



BIOARTPRODUCTS GmbH

**Master Protocol[®]
of Clinical Trials for Performance
& Biocompatibility of Dialysers**

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HEMODIALYSER

Membrane :
 Dialyser :
 Sterilisation :
 Area :

PATIENTS

10 stable end-stage-renal-failure patients

Inclusion criteria:

- 1. Patients who signed an informed consent form***
- 2. Patients between 18 and 75 years***
- 3. Patients who have been treated by hemodialysis for more than six month***
- 4. Patients who are on stable anticoagulation scheme***
- 5. Patients whose hematocrit is over 26***

Exclusion criteria :

- 1. Patients not meeting the inclusion criteria***
- 2. Gravida***
- 3. Patients with an unstable clinical condition***
- 4. Patients whose life expectancy is less than 12 month***
- 5. Patients with cardiac and vascular instability***
- 6. Patients with a positive anamnesis for first use syndrome***
- 7. Patients with known coagulation problems***
- 8. Single needle dialysis***

Treatment stop criteria

- 1. Patients' own decision***
- 2. Mechanical problems (e.g. leakage)***
- 3. Hypersensitive reactions (e.g. erythema, oedema)***
- 4. Insufficient compliance with treatment***
- 5. Change of anticoagulation scheme***
- 6. Other serious problems induced by the treatment***

BLOOD FLOW/ DIALYSATE FLOW

Blood flow according to patients' standard and dialysate flow (500 ml/min) should be unchanged for all patients throughout the study. During the clearance measurements the blood flow and ultrafiltration rate should be kept constant at $Q_b = 250 \text{ ml/min}$ and $\text{UFR} \leq 10 \text{ ml/min}$ for all patients.

PATIENTS' INFORMED CONSENT FORMS

It is the responsibility of the investigator to obtain the approval of the relevant ethical committees for the study, and to collect the written informed consent forms for all patients participating in the study. The signed and witnessed patient consent forms will be collected.

CONFIDENTIALITY

The study sponsors accept that the details of the study be kept confidential at all stages of the study. The sponsors have also the right to inspect results prior publication, according to existing confidential contract.

Parameters to be measured:

<i>Biocompatibility</i>	Pre	5 min	15 min	30 min	60 min	180 min
WBC	a	a	a	a	a	a
Platelet Count	a	a	a	a	a	a
Hb/HK	a	a	a	a	a	a
C3a	a	v	v	-	v	v
C5a	a	v	v	-	v	v
TAT	a	-	-	-	v	v
Elastase	a	-	-	-	v	v
Bradykinin	a	v	v	-	v	v
Residual blood Volume	-	-	-	-	-	*)

<i>Performance</i>	pre	30 min	180 min
Clearance Urea	a	a, v	a, v
„ Phosphat	a	a, v	a, v
„ Creatinine	a	a, v	a, v
β 2-M Clearance	a	a, v	a, v
blood albumin	a	-	a
dialysate albumin	-	-	d *) optional
S urea, β 2MG, albumin	-	**) a, v, f	**) a, v, f
UF-factor	-	***)	***)

a: arterial sample

v: venous sample

f: filtrate sample

d: dialysate sample

*) collected dialysate (method: see page 6)

**) together with UF-factor, but not with dialysers taken for biocompatibility measurements. Method: see page 6.

***) Sieving Coefficient, method: see page 5.

Residual Blood Evaluation

Standardization

Heparinization: 40 IU/kgBW initially
40 IU/kgBW continuously until 30 min before end of treatment

Retransfusion: with 250 ml saline solution, blood pump 250 ml/min,
until the venous drip chamber is reached.

Removal of the residual blood by means of ultrafiltration with 500 ml reverse osmosis water from dialysate compartment to blood compartment, 0.5 ... 1.0 bar water pressure. The Hb-concentration Hb_r of the 500 ml „ultrafiltrate“ have to be measured and the blood Hb_e at the end of treatment likewise. The residual blood amount V_r can be calculated by means of the formula:

$$V_r/\text{ml} = (Hb_r/Hb_e) * 500$$

The clotted fibers should be counted and judged by means of the marks:

number of clotted fibers	mark
0...10	1
11...20	2
21...50	3
51...100	4
> 100	5

Sieving Coefficient

Steps:

- Mode of the dialysis machine: Isolated ultrafiltration (Bergström procedure).
- The dialysate compartment must be emptied to collect undiluted filtrate.
- Collection of an arterial and a venous blood sample and filtrate
- Go back into the dialysis mode of the machine.

Calculation of the sieving coefficient:

$$S = c_f / (c_a + c_v) / 2 \quad (1)$$

Calculating S for small molecules like urea and creatinine only the arterial blood concentration c_a should be used:

$$S = c_f / c_a \quad (2)$$

Urea and creatinine are distributed intra- and extracellular with a transfer coefficient in the order of magnitude of the dialyser clearance. Therefore c_v will be smaller than in a homogenous solution and the sieving coefficient calculated by means of equation (1) is larger than 1.

Ultrafiltration factor k_{UF}

- Steps:
- Mode of the dialysis machine: Volumetric controlled ultrafiltration
 - Preset a high ultrafiltration rate (about 2.000 ml/h)
 - Measure the transmembrane pressure directly (do not rely on the machine display).
 - Measurement by means of a calibrated gauge on the same level (height): arterial pressure p_a (directly before the dialyser), venous pressure p_v (directly behind the dialyser), dialysate pressure p_d . Because of fluctuating pressure values reading of min/max-values and using the mean values is necessary.
 - Go back to the normal treatment mode.

Transmembrane pressure: $p_{tm} = (p_a + p_v)/2 - p_d$

UF-factor: $k_{UF} = UFR/p_{tm}$

Measurement of the total removal:

Collection of the total dialysate: Because of the large amount (about 100 l during 3 h) only a part of the dialysate should be branched off using an infusion pump or a flow divider with a constant rate (i.g. 10 ml/min, that means 1.800 ml during 3 h with the same concentration c_d as in the total dialysate. The actual dialysate flow rate Q_d of the dialysis machine including the ultrafiltration rate has to be measured during the treatment).

The totally removed amount M_e of a substance is:

$$M_e = c_d * Q_d * t \quad t: \text{collection time}$$