A Clinical Study Comparing the Basic Performance and Blood Compatibility Characteristics of Nipro ELISIO-H, Gambro Polyflux Revaclear, and Fresenius Optiflux Dialyzers

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Introduction

The dialyzer ELISIO-H is a new high-flux dialyzer made from POLYNEPHRON™ fiber designed and manufactured by Nipro Corporation Japan. The dialyzer has already been subjected to in-vitro testing, and all legally required biological safety tests have been conducted and certified by an external institute. A number of clinical studies have already been successfully completed for this membrane mainly in Japan and Europe. Nipro ELISIO-H dialyzers are commercially available for several years outside of U.S.A. On 20th December 2013, ELISIO-H dialyzer is 510k-approved for its sales in U.S.A.

Evaluation Objective

The aim of the study is to confirm the safety and clinical effectiveness of the Nipro ELISIO-H by compare the performance characteristics and hemo-compatibility of Nipro ELISIO-H with those of the commercially available dialyzers in U.S.A., Gambro Polyflux Revaclear and Fresenius Optiflux.

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Details

a) Membrane and Dialyzer Types

Dialyzer Labelling	Membrane	Dialyzer Manufacturer	UF Coeff. mL/h/mmHg	Surface m^2	Sterilization
Nipro ELISIO-H	POLYNEPHRON™	Nipro, Japan	67.0	1.5	Gamma
Gambro Polyflux Revaclear	PAES	Gambro USA	60.0	1.4	Steam
Fresenius Optiflux	Polysulfone	Fresenius, USA	60.0	1.6	ETO

b) Design:

Study Design: Clinical study according to the US Federal Law that means no necessity of the permission of authorities, but because of blood sampling a vote of an ethics committee should be procured.

c) Patients

Ten (10) stable patients receiving regular dialysis treatment will be chosen for this evaluation. The n of ten was chosen from previous experience with studies of this kind. However with the expectation of a 20% drop out rate a total of twelve patients will be selected from the patient population meeting the inclusion criteria. Standard hemodialysis will be performed with each dialyzer type.

d) Patient Inclusion Criteria

- ESRD patients 18 years or older
- Stable on hemodialysis for more than 3 months
- Stable hemoglobin 11 g/dl or greater, see attached DCI erythropoietin protocol.
- Stable AV fistula vascular access
- Stable anticoagulation and ESA regimen

- No active infection
- Able to sign informed consent and able to participate in the study
- Medically stable

e) Patient Exclusion Criteria

- Participation in another study which may interfere with the planned study
- Active infection
- Medical conditions which may interfere with the study (cardiac, liver disease,
- Hepatitis)
- Female who are pregnant or planning to be pregnant
- Problem with or allergy to anticoagulation
- Patient cannot tolerate Heparin
- Allergy to dialyzer material e.g. polysulfone

f) Withdrawal Criteria

- Patients own decision.
- Relocation, transportation
- Severe mechanical problems with dialyzers e.g. frequent fiber leakages.
- Hypertensive reactions e.g. erythema, edema.
- Non-compliance with therapeutic regimen.
- Change of anticoagulation scheme.
- Other serious problems induced by treatment.
- Any dialysis-related medical problem judged to be sufficiently serious by the principal investigator to necessitate patient withdrawal.

1. Methods

a) Pre-rinsing of Dialyzers

Setting up and preparation of the dialyzers will be performed per the clinic's normal procedure. This involves a pre-rinsing step before the start of dialysis.. The priming solution will not be infused to the patient. Dialysate flow rate is to be initiated at the beginning of the rinsing procedure. All the dialyzers will be pre-rinsed in the same procedure.

b) Heparinization

The usual heparin type and dosage normally used for each individual patient, including the administration regime (bolus injection and continuous infusion), will be maintained

for each patient unless specified otherwise by the investigator/physician during the evaluation. The total amount of heparin given per treatment will be documented.

c) Blood Flow / Dialysate Flow

Hemodialysis: Blood and dialysate flow rates should be between QB= 300 - 500 ml/min and QD= 2 times QB but should follow existing flow rates for the patient, based on clinic procedure. Blood flow and dialysate flow should remain unchanged for all patients for the duration of dialysis and throughout the evaluation. The ultrafiltration rate, appropriate for each patient and treatment will be maintained and recorded. The blood flow will also be determined in the fistula using a Doppler flow device.

d) Dialysis Regime and Number of Applied Dialyzers

Three consecutive treatments will be performed with each dialyzer type. Blood sampling for measurements will be taken as shown in appendix.

e) Performance and Hemocompatibility Parameters to be measured

Please refer to Appendix.

f) Blood Sampling

Blood will be collected pre-, during and post-dialysis at appropriate time intervals (see Appendix) for the evaluation of:

1. **Clearance** of urea, creatinine, phosphate, beta-2-microglobulin, myoglobin at 60 min. Five minutes before the collection the flow rate will be adjusted so that at time of collection, QB= 350 mL/min, QD= 700 mL/min and UF= 0 for all patients. Blood is to be collected from venous side first followed by arterial side.
2. **Removal Rate** for urea, creatinine, phosphate, beta-2-m and myoglobin at 0 min and 240 min will be calculated.
3. **Hemocompatibility**
   (a) Blood cell count (white blood cell and platelet counts).
   (b) Hb / Hct.
   (c) C5a (activation of complement)
   (d) Thrombin-Antithrombin Complex (TAT)

The samples will be collected after confirming that the blood and dialysate flows are at the targeted rates listed above, venous and arterial pressure at point of collection are to be recorded as well. For blood volumes see appendix B.

g) Visual estimation of the amount of clotted capillaries

After dialysis removal of the residual blood is performed by means of ultrafiltration with reverse osmosis water from dialysate compartment to blood compartment (0.5-1 bar water pressure and the overall appearance of dialyzer will be photographed, with focus on the clotted fibers and any residual header blood. This will be carried out at the end of each treatment for each dialyzer (3 times each dialyzer). The number of clotted capillaries in the dialyzer are counted after removal of the plastic casing and classified by the following table.

	Number of clotted fibers				
	0 – 10	**11 – 20**	**21 – 50**	**51 – 100**	**>100**
Score	1	2	3	4	5

2. Data Collection

All data, including blood flow rates, dialysate composition, heparin schedule (i.e. concentration in the pre-rinsing solution, bolus and infusion rates, all medications given to or taken by the patient, and standard dialysis symptom/events seen routinely in dialysis patients will be recorded in the case report form. The patients' records will contain the patients' names, dates of birth, patients' ESRD diagnosis, and duration of treatment on dialysis. Data will be entered into a locked dataset on a locked computer in the Nephrology Research Laboratory. Data will be analyzed in house with the exception of digital analysis of the photos taken of the dialyzers when dialysis is completed which will be done by the sponsor who will be blind to source of the photos. At this time it is not anticipated that any individual data, only aggregate results will be sent to the sponsor but if any individual data is sent to the sponsor will be blinded. All data will be stored by the Division of Nephrology in the Nephrology Research Laboratory for the designated time period and then destroyed.

8. Patient Informed Consent Form

The investigation has the character of a clinical study according to the US requirements and with reference to the European Standard ISO 14155 and the Declaration of Helsinki.
All patients must be informed about the aim of the study, the risks, and rights and have to sign a consent form.

9. Confidentiality

The principal investigator and evaluation sponsor accept that all details of the evaluation be kept confidential at all stages of the evaluation. The sponsor also has the right to inspect results prior to any publication or presentation; written consent from the evaluation sponsor is required before the results are published or presented at scientific meetings.

Date: _____ _____

Principal Investigator

_____ _____

Clinical Investigator Sponsor

Appendix A: Parameters

Sampling will be done for every dialysis treatment (3 times per dialyzer, per patient)

Performance		**60 min**
Clearance	Urea	V, A
‘’	Phosphate	V, A
‘’	Creatinine	V, A
“	ß2-m	V, A
“	Myoglobin	V, A

※Venous sampling will be first, followed by the arterial

※Do not adopt “slow flow sampling method”.

Performance		**pre**	**240 min**
Removal Rate Urea		A	A
‘’	Phosphate	A	A
‘’	Creatinine	A	A
“	ß2-m	A	A
“	Myoglobin	A	A

Sampling will be done once per patient, per dialyzer

Hemocompatibility	**Pre**	**15 min**	**30 min**	**60 min**	**240 min**
WBC	A	A	A	A	A
Platelet Count	A	A	A	A	A
Hb / Hct	A	A	A	A	A
C5a	A	A	A	A	A
TAT	A			A	A

Residual blood behaviour					*)

A: arterial sample (= pre-dialyzer)

V: venous sample (= post-dialyzer)

*) visual evaluation after intensive rinsing

Appendix B: Blood Volumes

Monday Wednwsday Friday Clearence Studies 84 cc/wk

	Pre	60' A	60' V	Post	
Monday	7 cc SST	7 cc SST	7 cc SST	7 cc SST	28 cc/day
Wednesday	7 cc SST	7 cc SST	7 cc SST	7 cc SST	28 cc/day
Friday	7 cc SST	7 cc SST	7 cc SST	7 cc SST	28 cc/day

Wednesday Compatibility Studies 47.5 ml/wk

	Pre	15'	30'	60'	Post	
CBC	2 cc Lavr	2 cc Lav	2 cc Lav	2 cc Lav	2 cc Lav	10 cc/day
C5a	**3** cc Lav	3 cc Lav	3 cc Lav	3 cc Lav	3 cc Lav	15 cc/day
TAT	4.5 cc Lt Blue	4.5 cc Lt Blue	4.5 cc Lt Blue	4.5 cc Lt Blue	4.5 cc Lt Blue	22.5 cc/day

Total blood volume = 131.5 ml/week x 3 weeks = **394.5 ml/Patient**

DCI Corporate Epogen Management Protocol

1) The goal of the protocol is to maintain Hgb at 11-12 g/dl. Erythropoietin doses are to be based upon the estimated dry weight.
2) The protocol will change the erythropoietin dose no more often than every 4 weeks except in the following cases:
    a. Discontinue erythropoietin when Hgb is greater than 13 g/dl.
    b. Increase the erythropoietin dose when Hgb is less than 11 g/dl and the previous dose change was a reduction in erythropoietin.
    c. Decrease erythropoietin dose based upon rules 8g-8i when Hgb is between 12-13 g/dl.
    d. Increase erythropoietin according to rule 8a when Hgb decreased from above 10 g/dl to below 10 g/dl.
3) If Hgb is greater than 13 g/dl then discontinue erythropoietin and check Hgb weekly. Resume erythropoietin at 25% less than the previous dose as soon as the Hgb is below 12.5 g/dl. If Hgb remains higher than 12.5 g/dl for more than three months return to the clinic's policy of testing Hgb.
4) For established patients who have had not had an erythropoietin within the last 3 months and have a Hgb <11 g/dl start erythropoietin at 300 units/kg/week; for a Hgb of 11-11.9 start erythropoietin at 150 units/kg/week.
5) For new patients without erythropoietin orders who have a Hgb <11 g/dl start erythropoietin 300 units/kg/week; for a Hgb of 11-11.9 start erythropoietin at 150 units/kg/week; for those with a Hgb > 11.9 g/dl do not start erythropoietin.
6) The weekly doses described in number 4 and 5 above will be equally divided into IV dosing for each HD treatment and will be given SQ as a single weekly dose for PD patients.
7) Increase erythropoietin dose by protocol no higher than 900 units/kg/week or 400,000 units per month.
8) For patients who have an erythropoietin (EPO) order and the order was not changed within the last 4 weeks or cases described in Number 2 above:
    a. If Hgb < 10 g/dl then increase EPO 50% but not less than 300 unites/kg/week.

b. If Hgb is between 10-10.9 then increase EPO 25% but not less than 75 units/kg/week.
c. If Hgb is between 11-11.9 and Hgb has decreased 0.5 g/dl or more since last dose change then increase EPO 10%.
d. If Hgb is between 11-11.9 and Hgb has increased/decreased 0.5 g/dl since last dose change then do not change EOP dose.
e. If Hgb is between 11-11.7 and Hgb increased0.5 g/dl or more since last dose change then do not change EPO dose.
f. If Hgb is between 11.8-11.9 and Hgb increased 0.5 g/dl since last dose then decrease EPO dose by 10%.
g. If Hgb is between 12-12.4 g/dl and Hgb decreased 0.5 g/dl or more since last dose change do not change EPO dose and check Hgb in 2 weeks.
h. If Hgb is between 12-12.4 and Hgb increased/decreased less than 0.5 g/dl since last dose change then decrease EPO 10% and check Hgb in 2 weeks.
i. If Hgb is between 12-12.4 g/dl and increased 0.5 g/dl or more since last dose change then decrease EPO 25% and check Hgb in 2 weeks.
j. If Hgb is between 12.5-13 g/dl and Hgb decreased 0.5 g/dl or more since last dose change then decrease EPO 10% and check Hgb in two weeks.
k. If Hgb is between 12.5-13 g/dl and Hgb increased/decreased less than 0.5 g/dl since last dose change then decrease EPO 25% and check Hgb in 2 weeks.
l. If Hgb is between 12.5-13 g/dl and Hgb increased 0.5 g/dl or more since last dose change decrease EPO 25% and check Hgb weekly.
m. If Hgb is greater than 13 then stop EPO and check weekly.

9) All erythropoietin dose decreases will be rounded to the nearest 200 units. All erythropoietin dose increases will be rounded up to the nearest 200 units. Dose will not be decreased below 400 unites.