Effect of self-administered intraperitoneal bemiparin on peritoneal transport and ultrafiltration capacity in peritoneal dialysis patients with membrane dysfunction. A randomized, multi-centre open clinical trial

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Abstract

Background. Progressive peritoneal membrane injury and dysfunction are feared repercussions of peritoneal dialysis (PD), and may compromise the long-term feasibility of this therapy. Different strategies have been attempted to prevent or reverse this complication with limited success.

Methods. We performed a randomized, open multi-centre trial, aimed at scrutinizing the efficacy of self-administered intraperitoneal (i.p.) bemiparin (BM) to modulate peritoneal membrane dysfunction. The main outcome variables were peritoneal creatinine transport and the ultrafiltration (UF) capacity, estimated during consecutive peritoneal equilibration tests. The trial included a control group who did not undergo intervention. The treatment phase lasted 16 weeks with a post-study follow-up of 8 weeks.

Results. Intraperitoneal BM did not significantly improve creatinine transport or the UF capacity, when the whole group was considered. However, we observed a time-limited improvement in the

UF capacity for the subgroup of patients with overt UF failure, which was not observed in the control group. Intraperitoneal injection of BM did not carry an increased risk of peritoneal infection or major haemorrhagic complications.
Conclusions. Our data do not support the systematic use of BM for management of peritoneal membrane dysfunction in PD patients. Further studies on the usefulness of this approach in patients with overt UF failure are warranted. Intraperitoneal administration of BM is safe in PD patients, provided regulated procedures are respected.

Keywords: bemiparin, heparin, high peritoneal transport, peritoneal membrane, ultrafiltration failure

Introduction

Peritoneal dialysis (PD) implies continuous contact between artificial, bioincompatible solutions and the abdominal cavity, which results in mesothelial denudation, fibrosis and, in many cases, chronic inflammation and angiogenesis affecting the peritoneal membrane [1–4]. The main but not unique clinical consequences are an increase in the solute transport rate and a decline of the ultrafiltration (UF) capacity, affecting between 20 and 50% of PD patients in the long term [5–9]. The nature of dialysate-induced damage to the peritoneal membrane is complex, but glucose and its degradation products (GDP), the use of lactate as a buffer and the acidity of dialysate, all appear to be pathogenic [10]. The pathophysiology of the phenomena leading to peritoneal injury has not yet been completely understood, but some mediators, including several cytokines, vascular endothelial growth factor, transforming growth factor β and fibrin are clearly implicated [11–13]. Different strategies oriented to modulate the activity of these mediators have been attempted, with the aim of preventing or reversing peritoneal membrane damage, with limited success. Intraperitoneal (i.p.) heparin represents a potential therapeutic approach in this setting. This family of substances have been shown to favour mesothelial growth and peritoneal membrane repair during experimental peritonitis [14,15]. In the clinical setting, Sjøland *et al.* [16] have shown that i.p. tinzaparin, a low molecular weight heparin (LMWH), has the potential to modulate an increase in peritoneal small solute

transport and to increase the UF capacity of long-term PD patients. Unfortunately, this study was prematurely aborted, due to the unacceptable incidence of peritonitis, which was attributed to frequent bag manipulation by the patients.

LMWH are broadly used anticoagulants with a longer half-life than classic heparin, a more predictable dose–response profile and a lower risk of bleeding and thrombocytopaenia [17]. Bemiparin (BM), a second-generation LMWH with an average molecular weight of 3.6 kDa, has successfully been used for prophylaxis and treatment of venous thromboembolism and extracorporeal circuit coagulation in haemodialysis (HD).

We present the results of a randomized, open multi-centre clinical trial aimed at testing the hypothesis that daily self-administered BM can improve peritoneal transport in PD patients with disorders of peritoneal function without inducing an increase in the risk of peritonitis or major bleeding.

Materials and methods

General study design

In this multi-centre open trial, stable patients on chronic PD therapy were randomized either to once daily i.p. BM injection (study group) or no intervention (control group). The latter was preferred over placebo because we considered that any increment in the risk of peritonitis brought on by any i.p. injection would be unacceptable in this group. The ensuing follow-up considered two phases, namely, a phase of randomized treatment, lasting 16 ± 1 weeks and a post-study follow-up phase, lasting 8 ± 1 weeks. The main study variables were scrutinized at Weeks 8 and 16.

Figure 1 presents the study diagram. Overall, 104 patients from 15 centres were included in the study, 93 were finally analysed and 55 fulfilled the study protocol. Randomization was computer generated and stratified by centre. Patients who discontinued the trial prematurely were not replaced.

All patients gave their written informed consent at the inclusion visit, 1 week before randomization. The study was performed in accordance with local regulations and the

Declaration of Helsinki. The protocol was reviewed and approved by the ethical committees for clinical research of each participating centre.

Inclusion and exclusion criteria

We applied the following inclusion and exclusion criteria for eligibility.

Inclusion criteria. i) Age >18 years. (ii) PD therapy for >6 weeks. (iii) Peritoneal dysfunction, defined by either a standardized UF capacity [standard 4-h peritoneal equilibration test (PET) with 3.86% glucose-based dialysate] <600 mL and/or higher than average peritoneal small solute transport (defined by a creatinine D/P ratio >0.65 after 4 h during the same PET). (iv) Icodextrin-based long dwell for at least 4 weeks before inclusion.

Exclusion criteria. i) Peritonitis in the previous 2 months. (ii) Patients with bleeding diatheses, bleeding episodes and/or increased risk of bleeding for any reason (e.g. active peptic ulcer, haemorrhagic stroke, aneurysms) at inclusion or during the previous 2 months. (iii) Major surgery in the previous month. (iv) Hypersensitivity to LMWH, heparin or substances of porcine origin. (v) Hypersensitivity to icodextrin. (vi) Ongoing systemic anticoagulation. (vii) Congenital or acquired bleeding diatheses. (viii) Clinical events or surgical interventions affecting the central nervous system, eyes or ears during the previous 6 months. (ix) Acute or chronic bacterial endocarditis. (x) Heparin-associated thrombocytopaenia. (xi) Hepatic insufficiency or aspartate aminotransferase (AST) and/or alanine transaminase (ALT) values 5-fold above the normal value, as established by the local reference range. (xii) Uncontrolled arterial hypertension (systolic blood pressure >200 mmHg and/or diastolic blood pressure >120 mmHg). (xiii) Suspected or demonstrated inability to accomplish the protocol and/or complete the study. (xiv) Participation in another clinical trial in the last 30 days. (xv) Life expectancy <6 months. (xvi) Pregnant, breast feeding or fertile women who are not using effective contraception.

Treatment

Control patients were kept on the same treatment they had been receiving prior to their inclusion in the study. The same applied for patients of the treatment group who, in addition, received i.p. BM (3500 U), administered from a prefilled syringe into the icodextrin bag for a longer (9–16 h) dwell period. Detailed practices, instructions and materials were specifically facilitated by their primary PD nurse to avoid microbial contamination during BM injection.

Preclinical studies of anti-FXa activity

A stability study was performed in order to confirm that there was no interference between icodextrin solution and BM 3500 IU action when administered together as well as between the solution and the primary packaging material. It was concluded that BM sodium is compatible (maintains activity) with icodextrin solution for at least 24 h at room temperature since no significant decrease or variations in anti-FXa activity was observed during that period.

Efficacy parameters

The main study variable was peritoneal function, defined by standardized UF capacity (water negative balance obtained during a 3.86% glucose exchange after a 4-h dwell time, estimated as the difference of weight of the bag prior to and at the end of the procedure) and/or peritoneal creatinine transport, estimated as the D/P ratio at 4 h. For the latter purpose, peritoneal effluent (Minutes 0 and 240 of dwell time) and blood samples were retrieved for estimation of creatinine levels. Dialysate creatinine was corrected for simultaneous glucose concentration. Peritoneal function was assessed at baseline, and again after 8 and 16 weeks, in all patients.

Safety parameters

The main safety parameter was the incidence of peritonitis, defined as a peritoneal effluent with >100 leucocytes/mm ^{3} and >50% polymorphonuclear leucocytes since

randomization through Week 16. Haemorrhagic and thrombocytopaenic events were also scrutinized and recorded.

Fulfilment of the following criteria led to classification as major haemorrhage: fatal outcome, haemorrhage associated with a drop in haemoglobin levels ≥2 g/dL, requiring transfusion of ≥2 U of cell concentrate or total blood, retroperitoneal or intracraneal haemorrhage or clinically important haemorrhage requiring the interruption of treatment. Incidence of serious adverse events (SAEs) and adverse events (AEs), discontinuations from the trial as a result thereof as well as plasma anti-factor Xa activity were also assessed as secondary safety parameters.

An independent Data and Safety Monitoring Committee (DSMC) was responsible for guaranteeing the safety of all patients, introducing changes in the protocol and/or proposing to halt prematurely if it deemed appropriate, and for assessing the causality of the SAEs.

Statistical analysis

Sample size was calculated on the assumption that the primary efficacy end point (UF capacity) would improve by 20% in the experimental group, as compared with the control group. Assuming a standard deviation of 150 mL for UF capacity, an α error of 5% and a power of 80% and predicting an accumulated 5% dropout rate, we concluded that 38 patients were required for each arm.

We evaluated the study variables both by intention-to-treat (ITT) and as per protocol (PP) analysis. The ITT population included all patients who were at least 1 day in the study with at least one efficacy data available, either UF capacity or creatinine peritoneal transport. The 'PP' population included only patients who completed at least 80% of the doses of BM. We used non-parametric tests for comparisons between variables, including Mann–Whitney's U -test for numeric variables and χ^2 distribution and Fisher's exact test for categorical variables.

To categorize the evolution of the main variables over time, we applied linear mixed model analysis, using an unstructured covariance matrix for quantitative variables (UF and creatinine transport) in the framework of 'generalized mixed models'. The results should be interpreted as following:

(1) Significant ‘group’ means the effect of receiving BM or not is significantly different, but the variation over time is not significantly different (parallelism maintained).
(2) Significant ‘time’ implies an effect of time to a similar extent in both groups.
(3) Significant ‘model’ means the interaction ‘group-time’ is significant to a P value <0.05.

Assuming that quantitative modifications in the UF capacity may be more or less clinically relevant depending on the magnitude of the change, we explored subgroups of patients classified according to their baseline UF capacity. This means that gaining 200 mL of capacity of UF is clinically more significant for patients with a baseline UF capacity <400 mL than for patients with values >600 mL. We established three subgroups according to their UF capacity at baseline:

Group with UF capacity <400 mL/4 h (UF < 400).
Group with UF capacity of 400–600 mL/4 h (UF < 600).
Group with UF capacity >600 mL/4 h (UF > 600).

Patients with UF failure at baseline (<400 mL/4 h) were categorized as:

responders’ whether increased their UF capacity over 400 mL/4 h
high responders’ whether increased their UF capacity >600 mL/4 h, either at Week 8 and/or Week 16.

A similar strategy was applied to baseline creatinine D/P ratio values. Patients were categorized into three subgroups, according to D/P values >0.81 between 0.65 and 0.81 and <0.65, and classified as responders or high responders when their D/P values fell one or two steps down in this classification, respectively, either at Week 8 and/or 16.
All statistical analyses were made with SAS version 9.1.3.
This clinical trial has been registered in ClinicalTrials.gov (reference number NTC00369096).

Results

The analysis of the study variables by ITT and PP showed similar results, and we are presenting only those obtained by ITT. Twelve patients in the BM group (26.7%) and 11 in the control group (22.9%) were not included in the ITT analysis, which finally considered 70 patients (Figure 1). Nineteen patients completed the study in the BM group (112 ± 7 days), receiving at least 80% of doses (89 days). Table 1 shows the main baseline demographic and functional peritoneal variables of the study groups. Randomization yielded essentially comparable groups, except for a higher proportion of males in the BM group.

We observed a significant time effect for the capacity of UF, which increased from baseline to Weeks 8 and 16 during ITT analysis to a similar extent in the study and control groups (Figure 2).

Figure 3 plots D/P creatinine ratios over time in both groups. Median values maintained apparently stable levels in both arms during the observation period. On the contrary, the mixed model analysis disclosed a similar significant trend to decrease (P = 0.009) in both groups over time. The interaction term time × group was not statistically significant (P = 0.993), indicating that BM did not bear any influence on these changes.

Analysis of subgroups according to water and solute transports at baseline

UF capacity. A significantly higher rate of responders was observed in the BM group at Week 8 when compared with the control group (P = 0.028) ( ). This difference did not persist at Week 16 (P = 0.374), consistent both with a time-limited response or insufficient statistical power at 16 weeks. Four patients in the BM group (36.4%), versus none in control group, behaved as high responders, meaning that they switched to a UF capacity >600 mL/4 h.

Mixed models analysis disclosed trends to both time (P = 0.010) and BM treatment (P = 0.029) increases of UF capacity in the subset of patients with baseline UF failure (<400 mL/4 h).

Peritoneal transport of creatinine. We observed no apparent effect of the study intervention on peritoneal small solute transport after stratification for baseline D/P creatinine. Actually, more responders were observed in the control than in the BM group for the subgroup with D/P >0,81, both at Weeks 8 and 16 (data not shown). Mixed model analysis confirmed both time and control group as significant but separated predictors of a decrease of the D/P creatinine ratio in the subset with higher baseline creatinine transport (D/P > 0.81). On the contrary, no apparent effect was observed for the other sub-groups (D/P > 0.65 and D/P < 0.65) (data not shown).

Adverse events

The final evaluation included 44 patients in the BM group and 49 patients in the control group. Forty-three patients suffered a total of 93 AEs. Table 3 shows the main AEs in each group.

Despite the potential risk of multiple i.p. injections in the BM group, nine controls (18.8%) and three BM users (6.7%) suffered peritonitis (difference not significant, despite the 3-fold higher incidence among non-BM users).

Peritoneal absorption of BM was confirmed in some patients, as manifested by a higher anti-Xa activity compared with the control group (Table 3). Remarkably, not all patients treated with BM showed increased anti-FXa activity. No patient in any group suffered a major haemorrhagic event. Minor bleeding was recorded in nine patients in the BM group and none in the control group (P < 0.0009). One patient in the BM group, also treated with aspirin, was withdrawn from the study after an uncomplicated epistaxis. One patient in each group developed mild thrombocytopaenia.

Incidence of mortality and SAE were equal in both groups. One patient in each group died during the study. The causes were myocardial infarction in the BM group (a relation to BM was not suspected) and peritonitis in the control group.

Discussion

PD can markedly distort the structure and function of the peritoneal membrane. The clinical repercussions of this phenomenon are variable, lying between minor changes in peritoneal solute transport rates and the capacity of UF in the best of cases to the dramatic

picture of encapsulating peritoneal sclerosis (EPS) at the other extreme. Acquired high solute transport and, particularly, UF failure are main clinically significant repercussions of long-term PD. UF failure affects 20 to 50% of PD patients and represents a cardinal cause of late technique failure and cardiovascular mortality for these patients [5–9].

Prevention and management of UF failure represents a challenge for PD nephrologists. Glucose-sparing strategies and the introduction of new, seemingly more biocompatible, solutions raised great expectations for prevention of this complication, which have not been so far conclusively fulfilled by clinical experiences. Dropout to HD is usually indicated once the problem is clinically overt, due to an evident shortage of therapeutic resources and to the ever-present fear of progression to EPS, if PD is not discontinued. Only peritoneal rest with intermittent heparin administration has offered some limited success [18,19], while other measures have generally proved inconsistent.

The potential of heparin and its derivates for prevention and repair of peritoneal membrane injury during PD is a matter of interest [14]. This family of compounds shows remarkable pleiotropic properties beyond their classic applications as anticoagulants. Fibrin provides a matrix for the initiation of peritoneal fibrotic processes, which heparin can modulate. Moreover, heparin displays anti-angiogenic, anti-inflammatory and antifibrotic properties [14]. However, experimental studies have not uniformly supported the usefulness of this approach. For instance, a recent study in rats did not find any benefit for the peritoneal membrane after 5 weeks of i.p. heparin therapy [15]. On clinical grounds, only one previous study has addressed this question. Sjöland *et al* [16] showed that i.p. tinzaparin may be able to reduce small solute peritoneal transport, to a statistically and, probably, clinically significant extent. The study was aborted early due to the unacceptably high incidence of peritonitis but, overall, supported the role of this therapy for management of acquired peritoneal membrane injury.

The current randomized trial could not demonstrate any significant overall improvement in the peritoneal function markers of a PD population with higher than average small solute transport and/or a low UF capacity. These findings argue against the systematic use of LMWH to prevent or reverse these manifestations of peritoneal membrane dysfunction. However, subgroup analysis disclosed a clear trend to a time-limited increase in the UF capacity for patients with overt UF failure, which did not persist at Week 16. This phenomenon may indicate that the beneficial effect of BM could be

transient in patients with established membrane injury but also a progressive loss of statistical power during follow-up. In any case, our data indicate that the potential long-term effect of LMWH on overt UF failure merits further study.

Our study provides clear evidence that daily injection of LMWH in PD bags is safe, provided the correct procedures are applied. No major haemorrhagic events or increased incidence of peritoneal infections were observed in the BM group, when compared with a control, no intervention group. Sporadic bag injection of different drugs (heparin, local anaesthetics, antibiotics) is common in PD patients for different reasons. There is no evidence that i.p. administration of antibiotics for peritonitis carry an increased risk of reinfection by different germs. On the other hand, i.p. insulin administration was common in the early decades of PD. This practice has markedly declined, but is still maintained routinely in many centres, and used temporarily as needed in many others. The main reasons for this decline are dosing and absorption issues, and the better performance of subcutaneous, newer, more convenient insulin preparations, rather than the risk of infections. The controversy on a potential higher incidence of peritonitis in diabetics treated with i.p. insulin is an old unresolved one [20].

The main strengths of this study are a clear reasonably founded hypothesis and a careful design with a sufficient follow-up. An adequate proportion of patients were able to fulfil the protocol. The main limitations are brought by concerns about the statistical power of the results, as in any trial yielding essentially negative results. The duality of the criteria for inclusion generated some confusion at the time of interpreting the results because high peritoneal transport and low capacity of UF are linked, but not interchangeable characteristics. This circumstance demanded subanalyses addressed to patients with either of these characteristics, which may have further limited the power of the findings. The apparent lack of effect of BM on anti-FXa activity may suggest non-compliance in some patients, although low peritoneal absorption is a plausible alternative explanation. Finally, a placebo-controlled design could have been more orthodox but was discarded because of the deemed unnecessary risk of peritonitis posed by sham injection to dialysate bags.

In conclusion, once daily i.p. administration of BM for up to 4 months does not appear to improve peritoneal dysfunction in PD patients with higher than average peritoneal small solute transport or a low UF capacity. However, sub-analyses of the main data suggest a

time-limited beneficial effect of BM on the UF capacity of patients with overt UF failure, warranting further studies to confirm these findings. Intraperitoneal administration of BM to PD patients was not associated with an increased risk of peritonitis or major haemorrhagic complications.

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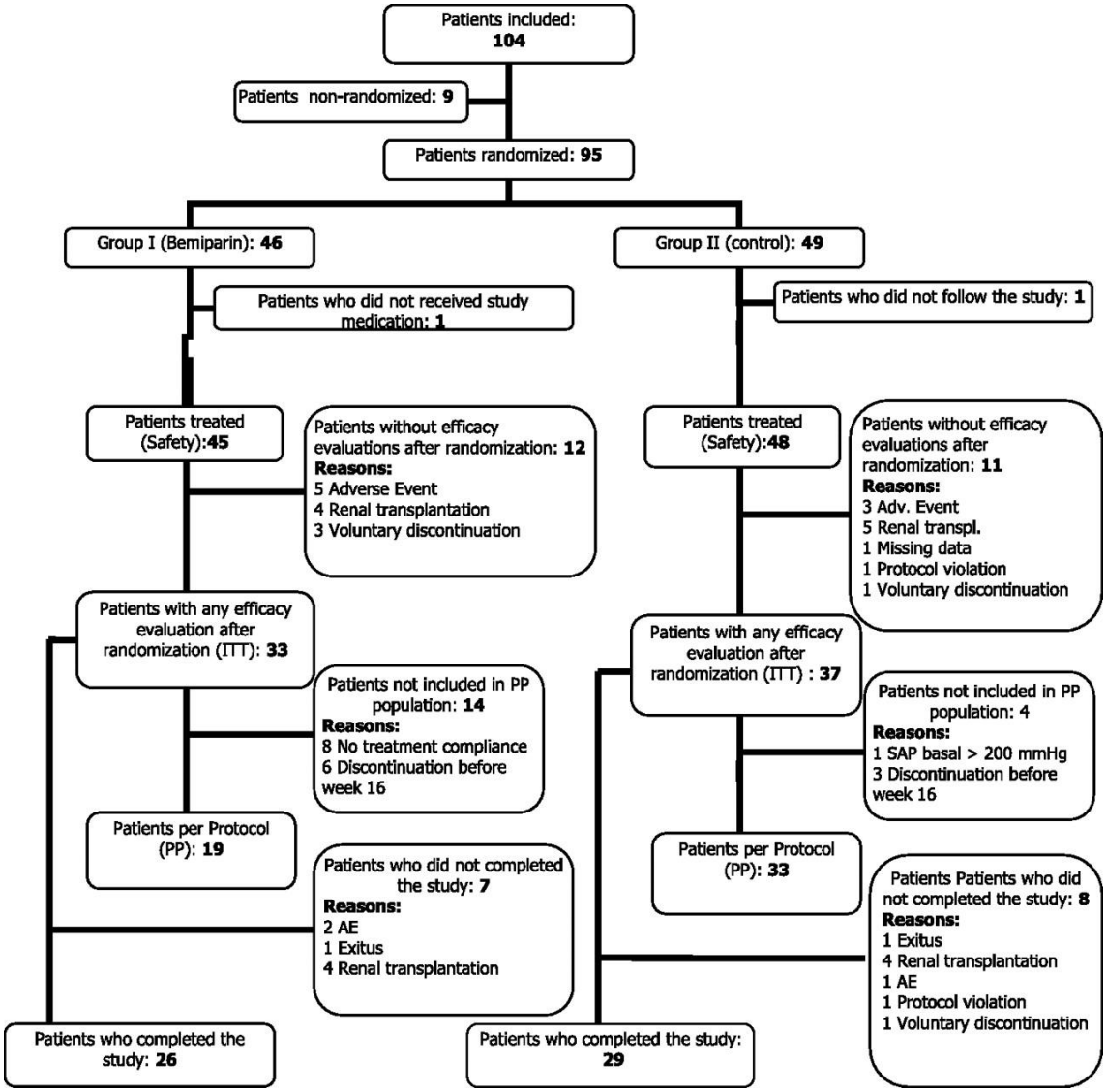


Fig. 1 Flow chart of patients included at each period and causes for dropout.

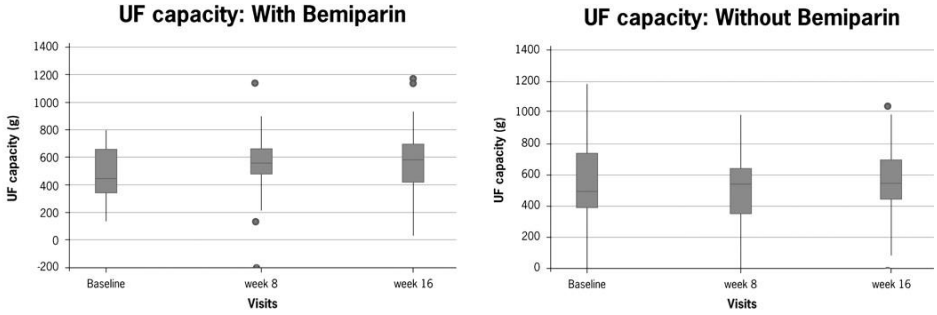
Table1. Demographic and peritoneal data at baseline (ITT)

	Group			P-value
	Total (n = 70)	BM (n = 33)	Control (n = 37)	
Gender				0.019
Men	50 (71.4%)	28 (84.8%)	22 (59.5%)	
Women	20 (28.6%)	5 (15.2%)	15 (40.5%)	
Age (years)				0.69
Mean (SD)	51.80 (17.62)	52.58 (18.40)	51.11 (17.11)	
Median (min; max)	52.5 (22.0; 85.0)	56.0 (22.0; 85.0)	51.0 (23.0; 84.0)	
BMI (kg/m^2)				0.43
Mean (SD)	26.20 (4.07)	25.80 (4.00)	26.56 (4.16)	
Median (min; max)	26.0 (17.2; 35.2)	25.4 (17.2; 34.9)	26.4 (19.9; 35.2)	
Mode of PD				0.65
APD	54	25	29	
CAPD	16	8	8	
Time on PD (months)				0.64
Mean (SD)	18 (15.8)	16.2 (14)	19.9 (18)	
Median (min; max)	11.1 (3; 59.1)	10.3 (3.1; 39)	14.5 (3; 59.1)	
Previous peritonitis				0.62
Yes	24	12	12	
No	46	21	25	
Urine volume (mL/24 h)				0.95

Table1. Demographic and peritoneal data at baseline (ITT)

		Group		P-value
Patients	46	21	25	
Mean (SD)	1153.09 (661.24)	1083.00 (404.92)	1211.96 (821.75)	
Median (min; max)	1175 (100.0; 3225.0)	1200 (300.0; 1730.0)	1000 (100.0; 3225.0)	
UF capacity (mL/4 h)				0.70
Mean (SD)	521.44 (258.13)	505.91 (194.79)	535.30 (305.88)	
Median (min; max)	500.0 (0.0; 1210.0)	460.0 (150.0; 820.0)	500.0 (0.0; 1210.0)	
Creatinine D/P ratio (mL/min)				0.53
Mean (SD)	0.73 (0.09)	0.74 (0.09)	0.72 (0.08)	
Median (min; max)	0.7 (0.5; 0.9)	0.7 (0.5; 0.9)	0.7 (0.5; 0.9)	

Min, minimum; max, maximum; BMI, body mass index; APD, automated PD; CAPD, continuous ambulatory peritoneal dialysis.



Bemiparin				Controls			
	Baseline	8 weeks	16 weeks		Baseline	8 weeks	16 weeks
N	33	33	33	N	37	37	37
Median	460	570[1]	585[1]	Median	500	550[1]	550[1]
Range	150; 820	-200; 1190	50; 1220	Range	0; 1210	0; 1000	0; 1080

[1] *p<0.0001 versus baseline. No differences between BM and Control Group were found at any visit*

Mixed models

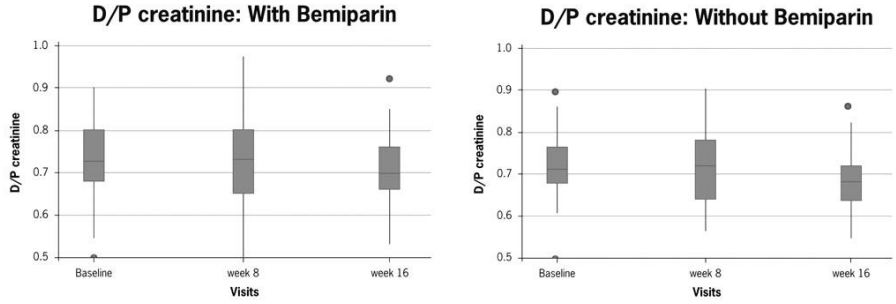
Effect		Degrees of freedom	F-value	p-value
Group	1	136	0.07	0.795
Time	2	136	1.54	0.218
Time * Group	2	136	1.18	0.311

PP Analysis:

Bemiparin				Controls			
	Baseline	8 weeks	16 weeks		Baseline	8 weeks	16 weeks
N	19	19	19	N	33	33	32
Median	550	580[1]	600[1]	Median	500	580[1]	600[1]
Range	200;820	-200; 920	100; 1220	Range	0; 1210	0; 1000	0; 1210

[1] *p<0.0001 versus baseline. No differences between BM and Control Group were found at any visit*

Fig. 2 Box plots of UF capacity in both groups during follow-up.



Bemiparin				Controls			
	Baseline	8 weeks	16 weeks		Baseline	8 weeks	16 weeks
N	33	32	33	N	37	36	37
Median	0.70	0.73	0.70	Median	0.70	0.72	0.68
Range	0.50; 0.90	0.50; 1.00	0.50; 0.90	Range	0.50; 0.90	0.60; 0.90	0.60; 0.90

No significant differences between BM and Control Group at any point

Mixed models

Effect		Degrees of freedom	F-value	p-value
Group	1	134	0.48	0.489
Time	2	134	4.88	**0.009**
Time * Group	2	134	0.01	0.993

PP Analysis:

Bemiparin				Controls			
	Baseline	8 weeks	16 weeks		Baseline	8 weeks	16 weeks
N	19	18	19	N	33	32	31
Median	0.73	0.74	0.71	Median	0.70	0.71	0.68
Range	0.70; 0.80	0.50; 0.90	0.50; 0.90	Range	0.70; 0.70	0.60; 0.80	0.60; 0.80

No significant differences between BM and Control Group at any point

Fig. 3 Box plots of D/P creatinine ratio in both groups during follow-up.

Table 2. UF capacity changes at Weeks 8 and 16 in patients with UF failure (UF < 400 mL/4 h) at baseline

	BM	Controls	P-value
Number of patients	11	9	
Responders at Week 8	7	1	0.02
Responders at Week 16	5	2	0.37
High responders at Week 8	4	0	0.09
High responders at Week 16	1	0	1.00

Mixed models

Effect		Degrees of freedom	F-value	P-value
Group	1	36	5.16	**0.029**
Time	2	36	5.16	**0.010**
Time × group	2	36	1.10	0.344

Table 3. Adverse events

	BM (*n* = 44)	Controls (*n* = 49)	P-value
Adverse events			
Number of patients with AE	18	25	NS
Total number of AE	45	48	NS
Serious AE	13	10	NS
Deaths	1	1	NS
Peritonitis	3 (6.7%)	9 (18.8%)	NS
Major haemorrhage	0	0	NS
Minor haemorrhage	9	0	0.0009
Thrombocytopaenia	1	1	NS
Anti-FXa activity			
At baseline	0.02 ± 0.02	0.02 ± 0.02	NS
At Week 8	0.1 ± 0.06	0.02 ± 0.02	0.0005
At Week 16	0.09 ± 0.09	0.02 ± 0.02	0.0005