Safety and efficacy of single-needle leukocyte apheresis (LCAP) for treatment of ulcerative colitis

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ABSTRACT

Background: Leukocyte apheresis (LCAP) is a safe and effective treatment for active ulcerative colitis (UC) in Japan. Nevertheless, a limitation of LCAP is its requirement for two puncture sites (double-needle [DN] apheresis), sometimes leading to problems with needle puncture. Single-needle (SN) apheresis is useful in hemodialysis and reduces needle puncture pain. If SN apheresis were found to be useful in LCAP for UC, it may reduce patient burden.

Aim: To compare the safety and efficacy of SN apheresis with that of DN apheresis.

Methods: Twenty-four patients with active UC were retrospectively enrolled. They underwent either SN apheresis (n=12) or conventional double-needle (DN) apheresis (n=12) at the Kurume University Hospital from February 2014 to March 2018. At each session, we recorded access problems defined by the time required to initiate apheresis and the frequency of puncture-related problems, as well as blood circuit clotting, defined as clotting necessitating interruption of apheresis and changing of the circuit. Efficacy was assessed using partial Mayo scores.

Results: The number of apheresis sessions was comparable between SN and DN apheresis (9.0 ± 2.0 times vs 9.6 ± 1.4 times, mean ± SEM). SN significantly reduced the time required to start apheresis (10.0 ± 5.4 min vs 19.4 ± 11.9 min, $P<0.05$) as well as needle puncture troubles (0.9% vs 11.5%, $p<0.05$). SN had comparable frequency of blood clotting episodes (5.6% vs 8.7%). SN apheresis had similar clinical efficacy ($P<0.001$ in SN and $P<0.01$ in DN). The improvement and remission rates were comparable between groups.

Conclusion: SN apheresis may be safe and effective and may reduce patient burden during UC treatment. Nevertheless, further comparative studies are needed.

Keywords: LCAP, leukocyte apheresis, single needle, ulcerative colitis

INTRODUCTION

Ulcerative colitis (UC) is a disorder of unclear etiology characterized by chronic relapsing inflammation of the colon. Intense infiltration of the colonic mucosa by leukocytes, including granulocytes, monocytes and lymphocytes, are the hallmarks of UC; therefore, removal of circulating leukocytes may be an attractive approach to treatment.

In leukocyte apheresis, an extracorporeal therapy for UC developed in Japan, circulating leukocytes are removed using a column. A randomized controlled trial in patients with UC demonstrated that leukocyte apheresis was more effective than sham apheresis (1). This therapy presents almost no risk of infection; therefore, it is regarded as a very safe therapeutic approach. Two filters are commercially available—the leukocytapheresis (LCAP) column (Cellsorba), and the granulocyte and monocyte apheresis (GMA) column (Adacolumn) (2, 3). Both columns are used in a similar fashion for extracorporeal apheresis; however, each device has a distinct profile with respect to the removed cell type and the removal rate: the LCAP column traps and removes granulocytes, monocytes, lymphocytes, and some platelets; the GMA adsorbs granulocytes and monocytes only. One session with the LCAP removes 13.0×10^9 leukocytes, whereas only 4.0×10^9 leukocytes are removed by the GCAP. Recent aggregate data suggest that the effects of LCAP and GMA columns may act, at least in part, through different mechanisms of action (4, 5). Therefore, the safety and efficacy of SN apheresis should be separately evaluated for each column.

Single-needle (SN) hemodialysis, also called short needle dialysis, is useful for the induction phase of hemodialysis, the needle puncture trouble on the blood feeding side, and the home dialysis (6). By contrast one limitation of leukocyte apheresis is its requirement for two puncture sites (double-needle (DN) apheresis), which sometimes causes problems related to needle puncture. If SN apheresis was available for the treatment of UC, patient burdens may be reduced. In fact, two recent reports showed that GMA using SN (SN-GMA) was useful for the treatment of UC (7, 8). Nevertheless,

to the best of our knowledge, nothing is known regarding the usefulness of LCAP using SN (SN-LCAP).

Based on this background, we evaluated for the first time the safety of SN-LCAP in patients with UC. We also preliminarily assessed the clinical efficacy of this therapy.

PATIENTS AND METHODS

Ethics

The study protocol was reviewed and approved by the Ethics Committee of Kurume University School of Medicine (No. 18046).

Patients

The study was conducted at Kurume University Hospital from February 2014 to March 2018. We enrolled 24 patients who were diagnosed with UC and had undergone LCAP. The eligible patients had an established diagnosis of UC confirmed with endoscopy and histopathology. LCAP was introduced in moderate-to-severe UC patients whom the attending physician had determined as having inadequate responses or who failed to tolerate one or more of the following conventional therapies: 5-aminosalicylates, corticosteroids, azathioprine, and anti-tumor necrosis factor-α antibody.

Study Design

Clinical notes were reviewed retrospectively. To eliminate selection bias, a continuous registration method was adopted in which all patients undergoing LCAP in our hospital were enrolled. The DN-LCAP group and the SN-LCAP group were treated during different time periods; the patient group during the first period received DN-LCAP and the patient group during the second period (since September 2016) received SN-LCAP. The observation period was started 2 weeks before the first LCAP session and finished 2 weeks after the final LCAP session.

Structure of the column

The LCAP column is composed of a cylindrically rolled nonwoven fabric of polyester fiber. The column has a double-layered structure with an inner main filter and an outer pre-filter. The main filter consists of a nonwoven fabric made of fibers with diameters of 0.8 to 2.8 μm, while the pre-filter is made of a nonwoven fabric comprised of fibers with diameters of 10 to 40 μm (9). The filling volume of the fabric is 10 mL. Considering the stable and effective performance of the column with respect to leukocyte removal (10), the specifications of LCAP were determined according to the fiber diameter, volume, and configuration of the nonwoven fabric, as described above. Blood entering the column flows from outside to inside the cylinder of nonwoven fabric, then exits from the center of the column. Leukocytes are adsorbed and removed as the blood passes through the nonwoven fabric filter.

Double-needle LCAP

The conventional DN-LCAP method is shown in **Figure 1** and **Table 1**. To avoid blood coagulation, heparin (2,000 units) is injected into the circuit. Blood is drawn from a cubital vein or a femoral vein into the circuit using a blood pump and is sent to the LCAP column (Cellsorba EX; Asahi Kasei Medical Co., Tokyo, Japan). The processed blood flows in the circuit and is returned to a cubital or a femoral vein on the opposite side of the body. The flow rate is adjusted to 40 mL/min, and approximately 1,800 mL of blood is processed per session (4).

Single-needle LCAP

SN-LCAP was performed based on the method used in SN-GMA (**Figure 2, Table 1**) (7, 8). Before transferring to a dialysis monitor (DCS-27, Nikkiso CO., Ltd, Tokyo, Japan), an LCAP column is used. The SN method involves one needle, one blood pump, and one valve. The system of the blood pump and vein clamping is automatically controlled as per the venous pressure and the set upper limit value of the SN control pressure. In the arterio-venous bloodline, blood is withdrawn from the patient, and positive pressure accumulates in the LCAP blood compartment. Once a preselected upper limit internal pressure of the circuit (180 mmHg) is reached, the blood pump head stops rotating in the venous phase, and the valve opens to return the blood to the patient until a preset

lower limit pressure (30 mmHg) is reached.

For the vascular access, delivery was performed from the arm veins, and a Happy Cass 17-G needle (Happy Cass, Tokyo, Japan) was used as a puncture needle for the DN method. By contrast, a Happy Cass 16-G single needle (Happy Cass) was used for SN apheresis. If puncture was difficult, a Happy Cass 17-G needle with a three-way stopcock was used. The DN method was performed at a flow rate of 40 mL/min for 60 min to achieve 1800 mL blood volume/session. In the SN methods, the LCAP blood flow rate setting was 40–100 mL/min, and the average blood flow rate of LCAP is 40 mL/min with the aim of processing 1,800 mL blood volume/session. The administration time can be set to one hour, similar to that in the DN method. Heparin (2000 units) was used as an anticoagulant.

Study evaluations

Information regarding clinical parameters, including demographic data (gender, age, disease extent and disease duration), disease activity and medications were collected at the time of the first LCAP session.

The subsequent LCAP procedure at each session was analyzed in this study. Access problems were defined as more than 30 min required to achieve puncture. Clotting problems were defined as clotting necessitating interruption of apheresis and changing of circuit.

To assess disease activity, partial Mayo scores was calculated at week 0 (baseline) and 2 weeks following the final LCAP session (11). The score is the sum of three sub-scores (i.e., stool frequency, rectal bleeding, and a physician's global assessment). Each sub-score ranges from 0–3, with higher scores indicating greater disease severity. The partial Mayo score ranges from 0–9. Clinical remission was defined as score ≤ 2 with no individual sub-score > 1 point (12).

Statistical analyses

Continuous data were compared using independent t-tests, and categorical data were compared using chi-square test. The associated P-values from the *t*-tests and chi-square tests were interpreted as statistically significant if the P-values were < 0.05. Statistical analysis was performed using JMP® 11 (SAS Institute Inc., Cary, NC, USA). Data were expressed as mean ± SEM.

RESULTS

Patient characteristics

The total study population comprised of 24 patients; 12 patients were treated with SN-LCAP and 12 were treated with DN-LCAP. The baseline background and disease characteristics, including sex, age, disease extent, disease duration, disease activity, laboratory parameters, and baseline treatment, for the two groups, were similar (**Table 2**).

Apheresis sessions

SN-LCAP totaled 108 sessions in 12 patients and DN-LCAP totaled 115 sessions in 12 patients, i.e., number of apheresis sessions was 9.0 ± 2.0 times in SN-LCAP treated patients and 9.6 ± 1.4 times in DN-LCAP treated patients. No significant differences were observed between the groups.

Access problems

The access problem at each time session was measured as the time required to start apheresis and puncture-related trouble. The time required to start apheresis was significantly shorter in the SN-LCAP group (10.0 ± 5.4 min) than in the DN-LCAP group (19.4 ± 11.9 min) (P<0.05) (**Figure 3A**). The frequency of puncture-related problems was significantly lower in the SN-LCAP group (0.9%) than in the DN-LCAP group (11.5%) (P<0.05) (**Figure 3B**).

Blood clotting episodes

There were no significant differences in frequency of blood clotting episodes between

the SN-LCAP (5.6%) and DN-LCAP groups (8.7%) (**Figure 4**).

Adverse Events

No adverse events were observed in either the SN-LCAP or the DN-LCAP group.

Clinical efficacy

We also compared clinical efficacy in the 12 patients treated with SN-LCAP and the 12 patients treated with DN-LCAP (**Figure 5**). The reduction in the partial Mayo score was comparable in both groups ($P<0.001$ in SN-LCAP and $P<0.01$ in DN-LCAP) (**Figure 5A**). The percentage of patients who achieved clinical improvement (**Figure 5B**) and clinical remission (**Figure 5C**) was also similar (100% vs 100% and 75% vs 75%, respectively). In addition, during the observation period (at least 24 weeks after the final apheresis session), corticosteroid-free remission was achieved in one of three patients (33.3%) in the SN-LCAP group and none of two patients (0%) in the DN-LCAP group. At the entry, only one patient in the DN-LCAP group received anti-tumor necrosis factor and continued on this after the final apheresis session.

DISCUSSION

The safety and efficacy of apheresis therapy using the SN method have been reported for hemodialysis (13, 14) and platelet apheresis (15). In hemodialysis, studies have demonstrated comparable efficacy of the SN method and the DN method for the treatment of chronic kidney disease with no significant adverse effects (13, 14). Hemodialysis with the SN method decreases the risk of early arterio-venous fistula failure, facilitating cannulation for nurses, and reducing the pain burden for patients (16-18). The limitation of SN hemodialysis is the inadequacy of treatment owing to lower blood flow, higher recirculation, and shorter treatment time, with suboptimal volume of cleared blood volume (14, 19). For platelet apheresis, reports have shown that the quantity and quality of obtained platelets were comparable for the SN and DN methods (20, 21).

Conventional leukocyte apheresis with DN method has been established as a safe and effective treatment strategy for active UC in Japan (22). Nevertheless, the most important problems of leukocyte apheresis with DN method in clinical practice are related to needle puncture, thereby increasing patient burdens. Because patients with active UC are often dehydrated, it is difficult to prepare two vascular routes for double needle apheresis, leading patients to suffer from puncture pain for longer periods. Therefore, the development of leukocyte apheresis with SN was expected to reduce the patient burden. To the best of our knowledge, this is the first study to perform SN-LCAP for the treatment of UC.

The primary aim of this study was to compare the safety of SN-LCAP with that of DN-LCAP. As expected, SN-LCAP decreased the time required to start apheresis at each session as compared to that of DN-LCAP. This appeared to be caused by the fact that SN-LCAP required puncture of only one arm, whereas DN-LCAP requires two arms. We also found that the puncture-related problems at each session was reduced in SN-LCAP as compared to DN-LCAP. Because patients with active UC suffer from dehydration and diarrhea, they may require puncture more often, leading to increased burdens during apheresis. Therefore, SN-LCAP may be more suitable than DN-LCAP for treatment of patients with such conditions. Taken together, the findings suggest that SN-LCAP may not only improve patient satisfaction but may also improve compliance, thereby possibly leading to improved long-term therapeutic efficacy.

Regarding clotting episodes during treatment, SN-LCAP (as opposed to DN-LCAP) may involve a risk of circuit coagulation because SN-LCAP has time to stop the circulation. Nevertheless, there were no differences in clotting time between SN-LCAP and DN-LCAP groups. This was also the case that circuit condensation was not increased in dialysis using the SN method.

A secondary aim was to compare the efficacy of SN-LCAP with DN-LCAP, despite the fact that the study was not designed to determine efficacy *per se*. Our data involved only a limited number of patients and therefore the statistical power was very weak.

Nevertheless, we found that reduction in clinical disease activity as assessed by partial Mayo scores was comparable in SN-LCAP and DN-LCAP groups. The subsequent analysis of improvement rate and remission rate between these groups was also comparable. An obvious next step is to enroll a larger number of patients and examine long-term outcomes as well as short-term efficacy. Furthermore, we should evaluate the efficacy of SN-LCAP in terms of endoscopic data to evaluate mucosal healing.

In summary, SN-LCAP reduced both the time required to start apheresis and needle puncture problems; it showed comparable frequency of blood clotting episodes. SN-LCAP had similar clinical efficacy to DN-LCAP. We conclude that SN-LCAP may be a safe and effective alternative for reducing patient burden during UC treatment. Further comparative studies with a prospective design are needed.

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FIGURE LEGENDS

Figure 1. Extracorporeal circuit of LCAP using the Cellsorba column. Cellsorba consists of two filters: an inner main filter surrounded by an outer prefilter. The inner main filter is composed of a fine fiber (0.8 – 2.8 μm in diameter), and the prefilter is composed of 10 to 40 μm of fabric. Both filters are wound into a cylindrical shape and sealed with polyurethane. Upon entering the upper portion of the cylinder, the blood is introduced to the prefilter and enters the inner main filter. Within the cylindrical portion of the column, leukocyte components are removed. Whole blood taken from a cubital or femoral vein is passed through the column, and is returned to an appropriate contralateral peripheral vein. In each LCAP session, 1,800 mL of whole blood were processed at a blood flow rate of 40 mL/min. Heparin was used as the anticoagulant.

Figure 2. The circuit diagram of single-needle (SN) LCAP. The arterio-venous blood line connects to a single blood access site using a three-way stopcock. Operation of the blood pump and vein clamp is automatically controlled depending on the upper and lower limit values of venous pressure and the set SN-switching pressure. While the blood pump is sending blood, the vein clamp is closed.

Figure 3. Comparison of the blood access problems of LCAP between double-needle (DN) and single-needle (SN) method. (A) The time required to start apheresis and (B) the frequency of puncture-related problems. A total of 108 sessions in 12 SN-LCAP-treated patients and 115 sessions in 12 DN-LCAP-treated patients were evaluated.

Figure 4. Comparison of blood clotting episodes of LCAP between double-needle (DN) and single-needle (SN) method. A total of 108 sessions in 12 SN-LCAP-treated patients and 115 sessions in 12 DN-LCAP-treated patients were evaluated.

Figure 5. Comparison of the clinical efficacy of LCAP between the double-needle (DN) and single-needle (SN) methods. Clinical efficacy was evaluated using the partial Mayo

score. (A) Changes in scores before and after treatment, (B) remission rates at 2 weeks after the final session and (C) improvement rates at 2 weeks after the final session. A total of 12 patients treated with SN-LCAP and 12 patients treated with DN-LCAP were evaluated.

Figure 1

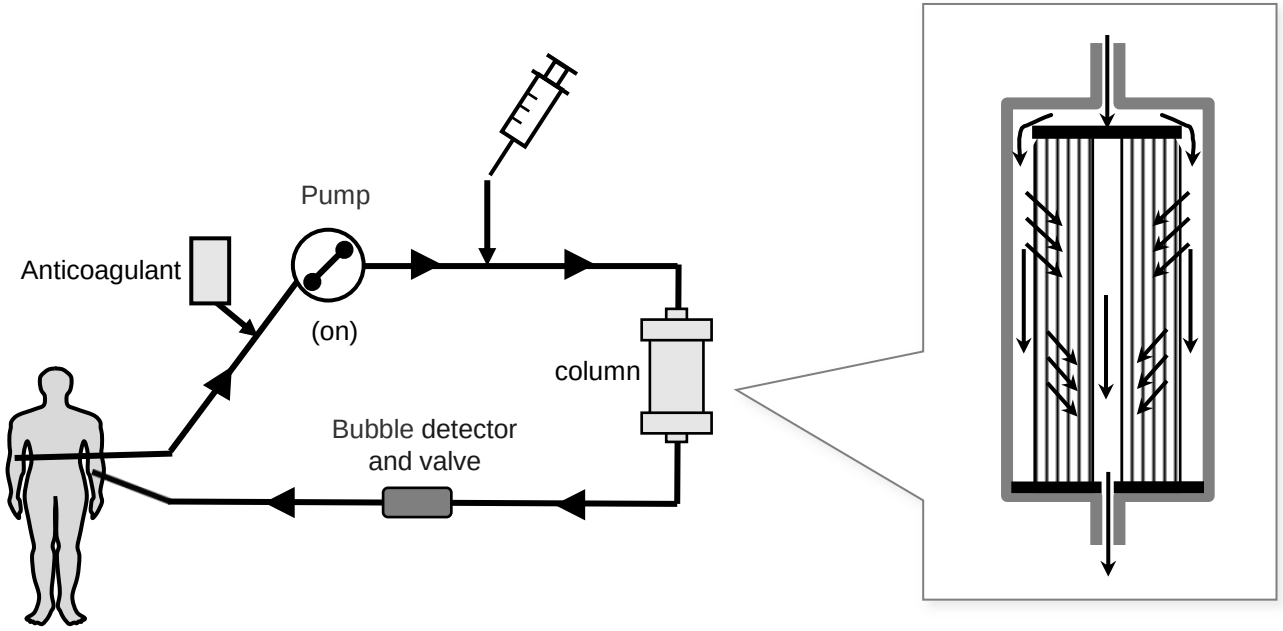


Figure 2

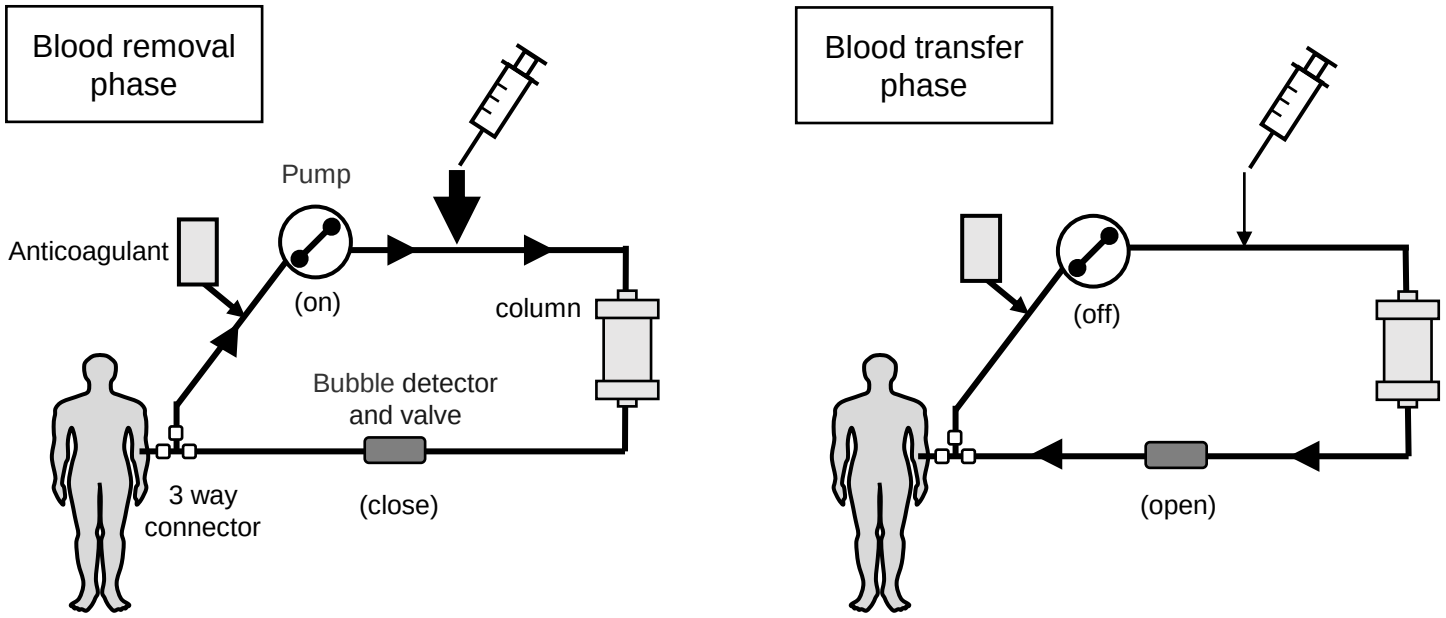
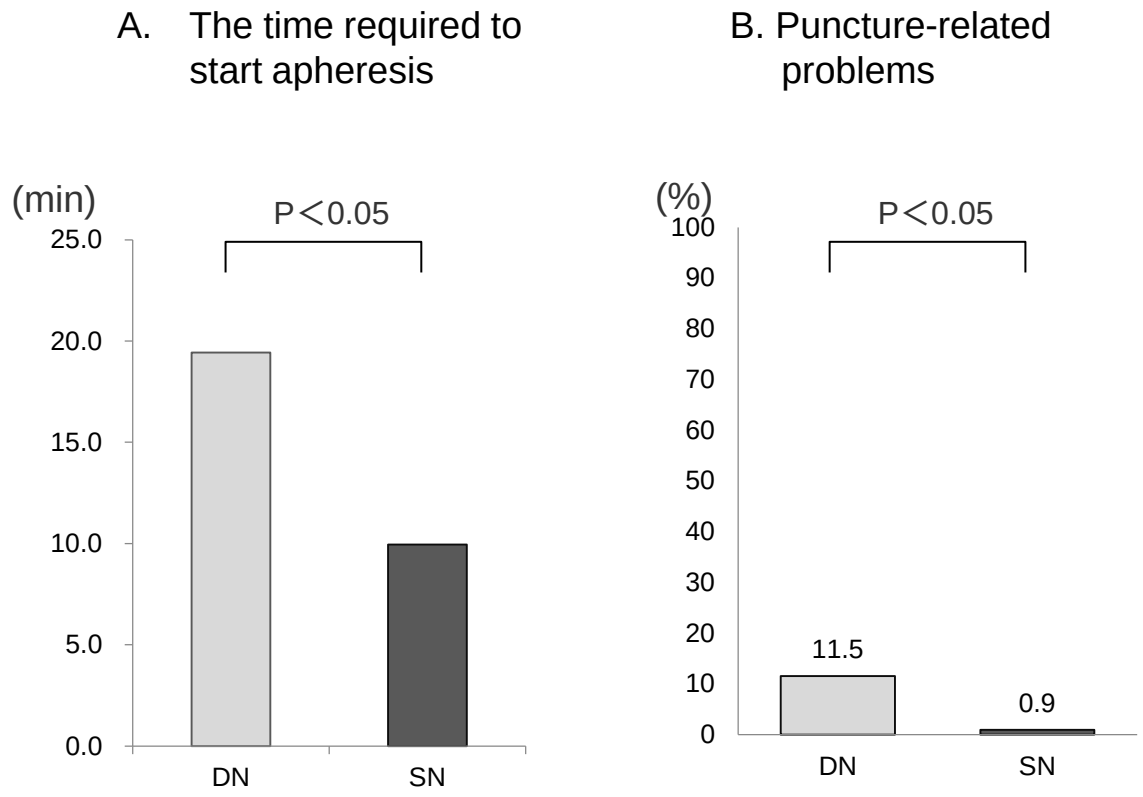


Figure 3



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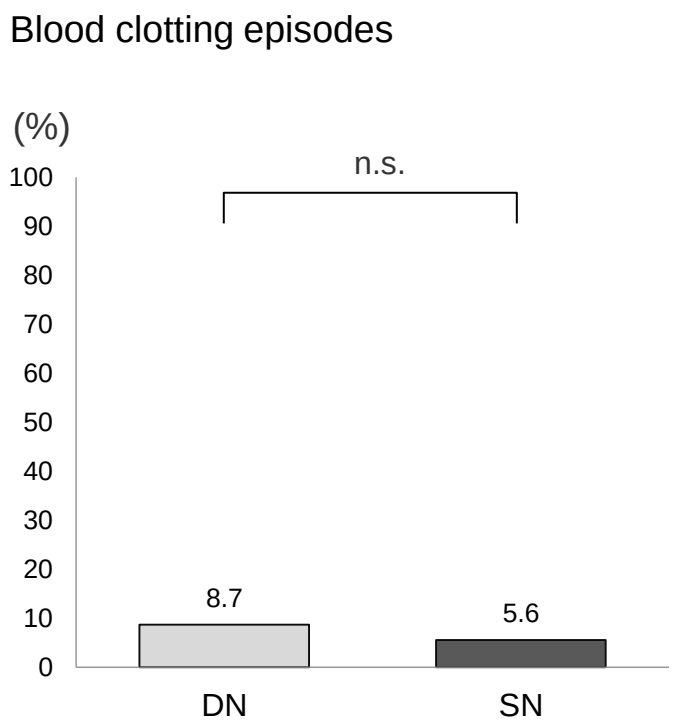

Figure 5

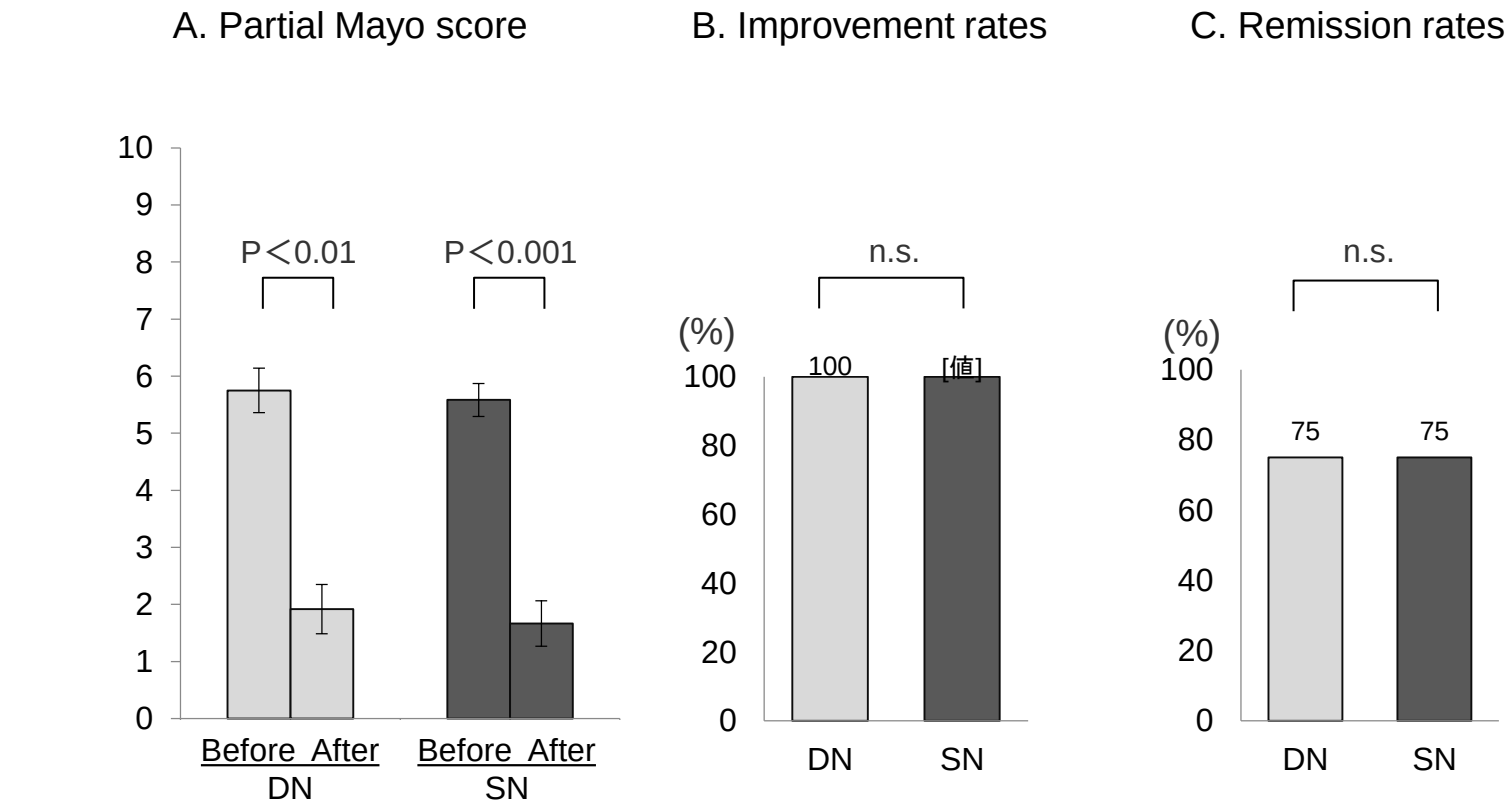

Table 1. Comparison of apheresis conditions between single-needle (SN) and double-needle (DN) LCAP.

	Double-needle (DN) LCAP	Single-needle (SN) LCAP
Blood flow rate setting	30-50 mL/min	40-100 mL/min
Average blood flow rate	40 mL/min	40 mL/min
Processing blood volume	1800 mL	1800 mL
Administration time	60 min	60 min
Anticoagulant	heparin 2000 units	heparin 2000 units
Preselected internal pressure		Upper limit 180 mmHg Lower limit 30 mmHg

Table 2. Baseline characteristics of the study population.

Sex, male-to-female ratio	3:9	5:7	n.s.
Age, years, mean ± SE	43.8 ± 4.2	44 ± 5.4	n.s.
Disease extent, total colitis/left-side colitis/proctitis	5/4/3	5/5/2	n.s.
Disease duration, months, median (IQR)	116 (72-190)	54 (30-133)	n.s.
Partial Mayo score, mean ± SE	5.8 ± 0.4	5.6 ± 0.4	n.s.
White blood cell counts ($x10^3/\mu l$), mean ± SE	8.4 ± 1.3	7.5 ± 0.8	n.s.
Platelet counts ($x10^4/\mu l$), mean ± SE	35.0 ± 7.4	32.5 ± 2.8	n.s.
C-reactive protein (mg/dl), mean ± SE	0.7 ± 0.4	0.4 ± 0.1	n.s.
Treatment			
5-Aminosalicylic acid (%)	9 (75)	6 (50)	n.s.
Prednisolone	2 (17)	3 (25)	n.s.
Immunomodulator	2 (16)	0 (0)	n.s.
Anti-tumor necrosis factor	1 (16)	0 (0)	n.s.
Antibiotics	1 (0)	1 (8)	n.s.