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Single Case

Low-Density Lipoprotein Adsorption by Centrifugal Plasma Separation Can Shorten Treatment Time

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Keywords
Focal segmental glomerulosclerosis · Dextran sulfate adsorption of low-density lipoprotein · Membrane separation · Centrifugal separation

Abstract
Low-density lipoprotein (LDL) apheresis is effective for nephrotic syndrome in drug-resistant focal segmental glomerulosclerosis (FSGS). Dextran sulfate adsorption of LDL (DSAL) is widely used for this purpose. The Liposorber LA-15 system performs DSAL by membrane plasma separation (mDSAL) using an MA-03 plasma purification device. However, sufficient blood flow (Qb) frequently cannot be obtained from a peripheral vein with mDSAL. The recommended plasma filtration flow rate (Qf) when using the OP-05W membrane plasma separator is no more than 1/3 of Qb, giving plasma removal efficiency (PRE) of about 30%. In contrast, the centrifugal blood component separator Spectra Optia has PRE of 87–92.5% because centrifugal separation enables effective separation of plasma components even at low Qb. Here, we present the case of a man in his 40s with FSGS, for whom we began treatment with mDSAL with the intention of completing a 12-session cycle, but extended treatment times were required due to low Qb. Therefore, we switched to DSAL by centrifugation (cDSAL) using the Liposorber LA-40 system from the 6th session onward. Treatment time decreased from 190 min for the fifth session using mDSAL to 140 min for the sixth session using cDSAL. Mean treatment time also decreased from 155 ± 9 min for mDSAL (5 sessions) to 119 ± 20 min for cDSAL (7 sessions). Moreover, the LDL removal rate at a processed plasma volume was similar for both modalities. In conclusion, cDSAL can enable efficient plasma separation even with low Qb, with a comparable LDL removal rate and shorter treatment time relative to mDSAL.

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Introduction

Focal segmental glomerulosclerosis (FSGS) is treated with high-dose steroid therapy or cyclosporine, but there are some refractory cases where these treatments do not induce remission. Medium- to long-term treatment by low-density lipoprotein apheresis (LDL-A) has been shown to be effective against nephrotic syndrome in patients with FSGS [1], and dextran sulfate adsorption of LDL (DSAL) is widely used for this purpose [2]. The Liposorber LA-15 system (Kaneka Medix), a device approved by the US Food and Drug Administration (FDA), performs DSAL by membrane plasma separation (mDSAL) using the MA-03 (Kaneka Medix) plasma purification device. However, in many cases, sufficient blood flow (Qb) cannot be obtained from a peripheral vein with mDSAL. In contrast, the centrifugal blood component separator Spectra Optia (TERUMO BCT) has a PRE of 87%–92.5% because centrifugal separation allows for effective separation of plasma components even at low Qb [3–5]. However, few studies have investigated DSAL using centrifugation (cDSAL). Here we present the case of a man diagnosed with FSGS at our university, for whom we began treatment with mDSAL with the intention of completing a 12-session cycle but ultimately switched to cDSAL using the Liposorber LA-40S (Kaneka Medix) for the 6th to 12th sessions after encountering issues with mDSAL.

Case Report

The patient was a man in his 40s who was diagnosed with FSGS at our university. We treated him with 5 cycles of mDSAL but were forced to extend the treatment time due to low Qb (≤50 mL/min). Therefore, we switched to cDSAL for the rest of the cycle from the 6th to 12th sessions. For mDSAL, we used the MA-03 device, with OP-05W as the separator, LA-15 as the adsorber, and heparin as the anticoagulant. For cDSAL, we used two devices, the Spectra Optia and AcuFil Multi-55X (TR-55X, Toray), with the LA-40 as the adsorber and ACD-A solution with heparin as the anticoagulant. For both mDSAL and cDSAL, we used a peripheral vein for vascular access, and the processed plasma volume was 2,100 mL, the same volume as the patient's circulating plasma volume (PV; approximately 1.0 PV) (Table 1). Treatment time was defined as the time from the start of blood withdrawal to achievement of the target processed plasma volume and completion of blood return.

To prepare the cDSAL circuit, one end of the normal Spectra Optia waste line was clamped with forceps, and the TR-55X withdrawal line with the LA-40 system attached was connected to the other end. A three-way stopcock was inserted into the Spectra Optia replacement line, Ringer's lactate solution was connected to the normal replacement line as a buffer, and the three-way stopcock was opened while using the replacement line (Fig. 1). The LDL-A treatment time was 190 min in the fifth session using mDSAL (Qb approx. 40 mL/min) but decreased to 140 min in the sixth session using cDSAL (Qb approx. 40 mL/min). Mean treatment time also decreased from 155 ± 9 min for mDSAL (5 sessions) to 119 ± 20 min for cDSAL (7 sessions). In addition, the LDL removal rates for a plasma volume of 2100 mL were 61.9% and 59.4% for mDSAL and cDSAL, respectively, which were measured only once for each (Fig. 2a). However, during cDSAL, ionized calcium fell into the range of 0.75–0.89 mmol/L (measured by an ABL90 FLEX blood gas analyzer) at 75, 90, and 105 min after the start of treatment, which was addressed by infusion of 10 mL of calcium gluconate (Fig. 2b). The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531097).

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Table 1. Modality of dextran sulfate adsorption of LDL

	mDSAL	cDSAL
Apheresis machine	MA-03 (Kaneka Medix Co., Ltd.)	Spectra Optia (Terumo BCT Co., Ltd.) TR-55X (Toray Medical Co., Ltd.)
Plasma separator	OP-05W (Asahi Kasei Medical Co., Ltd.)	(Centrifugation)
Anticoagulant (dose)	Heparin (1,000-U bolus plus infusion at 1,000 U/h)	Heparin (1,000-U bolus plus 3,000 U added to a 500-mL ACD-A bag, AC ratio 10:1)
Adsorber	LA-15 system (Kaneka Medix Co., Ltd.)	LA-40 system (Kaneka Medix Co., Ltd.)
Processed plasma volume	Plasma volume ×1.0 (2,100 mL)	Plasma volume ×1.0 (2,100 mL)
Vascular access	Peripheral vein	Peripheral vein
Blood flow rate Filtration flow rate	40–80 mL/min 12–24 mL/min	40–50 mL/min 26–30 mL/min

Discussion

Characteristics of plasmapheresis differ greatly depending on whether membrane separation or centrifugation is used. The Spectra Optia has significantly higher PRE than the OP-05W (84% vs. 27%, $p < 0.05$) [5]. Membrane separation requires low PRE relative to Qb (≤30%) to reduce the risk of hemolysis [6]. Therefore, a larger volume of blood must be processed to attain a plasma separation rate of 30 mL/min by membrane separation. To achieve this, a higher Qb (and vascular access allowing for greater blood flow) or a longer treatment duration may be required compared with centrifugation [7]. On the other hand, to achieve a higher Qb, catheter insertion into a central vein or arterial puncture is necessary; however, because this patient is an outpatient, management after catheter insertion is difficult, and frequent arterial punctures carries a high risk. In contrast, the Spectra Optia, which uses centrifugation, has a PRE of 84–92.5% [3–5], allowing for about 60% PRE relative to Qb. In our patient, the treatment time was shorter for cDSAL than for mDSAL at a comparable Qb because we obtained vascular access through a peripheral vein. The LA-15 and LA-40 systems used to treat familial hypercholesterolemia (FH) employ the same adsorption principle. The cDSAL circuit is used in a single pass and does not allow for activation process. Therefore, when used with cDSAL, the LA-15 system can only process up to 0.5 L, while the LA-40 system can process up to 3 L. We were able to use the LA-40 system with no issue in our patient with FSGS because his pretreatment LDL level was lower than that seen in FH, and the processing volume of 2,100 mL was equivalent to 1.0 PV in this patient. The LDL removal rate in FH is reported to be 63.7% [8], and we obtained a comparable LDL removal rate of about 60% for both mDSAL and cDSAL. Furthermore, because FSGS treatment improves lipid nephrotoxicity and drug sensitivity through adsorption of lipids [2], there should be no problem with LDL removal rate in both mDSAL and cDSAL. Removal rates of approximately 60% for both mDSAL and cDSAL were adequate for these purposes.

Either citrate (ACD-A) or heparin can be used as an anticoagulant, but from the perspective of platelet aggregation, heparin is more suitable for membrane therapeutic plasma exchange and ACD-A for centrifugal therapeutic plasma exchange [9]. The recommended range of the ACD-A to Qb ratio (AC ratio) for the Spectra Optia is 10:1–15:1. However, about 90% of the ACD-A used is discarded in centrifugal therapeutic plasma exchange, whereas the full amount of ACD-A is infused into the body in the cDSAL method that we used.

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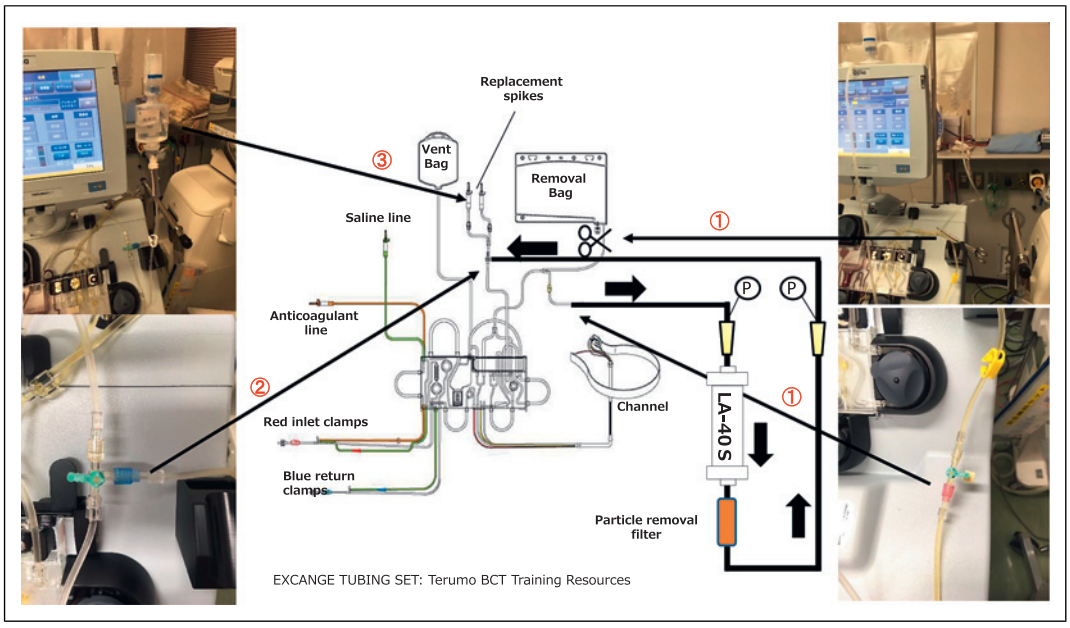

Fig. 1. cDSAL circuit. (1) The normal waste line of the Spectra Optia is clamped with forceps, and the bleeding circuit of the TR-55X with the LA-40S is connected to the other end. (2) The blood return circuit connected to the Spectra Optia's replacement line by inserting a three-way stopcock. (3) Ringer's lactate solution attached to a regular replacement line as a buffer. "p" indicates the pressure gauge. Arrows indicate plasma flow.

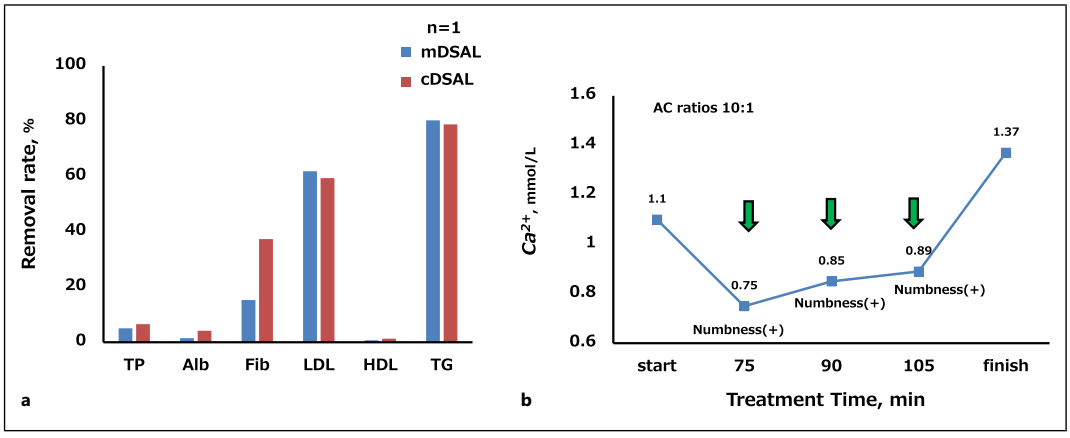

Fig. 2. Removal rate/calcium concentration. **a** Removal rate for a plasma volume of 2,100 mL. **b** Calcium concentration at a plasma volume of 2,100 mL. Arrows indicate tube injection of 10 mL of calcium gluconate hydrate. Alb, albumin; Fib, fibrinogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Plt, platelet; TG, triglyceride; TP, total protein.

Therefore, our patient's ionized calcium level dropped to 0.75 mmol/L when we used an AC ratio of 10:1, which we addressed by infusion of 10 mL of calcium gluconate. Handschel et al. used a 2,500-unit bolus of heparin plus 10,000 units of heparin in a 600-mL ACD-A bag, changed the AC ratio to the range of 20:1–25:1, and temporarily lowered the AC ratio to 18:1 if they observed platelet aggregation. They also suggested that even when a lower dose of ACD-A is used, hypocalcemia can be avoided by continuous infusion of calcium (0.026 mmol/min) [10]. In our patient as well, we used a 1,000-unit bolus of heparin plus 3,000 units of heparin

in a 500-mL ACD-A bag and set the AC ratio to 10:1. We were also able to avoid hypocalcemia by continuous infusion of 5 mL of calcium gluconate into 500 mL of processed plasma. Therefore, we conclude that when facing an unsatisfactory blood withdrawal rate during treatment for FSGS or a similar condition, cDSAL can enable efficient plasma separation even with blood withdrawal from a peripheral vein, with a comparable LDL removal rate and shorter treatment time relative to mDSAL.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Subjects have given their written informed consent to publish their cases. This study protocol was reviewed and approved by Ethics Review Committee of Tokyo Medical and Dental University Hospital, approval number M2019-313. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received for this study.

Author Contributions

Atushi Ohkubo wrote the manuscript; Shotaro Naito supervised and corrected the manuscript; and Takatoshi Sakurasawa performed LDL-A in this case.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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