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Original Article

Single Needle Granulocyte and Monocyte Apheresis for Ulcerative Colitis: A Retrospective Safety Analysis

TETSUROU IMAI, HIROSHI YAMASAKI*,†,§, KEIICHI MITSUYAMA†, OSAMU YAMAGA, GAKU SUGIHARA, YUSUKE KAIDA**, RYO SHIBATA**, TAKUMA HAZAMA**, SHINICHIRO YOSHIOKA*,‡, TAKUJI TORIMURA*, KEI FUKAMI** AND NORIO YAMASHITA‡

*Kurume University Hospital Clinical Engineering Center, *Division of Gastroenterology, **Division of Nephrology, Department of Medicine, †Inflammatory Bowel Disease Center, Kurume University School of Medicine, ‡Kurume University Hospital Advanced Emergency Medical Service Center, Kurume 830-0011, §Hakuai Hospital, Kurume 839-0863, Japan*

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Summary: ***Introduction*:** Granulocyte and monocyte apheresis (GMA) is an effective treatment strategy for active ulcerative colitis (UC) in Japan. Single needle (SN) apheresis reduces needle puncture pain in patients because it requires only one puncture site. We evaluated whether single-needle apheresis could be a safe and effective means of reducing patient burden.

***Method*:** We performed a retrospective study of active UC patients who were treated with either SN apheresis or conventional double-needle (DN) apheresis at the Kurume university hospital from April 2014 to March 2018. All the patients treated with GMA after September 2016 underwent SN apheresis. Thus, the two groups predominantly belonged to different time periods. We assessed the safety of SN apheresis.

***Result*:** Six patients underwent SN apheresis, and 6 underwent DN apheresis. The average time to the start of apheresis was significantly reduced from 23.1 minutes in the case of DN apheresis to 12.6 minutes for SN apheresis. In addition, the number of difficult punctures was significantly reduced with SN apheresis. There were no differences in adverse events between SN and DN apheresis. Treatment benefits, remission rate and disease activity were similar between SN and DN apheresis.

***Conclusion*:** SN apheresis reduced both the time to treatment initiation and pain during puncture, and there was no difference in the number of blood clotting episodes as compared with DN. Although further comparative studies are needed, SN apheresis may be a safe alternative for patients to reduce the strain of treatment.

Key words single needle, granulocyte and monocyte apheresis, ulcerative colitis

INTRODUCTION

The number of patients with ulcerative colitis (UC) is rising steadily, mainly in developed countries [1]. Young patients can also develop UC, and its etiology remains unknown. The fact that the patient's quality of life (QOL) remarkably worsens with the progression in symptom severity is a challenge. In patients who perform severe to moderate activities, immunosuppressive therapy (e.g., steroids) is the main treatment

Corresponding Author: Hiroshi Yamasaki, M.D., Ph.D., Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan. Tel: +81-942-31-7561, Fax: +81-942-34-2623, E-mail: yamasaki_hiroshi@kurume-u.ac.jp

Abbreviations: DN, double-needle; GMA, granulocyte and monocyte apheresis; LCAP, leukocytapheresis; QOL, quality of life; RCT, randomized controlled trial; SN, single needle; UC, ulcerative colitis.

method, and many patients continue treatment despite being at risk of infection, lymphoma, and other cancers. Leucocyteapheresis therapy has mainly been developed in Japan. This treatment method has almost no risk of infection; therefore, it is believed to be a very safe treatment approach.

There are two selective adsorption apheresis devices that remove leukocytes from whole blood and are available in Japan and Europe-the Cellsorba leukocytapheresis (LCAP) column and the Adacolumn granulocyte and monocyte apheresis (GMA) device [2]. Clinical trials have been conducted in Japan and the Western countries. Leukocytapheresis was more effective than sham apheresis in a randomized controlled trial (RCT) conducted in Japan [3]. In contrast, no significant differences were observed in a large-scale RCT trial conducted mainly in the Western countries between the two groups in terms of major clinical end-points [4]. Various factors may have contributed to this result, one of which may be a high withdrawal rate.

In the field of dialysis, single-needle (SN) dialysis, also called short needle dialysis, is reportedly useful for hemodialysis in the induction phase, needle puncture trouble on the blood feeding side and home dialysis [5]. UC patients sometimes experience needle puncture troubles in leukocytapheresis therapy. Therefore, SN apheresis has been reported useful [6]. Currently, SN apheresis requires the use of dialysis equipment. The GMA therapy usually uses dialysis equipment; therefore, we initiated SN apheresis in GMA therapy after obtaining approval from the Kurume University Ethics Committee. Regarding the use of dialysis equipment, we considered that GMA therapy poses few challenges because it has been used for about 50 years in the field of dialysis and has undergone several advancements, thus ensuring high safety [7].

We reported on the safety of using SN granulocyte and monocyte apheresis to lower patient burden. We performed a retrospective analysis from April 2014 to March 2018. SN apheresis in GMA therapy was started from September 2016 at our hospital. We found that the efficacy of the SN apheresis was similar to that of double needle (DN) apheresis. In addition, SN apheresis significantly reduced the average time until the start of GMA compared with DN apheresis. One of the underlying reasons was the reduction in the rates of needle puncture problems. However, there was no difference in the safety of the two methods.

Based on these results, we believe that SN apheresis may not only improve patient satisfaction, but could also directly influence the treatment effect in the long term by promoting compliance. In addition, leukocytapheresis therapy, including GMA, has few adverse effects and is expected to produce a better therapeutic effect in combination with other treatments in the future.

METHOD

Patients

The study was conducted at Kurume University from April 2014 to March 2018. The Kurume university ethics committee approved the protocol. All the authors had access to the study data and approved the final manuscript. We enrolled 12 patients who were diagnosed with UC and had undergone GMA therapy. The eligible patients had an established diagnosis of UC confirmed with endoscopy and histopathology. GMA therapy was introduced in moderate to severe UC patients whom the attending physician had assessed to have inadequate response or who failed to tolerate 1 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. The study protocol was reviewed and approved by the Ethics Committee of Kurume University School of Medicine (No. 18046). In order to eliminate selection bias, a continuous registration method was adopted where all the patients treated with GMA in our hospital were enrolled. Our hospital began to use SN apheresis in September 2016; therefore, all patients since that time underwent SN apheresis. Thus, the two study groups predominantly belong to different time periods. The treatment strategy for each patient, including the course (the range of 5-10 sessions) of GMA was determined by the attending physician. The observation period was from 2 weeks before the first GMA session to 2 weeks after the last GMA session.

Treatment procedure

The SN method was performed as previously described [8]. With respect to the GMA therapy, a special device was used, and before transferring to a dialysis monitor (DCS-27, Nikkiso CO., Ltd, Tokyo, Japan), an Adamonitor® (Otsuka Electronics Co., Ltd, Osaka, Japan) was used for the DN method. For the SN method, a dialysis monitor was 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 arteriovenous bloodline, blood is withdrawn from the patient, and positive pressure is built up in the Adacolumn blood compartment. Once a preselected upper limit internal pressure of the circuit (180 mmHg) is achieved, 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. Regarding vascular access, in the DN method, delivery was performed from the veins of the arms and a Happy Cass 17G needles were used as the puncture needles. In the SN method, an SN needle (16G) was given priority to reduce blood recirculation; however, in cases where puncture was difficult, a smaller diameter Happy Cass needle with a small diameter (17G, 18G) was was used. The DN method was performed at a flow rate of 30 mL/min for 60 min in order to achieve 1800 mL blood volume/session. In the SN methods, the GMA blood flow rate setting is 40-100 mL/min, and the average blood flow rate of GMA is 30 mL/min with the aim of processing 1800 mL blood volume/ session. The administration time can be set to one hour, similar to that in the DN method. When using heparin as an anticoagulant, it is applied with the first 1500-2000 units. Nafamostat mesylate was administered at 30-50 mg/h.

Study Evaluations

Information regarding clinical parameters, including demographic data, disease status, and medications was collected at the time of the first GMA session and analyzed. Demographic data comprised sex, age, extent of the disease, and duration of the disease. In addition, details of the granulocyte and monocyte apheresis procedures were included in the analysis. The time to introduce apheresis therapy and the presence or absence of needle puncture trouble, which was defined as requiring more than 30 minutes to achieve puncture, or blood circuit blood clotting, was investigated at all GMA sessions. Blood circuit clotting was defined as clotting necessitating interruption of GMA and change of circuit. Adverse events and concomitant medication use were recorded throughout the study period. In order to assess disease activity, partial Mayo scores (PMS) were calculated at week 0 (baseline) and 2 weeks after the final GMA session [9]. The PMS is the sum of 3 subscores (i.e., stool frequency, rectal bleeding, and a physician's global assessment). Each subscore ranges from 0-3, with higher scores indicating greater disease severity. The partial Mayo score ranges from 0-9. Clinical remission was defined as a PMS ≤ 2 points with no individual subscore > 1 point.

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-value was < 0.05. Statistical analysis was performed using JMP® 11 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics

The total study population comprised 12 patients, with 6 in the SN group and 6 in the DN group. Six patients received 55 SN apheresis sessions, and the other 6 received 49 DN apheresis sessions. The baseline disease characteristics of the two groups were similar, except in terms of the extent of the disease. Total colitis type was higher in the DN group than in the SN group. Concomitant medication use was well balanced across the treatment groups (Table 1).

Blood access

The average time to start apheresis was significantly reduced, from 23.1 minutes in the DN group to 12.6 minutes in the SN group (Figure 1A). In addition, the incidence of needle puncture trouble was reduced from 43% in the DN apheresis to only 2% in the SN apheresis (Figure 1B).

Safety analysis

With respect to the frequency of blood circuit clotting, there was no significant difference between SN apheresis (6%) and DN apheresis (0%) (Figure 2). During the study period, no other adverse events were observed in either the SN apheresis or the DN apheresis.

Efficacy

The percentage of patients who achieved remission was the same in both groups (SN group, n = 3, 50% and DN group, n = 3, 50%) (Figure 3A). The reduction in PMS was also similar in both groups (Figure 3B). Treatment benefits, remission rate and disease activity were similar in SN apheresis and DN apheresis.

TABLE 1.
Baseline characteristics of the study population

Patient characteristics			
	DN (N=6)	SN (N=6)	*P* value
Sex, male/female	1/5	2/4	0.5
Age, years, mean	39.7 ±13	42±18	0.82
The extent of the disease	Total colitis/ left-side colitis/ proctitis	Total colitis/ left-side colitis/ proctitis	
	6/0/0	2/4/0	0.014/0.052/1
Disease duration, months (median, IQR)	114.3±126	171±140	0.24
Partial Mayo score, mean	6.17±0.9	5.83±1.25	0.67
Treatment			
5-aminosalicylic acid (%)	5 (83)	5 (83)	1.0
Prednisolone	2 (33)	4 (66)	0.248
Immunomodulator	1 (16)	3 (50)	0.22
Anti-tumor necrosis factor	1 (16)	0 (0)	0.296
Antibiotics	0 (0)	0 (0)	1

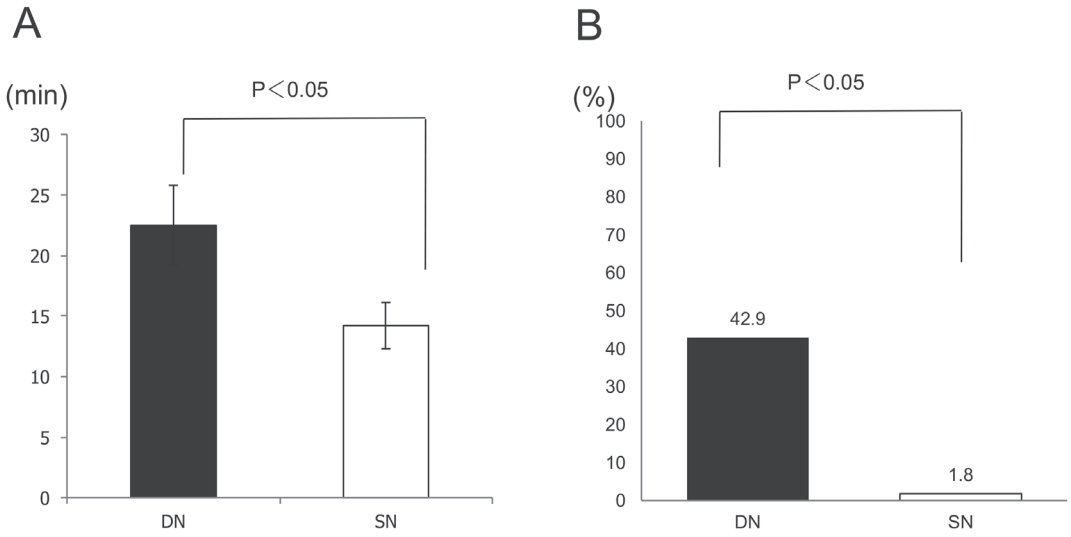

Fig. 1. Blood access: (A) Average time to introduce GMA and (B) the number of puncture-related problems

DISCUSSION

SN apheresis significantly reduced the average time until the start of GMA compared to DN apheresis; further, we believe that the occurrence of challenging cases of needle puncture may be reduced. There was no difference in the treatment safety of the two methods. Therefore, the SN method could help reduce the pain of apheresis treatment, increase the quality and satisfaction of care, and promote clinical compliance.

SN apheresis is already being used for hemodialysis [10, 11] and platelet apheresis [12], and its effectiveness and safety have already been reported. Hemodialysis patients were treated using the SN technique for the following reasons: to decrease the risk of early arteriovenous fistula failure, to facilitate cannulation

for nurses, and to reduce the pain burden for the patient [13-15]. However, the use of SN dialysis is mainly limited by the inadequacy of treatment due to lower blood flow, higher recirculation, and shorter treatment time with suboptimal amount of cleared blood volume and low KT/V [11,16]. Recently, several studies have demonstrated comparable effects of SN hemodialysis and DN hemodialysis in patients with chronic kidney disease without any adverse effects [10,11]. Further, platelet collection is similar in quantity and quality between SN plateletpheresis and conventional DN plateletpheresis cl [17,18]. It has also been reported that SN-intensive GMA might be an adequate and novel therapeutic option for active UC as an alternative therapy before the initiation of corticosteroids [8].

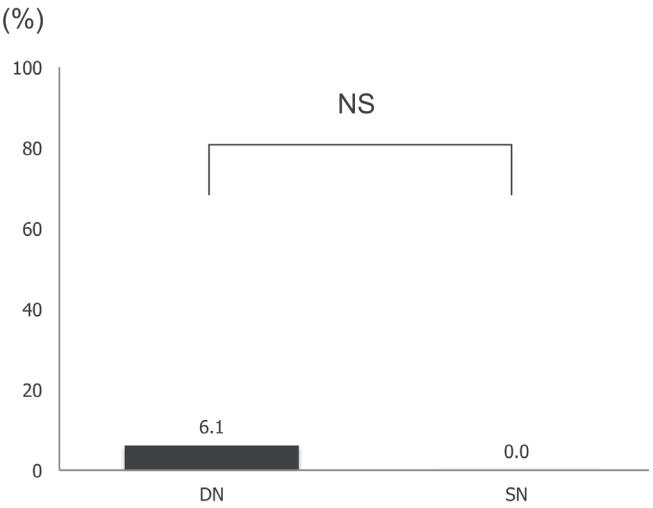

Fig. 2. Comparison of the rate of blood circuit clot problems: SN apheresis totaled 55 sessions and DN apheresis totaled 49 sessions

It is difficult to prepare two routes of double needle GMA at each treatment because UC patients in the active phase are often dehydrated because of diarrhea. Patients may also discontinue GMA treatment at an early phase because of the pain. More recently other effective medicines, such as biologic preparations, initiator inhibitors, and low molecular weight compounds, have been successively developed and apheresis therapy is being replaced by intravenous drip and several hours of oral administration. However, the SN method that we used requires only one route, and administration can be completed in one hour, similar to that in the conventional method. However, the new treatment involves suppression of certain types of immunity, potentially increasing the risk of specific infections. Apheresis treatment has a long history in Japan, and the only reported severe adverse effect is venous thrombosis, which occurs rarely.

This study aimed in particular to highlight the simplicity and safety of the SN method. The SN method involves a significantly shorter time to initiation of treatment than the DN method. This is attributable to the fact that in the conventional method, 42% (21 times) of the cases required more than 30 minutes for puncture. However, this percentage decreased signifi-

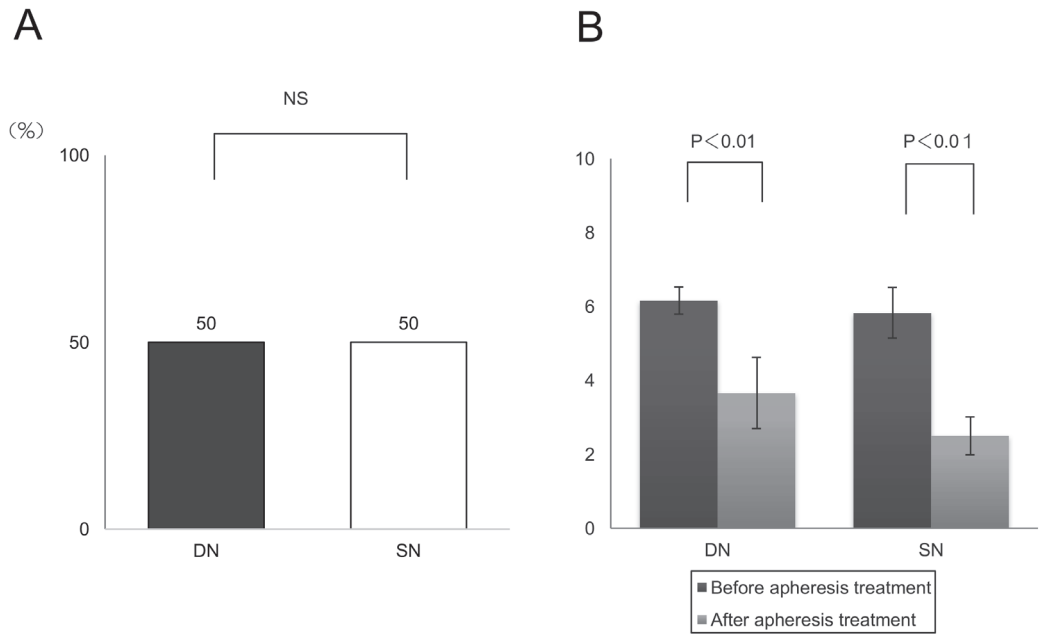

Fig. 3. Efficacy outcomes (A) remission rates at 2 weeks after the last session, (B) partial Mayo score before and after treatment

cantly to only 2% in the SN method, and only one arm needed to be punctured; one of the reasons for this difference was believed to be the challenge of performing a puncture in both arms. In the UC activity phase, patients who have exacerbated dehydration may need to undergo puncture several times, leading to an increase in the number of dropouts. Even in large-scale, double-blind studies conducted in Western countries, numerous patients dropped out, and this was believed to affect the therapeutic effect of GMA [4]. Recently, more attention is being given to the patient's QOL [20]. Our institute has a specialized facility, the IBD Center, that aims to deliver a higher standard of treatment. Moreover, treatment satisfaction is directly linked to QOL in everyday life. Thus, improving the treatment method is crucial and should be given due consideration in the future.

In GMA, a few severe adverse effects, such as venous thrombosis, may occur. The SN method has a stopping time; therefore, it involves a risk of circuit coagulation. However, in our study, the frequency of circuit condensation was comparable between the SN and DN groups. In the field of dialysis also, the frequency of circuit condensation is not increased in SN. UC patients are often dehydrated; therefore, we think that further examination is necessary in many cases.

The limitations of this study include the fact that it is not a prospective or randomized comparison. There were wide variations in the baseline patient characteristics that made it challenging to compare the two populations. Further, in the present study, there was bias in the disease type (Table 1). Future cohort studies and intervention studies should focus on matching the baseline patient characteristics in the two groups to facilitate valid comparisons. Furthermore, each group contained only 6 patients. Thus, statistical power to compare those two groups was very weak for efficacy analysis. There, however, are a sufficient number of sessions of apheresis in each group for safety analysis.

To the best of our knowledge, only one report has assessed GMA treatment using the SN method [8]. Ours is the first study to perform an in-depth analysis of the safety of SN apheresis.

In conclusion, changing to the SN method led to a shortening in the time to treatment initiation and alleviation of puncture pain, and showed no difference in the incidence of coagulation. The SN method may be more suitable than the DN method for treatment of UC patients, who often have difficulty with two-route double needle GMA because they often suffer from dehydration due to diarrhea. Hence, SN apheresis may be a useful replacement for DN apheresis. The use of SN apheresis may not only improve patient satisfaction, but may also promote compliance, thereby improving the long-term therapeutic effect. In the future, we plan to enroll more patients and examine not only the treatment, but also assess long-term outcomes.

COMPETING INTERESTS: The authors have declared that no competing interests exist.

CONTRIBUTORS: T.I. and H.Y. designed the research. T. I., H Y., O Y., G S., Y. K., R S, T. H. and S. Y. performed the study. T.I. and H.Y. analyzed the data. K.M., T.T., K. F., and N. Y. supervised the project.

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