HA therapy, appropriate selection criteria are required. Moreover, a less invasive stand-alone therapy for postoperative application would be desirable.

CONFLICT OF INTEREST

The authors of the manuscript declare that they have no conflicts of interest associated with this study.

AUTHOR CONTRIBUTIONS

Study design: Asch, Leistner, Niehaus
Data analysis: Asch, Kaufmann, Walter
Data interpretation: Asch, Kaufmann, Walter
Drafting the article: Asch
Statistics: Kaufmann
Data collection: Kaufmann
Critical revision of the article: Walter, Danner, Perl, Kutschka, Niehaus
Other: Leistner, Kutschka

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