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Changes in cytokine concentrations during passage through a granulocyte and monocyte adsorption column in a porcine lipopolysaccharide-induced inflammation model

Tomoyuki Nakamura¹, Kazuhiro Moriyama^{2*} , Toshikazu Sakai³, Yu Kato⁴ and Osamu Nishida¹

Abstract

Background Sepsis 3 definitions have shifted the focus from nonspecific inflammation to sepsis as an organ dysfunction caused by a dysregulated host response to infection. Neutrophils have become therapeutic targets because of their intimate but complex involvement in sepsis. We conducted ex vivo and animal experiments to apply a granulocyte and monocyte adsorption column, which is clinically used for inflammatory bowel disease, in sepsis. In this study, the biocompatibility was evaluated in sepsis-like hypercytokinemia.

Methods Six female outbred pigs were anesthetized. Extracorporeal direct hemoperfusion (DHP) with an Adacolumn or a sham column was initiated after lipopolysaccharide (LPS) administration. The DHP was performed for 2 h at a blood flow rate (QB) of 30 or 60 mL/min. Blood samples were collected before and during the DHP (30, 60, 90, and 120 min). The percentage change in white blood cell count, platelet count, and cytokine concentration was compared between the Adacolumn and sham columns.

Results The percentage change in white blood cells were 96 (95–98)% and 106 (101–108)% in the Adacolumn and sham groups, respectively, at QB=60 mL/min ($p < 0.01$). The percentage change in platelets were 95 (90–96)% and 97 (93–99)% in the in the Adacolumn and sham groups, respectively, at QB=60 mL/min (not significant; n.s.). At QB=60 mL/min, the percentage change in tumor necrosis factor- α , interleukin (IL)-6, and IL-10 were 92 (81–106)%, 95 (93–102)%, and 98 (95–100)%, respectively, for the Adacolumn and 100 (95–102)%, 98 (87–104)%, and 97 (93–99)%, respectively, for the sham column. The percentage change in white blood cell counts, platelet counts, and all cytokines at QB=30 and 60 mL/min showed similar trends.

Conclusion The biocompatibility of the Adacolumn was evaluated using a porcine LPS-induced inflammation model. No decrease in platelet counts or significant cytokine production was observed, suggesting that the Adacolumn could be safely used in patients with sepsis with QB=30–60 mL/min for 2 h. However, production of mediators other than cytokines remains unknown and requires further investigation.

Keywords Adacolumn, Sepsis, Biocompatibility, Cytokines, Porcine model

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Background

Sepsis-3, defined as life-threatening organ damage resulting from an uncontrolled host response to infection, has shifted the focus from non-specific inflammation to organ dysfunction caused by a dysregulated host response to infection [1]. Increasing evidence supports a central role of the immune system in sepsis; however, the current view of how sepsis affects immunity and vice versa is still rudimentary [2]. Neutrophils play essential roles in controlling infections under normal conditions. However, under hypercytokinemia, they cannot migrate to the infection site and their lifespan, which is normally short, is prolonged, resulting in persistent tissue damage and the development of organ dysfunction via release of several cytotoxic mediators, such as free radicals, proteolytic enzymes, and neutrophil extracellular traps (NETs) [3, 4]. The production of NETs causes microcirculatory disturbances that may lead to organ damage [5, 6]. The intimate but complex involvement of neutrophils in sepsis makes them promising targets for therapeutic intervention. Several approaches have been developed to therapeutically target neutrophils [7, 8].

In Japan, 40% of patients requiring blood purification have sepsis [9]. Blood purification for sepsis has long targeted molecules such as endotoxins and cytokines. Although polymyxin B-immobilized fiber columns (PMX) and cytokine-adsorbing hemofilters (CAH) are currently used in practice [10–12], blood purification methods targeting immune cells do not exist. However, in chronic inflammatory settings, such as inflammatory bowel disease (IBD), granulocyte and monocyte adsorption apheresis (GMA) with Adacolumn (JIMRO Co., Ltd., Takasaki, Japan) has been used safely in clinical practice.

We previously reported the basic performance of the Adacolumn in ex vivo experiments using lipopolysaccharide (LPS)-challenged porcine blood [13].

This study aimed to investigate whether leukocytes adsorbed on the Adacolumn produce cytokines or whether platelets are adsorbed on the column. We used a porcine LPS-induced inflammation model to mimic sepsis and determine whether Adacolumns could be safely used in patients with sepsis.

Experiment 1: porcine model

Materials and methods

Study animals

This study was approved by the Institutional Animal Care and Use Committee of the Fujita Health University (approval number: M3762). Six female outbred pigs (age: 3–4 months; body weight: 35–40 kg) were used in the study. The pigs were housed under standard environmental conditions for at least 2 d before each experiment.

Animal preparation

Considerations were made to minimize the number of animals used in the experiments as much as possible and choose methods that caused as little pain to the animals as possible. The pigs were anesthetized. Intramuscular injections of ketamine (5 mg/kg), atropine (10 µg/kg), and midazolam (0.5 mg/kg) were administered for premedication. Anesthesia was initiated with intravenous injection of ketamine (5 mg/kg) and midazolam (0.5 mg/kg), followed by 2% sevoflurane in oxygen. Subsequently, LPS-induced inflammation was induced by intravenous infusion of a saline solution containing 10 µg/kg of LPS (*Escherichia coli* 0111) for 30 min.

Adacolumn

The device contained a 335-mL column filled with 220 g of specially processed cellulose diacetate beads approximately 2 mm in diameter [14]. Granulocytes and monocytes are known to highly express complement component C3 (CR3, also known as CD11b/CD18, Mac1, or integrin α M β 2) and Fc gamma receptors (Fc γ Rs) [15]. The Adacolumn beads are coated with immunoglobulin G and inactivated complement-3b (iC3b) when the blood goes through the column, which function as ligands for the Fc γ Rs and CR3 expressed in the activated granulocytes and monocytes, respectively, allowing selective adsorption of these cells [16].

Experimental protocol

Vascular catheters for extracorporeal circulation (GamCath; Gambro Dialysatoren GmbH, Hechingen, Germany) were placed in the right external jugular and right femoral veins. The blood was debranched from the external jugular vein and returned to the femoral vein. An Adacolumn and sham column (control column not filled with Adacolumn beads) were connected using a two-way circuit (Fig. 1). This circuit is characterized by the simultaneous passage of blood from the same individual through two columns.

Extracorporeal direct hemoperfusion (DHP) was initiated 30 min after continuous LPS administration. The DHP was performed using a TR-525 (Toray Industries, Inc., Tokyo, Japan) for 2 h at a blood flow rate (QB) of 30 or 60 mL/min. Approximately 4000 IU of unfractionated heparin was injected intravenously at the start, and 4000 IU/h was administered continuously thereafter. Blood samples were collected before and at 30, 60, 90, and 120 min after DHP initiation. Blood samples were collected from three sampling sites: the inlet side of both columns, outlet of the Adacolumn, and outlet of the sham column. Blood cell counts and tumor necrosis factor- α (TNF- α), interleukin (IL)-6, IL-8, and IL-10

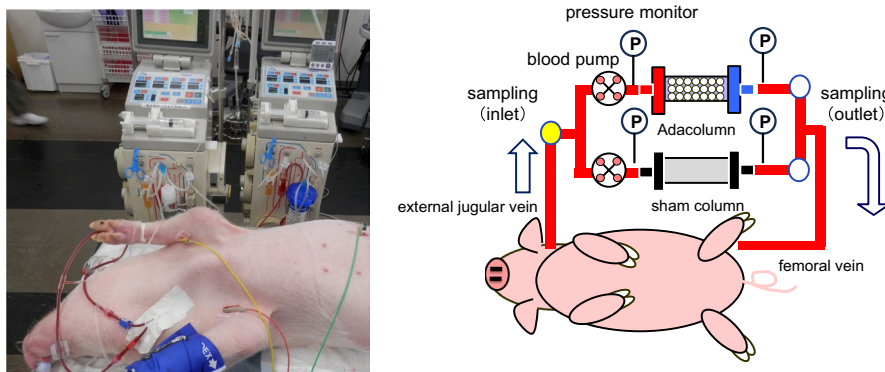


Fig. 1 Schematic picture of the extracorporeal circuit. An Adacolumn and sham column were connected using a two-way circuit. The blood was debranched from the external jugular vein and returned to the femoral vein. Blood samples were collected from three sampling sites: the inlet side of both columns, outlet of the Adacolumn, and outlet of the sham column. The adsorption and production of blood cells and cytokines were compared using percentage change (ratio of outlet to inlet concentration multiplied by 100)

were measured. The percentage change (ratio of outlet to inlet concentration multiplied by 100) in white blood cell counts, platelet counts, and cytokine concentrations was compared between both columns.

Measurements

Cytokine levels were measured by enzyme-linked immunosorbent assay (ELISA) using the following commercial kits: porcine IL-6 Quantikine ELISA (R&D Systems, Minneapolis, MN, USA), porcine IL-8/CXCL8 Quantikine ELISA (R&D Systems), porcine IL-10 Quantikine ELISA (R&D Systems), and porcine IL-10 Quantikine ELISA (R&D Systems) kits, according to the manufacturer's instructions.

Statistical analysis

Percentage change data are expressed as medians (25–75% interquartile range). The nonparametric Mann–Whitney *U* test was used for statistical analysis to compare the percentage change between the Adacolumn and sham column. Statistical significance was set at $p < 0.05$. Data of white blood cell and platelets counts are expressed as the mean \pm standard deviation (SD).

Results

White blood cells and platelets before and after column

DHP was performed in six pigs, three for each group at 30 and 60 mL/min, and the data were summed for 12-point percentage changes at four timepoints: 30, 60, 90, and 120 min. The trends in white blood cell counts during 2 h of DHP and 12-point percentage changes are shown in Fig. 2. The percentage changes were 96 [95–98]% and 106 [101–108]% in the Adacolumn and sham groups, respectively, at QB=30 mL/min ($p < 0.01$) and 92 [90–98]% and 104 [100–105]% in the Adacolumn and

sham groups, respectively, at QB=60 mL/min ($p < 0.01$). No differences were observed in white blood cell count between QB=30 and 60 mL/min.

The trends in platelet counts during 2 h of DHP and the 12-point percentage changes are shown in Fig. 3. The percentage changes were 95 [90–96]% and 97 [93–99]% in the Adacolumn and sham groups, respectively, at QB=30 mL/min (n.s.), and 95 [93–100]% and 98 [96–100]% in the Adacolumn and sham groups, respectively, at QB=60 mL/min (n.s.). The changes in platelet counts when blood passed through the columns were comparable between the two columns and no significant decrease was observed.

Cytokine concentrations at column inlet and outlet

Three of the six pigs, numbered one to three, were subjected to DHP at QB=30 mL/min, and three pigs, numbered four to six, were subjected to DHP at QB=60 mL/min. Plasma cytokine concentrations at each blood collection point for each individual are shown in Fig. 4. However, IL-8 could not be evaluated because many results were below the detection limit, even over time.

Percentage change in cytokine concentration during passage through column

As shown in Fig. 4, the blood cytokine concentrations increased with time and were high at 90 and 120 min. Since there were no missing data at these two timepoints, the median values at 90 and 120 min for the three pigs were compared between the Adacolumn and sham column at QB=30 and 60 mL/min. The percentage change in TNF- α , IL-6, and IL-10 at QB=30 mL/min were 102 [95–116]%, 85 [82–91]%, and 100 [94–103]% for the Adacolumn, respectively, whereas, the percentage change in the sham columns were 99 [96–102]%, 91 [87–102]%, and 96 [91–101]%,

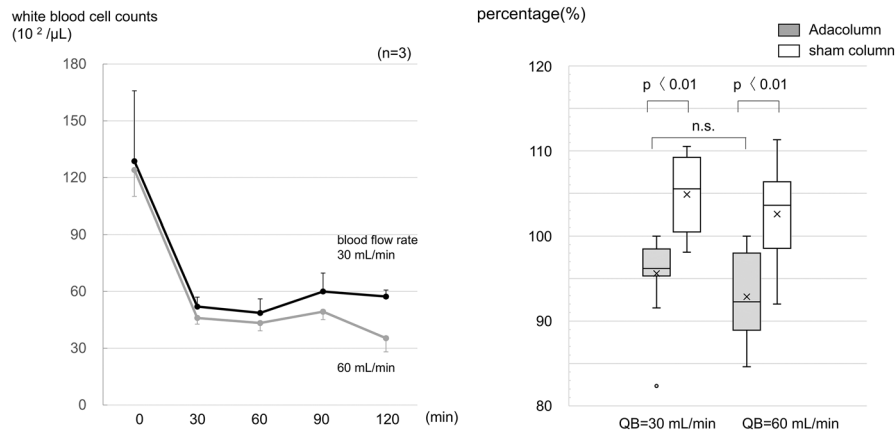


Fig. 2 Trends in white blood cell counts and percentage change during passage through the columns. Because of the small sample size, the trends in white blood cells are expressed as mean \pm standard deviation (SD) ($n=3$) (left). The percentage change in the white blood cell count as blood was passed through the column is indicated by the percentage change. Boxplot demonstrating the upper quartile, median, and lower quartile along with the maximum and minimum values obtained for the percentage change in white blood cell counts in the Adacolumn and sham column groups (right). X shows the average value. n.s., not significant; QB, blood flow rate

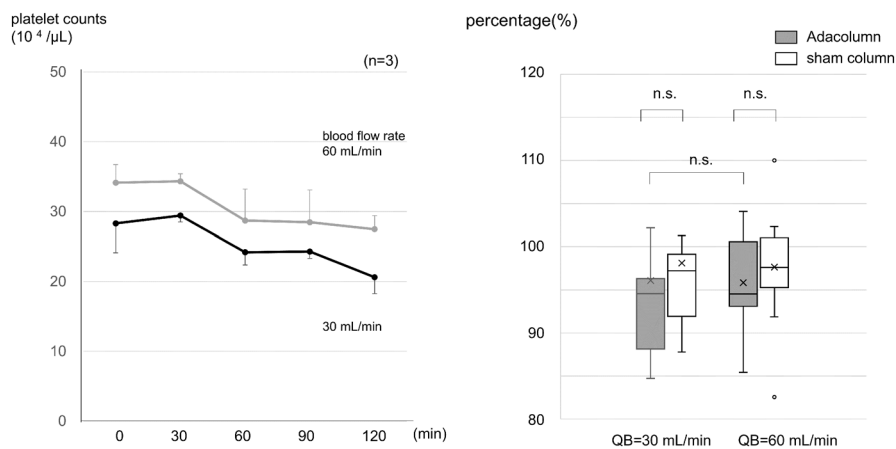


Fig. 3 Trends in platelet counts and percentage change during passage through the columns. Because of the small sample size, trends in white blood cells are expressed as mean \pm SD ($n=3$) (left). The percentage change in platelet count as blood was passed through the column is indicated by the percentage change. Boxplot demonstrating the upper quartile, median, and lower quartile along with the maximum and minimum values obtained for the percentage change in platelet counts in the Adacolumn and sham column groups (right). X shows the average value. n.s., not significant; QB, blood flow rate

respectively. The percentage change in TNF- α , IL-6, and IL-10 at QB=60 mL/min were 92 [81–106]%, 95 [93–102]%, and 98 [95–100]% for the Adacolumn, respectively, whereas, those for the sham columns were 100 [95–102]%, 98 [87–104]%, and 97 [93–99]%, respectively. The cytokine levels at both QBs were not significantly different between the two groups (Fig. 5).

Experiment 2: batch-wise test

Materials and methods

The experiments were based on previously reported Adacolumn bead adsorption tests [17]. The test

solution was prepared by dissolving cytokines [recombinant human (rh) TNF- α , rhIL-6, and rhIL-8 (all from FUJIFILM Wako Pure Chemical Co., Osaka, Japan)] in phosphate buffer (pH 7.2). The test solutions were filled into 5 mL sterile plastic syringes (Terumo Corporation, Tokyo, Japan) with the Adacolumn beads at a 1 mL:2 g ratio and without beads (control group), and incubated at 37 $^{\circ}\text{C}$ for 30 min. Cytokine concentrations were measured before and after incubation.

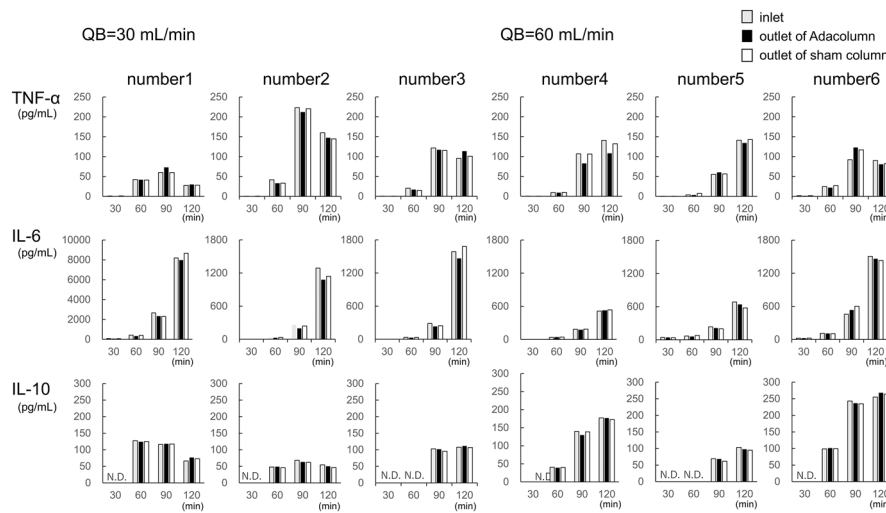


Fig. 4 Plasma cytokine concentrations before and after passing through the columns. Three of the six pigs (numbered one to three) were subjected to extracorporeal circulation at blood flow rate (QB) = 30 mL/min, and three pigs (numbered four to six) were subjected to extracorporeal circulation at QB = 60 mL/min. Cytokine concentrations in the blood at each time point are shown for each individual. TNF: tumor necrosis factor; IL: interleukin,

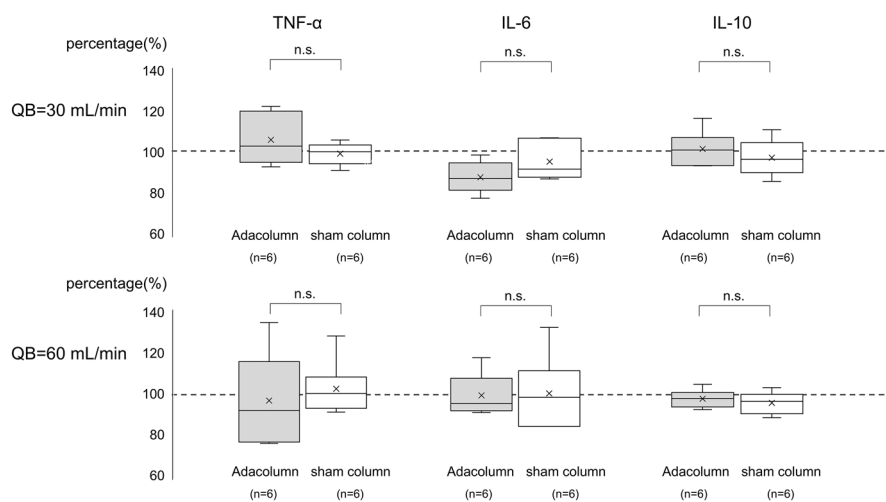


Fig. 5 Percentage change in the concentration of TNF- α , IL-6, and IL-10 during passage through the columns. The percentage change in cytokine concentration as blood was passed through column is indicated by the percentage change. Boxplot demonstrating the upper quartile, median, and lower quartile, along with the maximum and minimum values. X shows the average value. n.s., not significant; TNF, tumor necrosis factor; IL, interleukin; QB, blood flow rate

Measurements

Cytokines were measured by ELISA using the following commercial kits: Quantikine HS ELISA human TNF- α immunoassay (R&D Systems, Minneapolis, MN, USA), human IL-8 ELISA (Life Technologies, Tokyo, Japan), and human IL-6 (Fujirebio Inc., Tokyo, Japan) kits, according to the manufacturer’s instructions.

Statistical analysis

All results are expressed as the mean \pm SD. Student’s *t*-test was used to compare data between two groups. Statistical significance was set at $p < 0.05$.

Results

Batch tests were performed to confirm the cytokine adsorption properties of Adacolumn beads. The initial concentration of TNF- α was 12,600 pg/mL; after 30 min of incubation, the concentration was $13,000 \pm 497$ pg/mL

and $11,567 \pm 1,087$ pg/mL in the control and Adacolumn beads groups ($n=3$), respectively. Furthermore, IL-6 concentration went from 34,400 pg/mL to $34,867 \pm 694$ pg/mL in the control group and to $29,900 \pm 29,909$ pg/mL in the Adacolumn beads group. The IL-8 concentration went from 67,100 pg/mL to $65,200 \pm 726$ pg/mL in the control group and to $58,667 \pm 3,984$ pg/mL in the Adacolumn beads group. The ratio of TNF- α , IL-6, and IL-8 between the Adacolumn and control groups were 0.89 for TNF- α , 0.86 for IL-6, and 0.90 for IL-8. The concentrations of TNF- α , IL-6, and IL-8 after incubation were significantly lower in the Adacolumn group (Fig. 6).

Discussion

Adacolumn was first approved in Japan as a GMA for IBDs in 1999. The safety profile of the GMA is a major advantage. Post-market surveillance from 53 medical institutions in Japan provides the largest ever clinical safety data; adverse events were of low to mild severity [18]. It has since been approved for Crohn’s disease [19], pustular psoriasis [20], and psoriatic arthritis [21]. Furthermore, it has been used in general clinical practice in approximately 66,000 patients with few reports of serious side effects and is recognized as a safe treatment method.

However, the degree of blood cell stimulation may differ between patients with chronic inflammation and sepsis. In particular, the degree of cytokine production from granulocytes and monocyte adsorbed on the column, and the decrease in platelet count, should be evaluated for safe use in patients with sepsis. The Adacolumn has been used for outpatients with chronic inflammation with QB=30 mL/min and 1 h of DHP; however, increased

blood flow is usually required for its use in sepsis in the intensive care unit. In this experiment, the perfusion time was 2 h and the QB was set at 30 and 60 mL/min.

First, leukocyte adsorption by Adacolumn was observed at both QBs over a 2-h period. Notably, the percentages of granulocytes and monocytes targeted by the Adacolumn-DHP were lower in pigs (approximately 35%) than in humans. The mechanism of adsorption of porcine granulocytes and monocytes to Adacolumn is not yet clear. Recent studies have advanced the similarity between human and porcine surface markers [22], and the fact that monoclonal antibodies that inhibit CD11b or the α -chain of CR3 inhibit the phagocytosis of polymorphonuclear neutrophils (PMNs) to iC3b-opsonized particles and their ability to adhere to plastic suggests that porcine CD11b may function similarly to its human counterpart. CD11b is thought to have a similar function to that of human CD11b [23]. This suggests that the mechanism of neutrophil adsorption on Adacolumn is similar in humans and pigs. Platelet counts are often reportedly lower in patients with DHP [24]. However, no differences were observed in the percentage change in the platelet count between the Adacolumn and sham column. This suggests that fewer adverse events occur when this technique is applied to patients with sepsis having low platelet counts or complicated disseminated intravascular coagulation.

We reported the results of basic ex vivo experiments to develop a new blood purification system for regulating excessive immune reactions in sepsis using an Adacolumn and a CAH (AN69ST hemofilter). The phagocytic activity of granulocytes decreases and adhesiveness

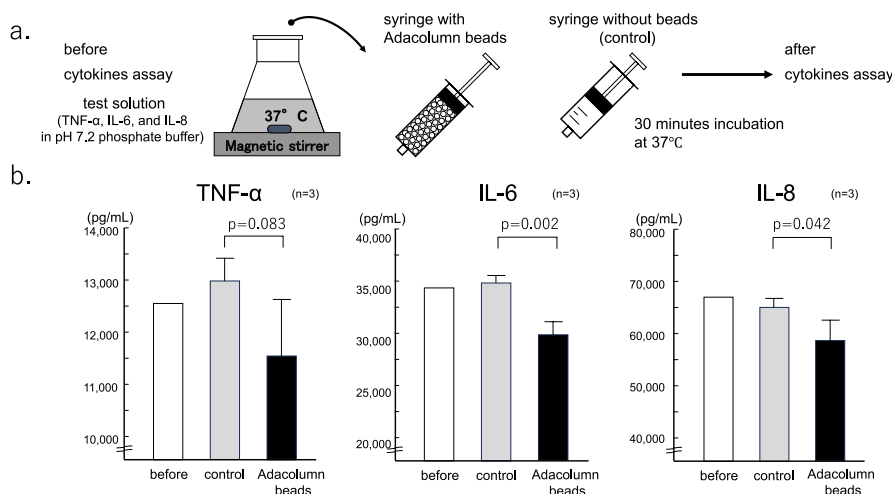


Fig. 6 Cytokine concentration after incubation with Adacolumn beads in the batch-wise test. **a** The test solutions were filled into 5-mL sterile plastic syringes with or without (control group) the Adacolumn beads, and incubated at 37 °C for 30 min. **b** Cytokine concentrations were measured before and after incubation. Because of the small sample size, data are expressed as mean \pm SD ($n=3$). TNF, tumor necrosis factor; IL, interleukin

increases; however, the number of CD11b-positive cells markedly decreases [13]. This study showed that the second filter can adsorb cytokines, but the study did not examine pathogen associated molecular patterns or damage-associated molecular patterns, and the results were unknown. In this study, producing cytokines upstream of the Adacolumn was necessary to confirm the cytokine adsorption capacity of the CAHs downstream of the blood purification system. To this end, a large amount of LPS was injected into porcine blood, which was repeatedly circulated in a closed circulation system for 6 h. Naturally, this *ex vivo* experiment is distinct from clinical practice; therefore, we were interested in the extent of cytokine production under conditions similar to those in clinical practice. Therefore, we conducted the current study using a porcine LPS-induced inflammation model.

To the best of our knowledge, this is the first study to evaluate the biocompatibility of the Adacolumn in pigs with sepsis-like inflammation. The cytokine concentrations were measured over 2 h. Therefore, the cytokine concentrations were measured over time in all individuals at 90 and 120 min. Contrary to expectations, the cytokine concentrations in the blood passing through the Adacolumn tended to be lower than those passing through the sham column. Therefore, we evaluated the cytokine adsorption capacity of the beads using an *in vitro* phosphate buffer system (Methods 2). The results showed weak adsorption of TNF- α , IL-6, and IL-8 on the Adacolumn beads. This explains why cytokine concentrations may decrease when passing through the Adacolumn.

Interestingly, in reviewing research on chronic inflammation such as IBD, Adacolumn DHP not only reduces inflammation by adsorbing granulocytes and monocytes but also immunomodulates leukocyte anti-inflammatory activity when they pass through a column. The cytokine-producing capacity of neutrophils is reduced in patients with IBD after passing through the Adacolumn, and the number of anti-inflammatory CD10-negative premature granulocytes increases, indicating an increased turnover of these cells in circulation [17, 25]. Recently, Adacolumn beads have been suggested to modulate the immune system by inducing anti-inflammatory myeloid-derived suppressor cells via iC3b activation [26] and phagocytosis-induced cell death responses [27]. These immunomodulatory effects may contribute to the suppression of inflammation during sepsis. However, further studies are required to confirm these effects in patients with sepsis.

This study has several limitations. First, although LPS-induced models are important for elucidating the integrated pathophysiology of infection and inflammation, this approach has limitations because it does not

completely mimic the physiological changes that would occur during bona fide sepsis. However, since the purpose of this study was not to evaluate sepsis pathogenesis but to confirm the biocompatibility of Adacolumn beads with granulocytes and monocytes under hypercytopenemia, we believe that this inflammation model will allow us to evaluate the results. In fact, the average concentration of IL-6 at 120 min in the six pigs was 2300 pg/mL, which is higher than that detected in sepsis (approximately 1000 pg/mL) [28] and may be used for evaluation. Second, the sample size used in this study was small. Although we considered using small animals such as rats to increase numbers, we chose a porcine model that is structurally and immunologically similar to humans. The porcine immune system resembles humans for >80% of analyzed parameters in contrast to the mouse with only about 10% similarity [29]. In addition, by running the Adacolumn and sham column from the same pig, we theorized we could minimize the individual difference factor as much as possible and withstand the evaluation. Third, this study evaluated only the production of biocompatible cytokines. Therefore, the production of factors such as those resulting from hypotension, which were not measured, remains unknown. When an Adacolumn is used to treat sepsis, continuous hemo(dia)filtration is combined in many cases. When using the Adacolumn and hemofilter simultaneously, connecting the Adacolumn upstream and the hemofilter downstream in series and parallel is recommended [30]. Finally, in this study, the blood flow rate was set at 30 mL/min and 60 mL/min, but the optimal blood flow rate, and duration time for the granulocyte adsorption rate and the number of granulocytes adsorbed, needs further investigation.

In summary, Adacolumn-DHP was performed for 2 h at QBs of 30 and 60 mL/min using a porcine model with an intravenous endotoxin. White blood cell counts decreased significantly before and after passing through the Adacolumn, whereas platelet counts did not. No significant production of TNF- α , IL-6, and IL-10 was observed when passing through the column.

Conclusion

The biocompatibility of the Adacolumn was evaluated using a porcine LPS-induced inflammation model. No decrease in platelet counts or significant production of cytokines was observed, suggesting that the Adacolumn could be safely used in patients with sepsis with QB=30–60 mL/min for 2 h. However, production of mediators other than cytokines remains unknown and requires further investigation.

Abbreviations

NETs	Neutrophil extracellular traps
PMX	Polymyxin B-immobilized fiber column
CAH	Cytokine-adsorbing hemofilter
IBD	Inflammatory bowel disease
GMA	A granulocyte and monocyte adsorption apheresis
LPS	Lipopolysaccharide
CR3	Complement component C3 receptor
FcγR	Fc gamma receptors
iC3b	Inactivated complement-3b
DHP	Direct hemoperfusion
ELISA	Enzyme-linked immunosorbent assay
QB	Blood flow rate

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Not applicable.

Author contributions

T.N. and K.M. wrote the manuscript and analyzed the data. K.M. and O.N. designed the study and revised the manuscript. T.N., T.S., Y.K., and K.M. contributed to the data collection. K.M., T.N., T.S., Y.K., and O.N. discussed the results and contributed to the final manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data used in this article are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Animal Care and Use Committee of the Fujita Health University (approval number: M3762).

Consent for publication

Not applicable.

Competing interests

Kazuhiro Moriyama is a member of the Endowed Chair of JIMRO Co., Ltd., and has consulting contracts with Baxter Ltd., Toray Industries Inc., and Asahi Kasei Medical Co., Ltd.. The remaining authors declare no conflicts of interest.

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