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Short Communication

Mid-Dilution Hemodiafiltration Compared to Pre- and Post-Dilution Hemodiafiltration: A Study Preparatory to a Prospective Randomized Trial -

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ABSTRACT

Background: The aim of this pilot study was to compare the three currently available on-line hemodiafiltration techniques: Mid-Dilution (MID), Post-Dilution (POST) and Pre-Dilution (PRE) concerning middle molecular solute removal and tolerability in reference to intradialytic stability of hemodynamic parameters as well as patient wellness.

Materials and methods: We enrolled 6 patients suffering from end stage Chronic Kidney Failure (mean age: 56 ± 18 years; 5 men, 1 woman) on regular thrice weekly hemodialysis treatment. All of them were anuric and had well functioning native AV fistulas for blood access. Every patient underwent three consecutive treatment periods of five weeks each, with the three above mentioned techniques. At the end of the five weeks, during the first and last dialytic session of the week, we performed a thorough hematochemical evaluation. We distributed patients in three groups following a crossover; Latin squares design, randomly assigning them to the sequence. In order to make comparable these three techniques, differing in substitution flow and technical features of the hemodiafilters, we made the duration of dialysis treatment and substitution flow fit to reach a Kt/V single pool equal or higher than 1.3.

We analyzed our data with a Covariance Analysis Model (ANOVA).

Results: All three study subsets (with the three methods) were accomplished without significant intradialytic adverse effects. Blood pressure values maintained steady across the study, not differing from the usual values of enrolled patients.

Our data showed, regarding β2 microglobulin, a significant statistical difference in post dialytic value matched for hemoconcentration (p-value = 0.0473) between MID and PRE techniques in favour of MID, and a better trend (without statistical significance) than POST. Finally our study showed, confirming medical literature reports, that mid-dilution hemodiafiltration leads to an albumin loss greater than what occurred in pre and post-dilution hemodiafiltration techniques.

Discussion and conclusion: Our study is to be considered a pilot one, being performed in a small sample of patients with the aim of a larger clinical trial, but our first results showed that MID is a technique, being better in removing β2 microglobulin than PRE and having a better trend even compared to POST. Furthermore, the 3 techniques showed the same good tolerability.

Keywords: β2 microglobulin removal; Hemodiafiltration; Mid-dilution; Post-dilution; Pre-dilution

INTRODUCTION

This study was designed to compare on a small scale, as a pilot experience for a larger clinical trial, three on-line hemodiafiltration techniques currently available, concerning middle molecular solute removal and tolerability in reference to intradialytic stability of hemodynamic parameters as well as patient wellness.

Theoretical remarks

We define "mid-dilution" a sort of hemodiafiltration technique differing from the other usual hemodiafiltration variants insomuch as substitution fluid is infused between two filters set in sequence, one inside the other. Mid-dilution hemodiafiltration needs therefore a largely modified dialyser compared to the usual hemodiafilters. Currently, in two other versions of the hemodiafiltration technique already available, the substitution fluid is infused either afterwards (post-dilution), or before dialyser (pre-dilution).

Both pre-dilution and post-dilution hemodiafiltration have several intrinsic problems: pre-dilution infusion of substitution fluid has negative effects on low molecular weight toxins clearance, by reducing their concentration gradient. Post-dilution infusion, on the other hand, can cause hemoconcentration.

In brief, pre-dilution hemodiafiltration benefits are represented by high ultrafiltration rate, with a smaller hemoconcentration risk and higher medium size molecules clearances, whereas disadvantages consist in the dilution of the entering blood that causes a clearance reduction of the small size molecules. Post-dilution hemodiafiltration benefits consist, on the other hand, in high clearance of both small and middle size molecules, paying a price in terms of ultrafiltration rate reduction and subsequent hemoconcentration risk [1,2].

Mid-dilution hemodiafiltration mixes up pre-dilution with post-dilution, infusing substitution fluid in the blood flow between two filters in series. In this way high ultrafiltration-substitution rate achievable with a first stage in post-dilution followed by a second in pre-dilution should obtain high solutes clearance, either of low or middle molecular weight, with high β2 microglobulin clearance and best performances in terms of Kt/V (urea clearance).

To confirm these promising theoretical constructs, we carried out in our Unit a small pilot study, as a basis for a larger trial on a hemodialysis population, in order to compare mid-dilution to pre- and post-dilution hemodiafiltration.

MATERIALS AND METHODS

Patients

Inclusion criteria: age over 18 years, on chronic hemodialysis (three times a week), lasting over 6 months, steady clinical conditions, without ongoing acute or chronic infections, neoplastic diseases, malnutrition, or malfunctioning of vascular access or blood flow below 300 ml/ min.

We enrolled 6 patients: (mean age: 56 ± 18 years; 5 men, 1 woman) suffering from End Stage Chronic Renal Disease on regular thrice weekly hemodialysis (N = 5 bicarbonate hemodialysis; N = 1 hemodiafiltration on line in post dilution).

Underlying renal diseases were: diabetic nephropathy (N =1), glomerulonephritis (N = 1), Autosomal Dominant Polycystic Kidney Disease (ADPKD) (N = 2), nephrosclerosis (N = 1), unknown nephropathy (N = 1). Mean dialytic vintage was 7 ± 5,6 years. All patients were anuric and had well functioning native AV fistulas for blood access. The patient's concomitant medications were continued in an unchanged manner including heparinization for dialysis treatment under study conditions.

Study design

Each patient underwent three consecutive treatment periods, lasting five weeks each, with the three hemodiafiltration methods.

We randomly assigned patients to each technique according to a Latin squares crossover scheme, as follows: Defining: A = HDF on-line mid-dilution

B = HDF on-line post-dilution

C = HDF on-line pre-dilution

Treatments scheme and patients randomization:

Patient	5	2	1	4	3	6
Technique	B	C	A	B	C	A
	A	B	C	C	A	B
	C	A	B	A	B	C

Each treatment period lasted 5 weeks, so divided:

a) First week to reach the Kt/V targets we specify afterwards.

b) The remaining 4 weeks with the technique assigned (see chart above)

Clinical and laboratory examinations

For each of the three treatment periods, at the fifth week, in the first and last hemodialysis session of the week, we performed the following laboratory examinations:

1. Plasma concentrations of serum electrolytes (sodium, potassium, calcium, inorganic phosphorus, magnesium) were measured in blood samples drawn from the arterial blood line before the start and at the end of the treatment.
2. Blood urea nitrogen, creatinine, total protein, plasma albumin concentration, hematocrit, β2- microglobulin were measured in blood samples drawn from the arterial blood line before the start and at the end of the treatment.

Only at the start of the last hemodialysis session of the fifth week, for each of the three treatment periods, in blood samples drawn from the arterial blood line before the start of the treatment, we measured also: iPTH, transferrin, ferritin, C - reactive protein and homocysteine.

For each of the three treatment periods, at the fifth week, during the first and last hemodialysis session we recorded blood pressure values and heart rate, at the beginning, middle and end of the hemodialysis session.

For each of the three treatment periods, only during the last hemodialysis session of the fifth week we also performed an electrocardiogram one hour after the treatment beginning.

Finally, for each of the three treatment periods, at the first hemodialysis session of the fifth week we also calculated single pool Kt/ V for urea by means of second generation logarithmic estimates of single pool, variable volume Kt/V in according to Daugirdas [3,4].

During each hemodialysis session, besides the usually recorded parameters according to our protocol, we recorded every symptomatic hypotension episode (defined as symptomatic drop of systolic pressure ≥ 20 mmHg, needing physiological solution infusion, plasma expanders or changes in the blood flow, or ultrafiltration rate parameters previously set), every hypertension episode (defined as a symptomatic systolic blood pressure rise over 160 mmHg, higher than 20 mmHg from basal values, needing a therapeutic intervention), every cardiac arrhythmia, dyspnea, fever, cramps, headache, hitching, nausea and vomiting.

Sample method

Predialytic blood samples were drawn by arterial blood line before the start of the treatment. Post dialytic blood samples were drawn by arterial blood line at the end of the treatment after reduction of the blood flow to 100 ml/ min and dialysate flow turned off for 15 seconds ("slow flow" technique) [3,5,6].

Dialysis targets for the comparison

In order to compare the three hemodiafiltration techniques (differing in substitution flow and technical features of the hemodiafilters), we aimed to reach the same, adequate delivered dose of hemodialysis. For this reason, all the three hemodiafiltration techniques were performed optimizing duration of dialysis treatment and substitution flow to attain a Kt/V single pool, variable volume equal or higher than 1.3 (higher therefore to the minimum delivered dose of hemodialysis according to the NKF/DOQI Guidelines) [3].

Substitution rate and duration of dialysis treatment according to each hemodiafiltration techniques were set as follows (data are mean values ± standard deviation):

Method	Mid dilution	Post dilution	Pre dilution
Duration of dialysis treatment (minutes)	234 ± 13	235 ± 12	235 ± 12
Substitution rate (lt/h)	7,9 ± 1,8	4,3 ± 0,7	12,7 ± 0,5

Blood flow and dialysate flow were set throughout the study and were kept constant for all study sessions according to the following parameters:

blood flow (effective) = 300 ml/ min	dialysate flow = 500 ml/ min

The ultrafiltration rate of each session was set according to individual patient's interdialytic weight gain.

Hemodiafilters and monitors

Hemodiafiltration sessions were performed using dialysers and dialysis machines in accordance with each hemodiafiltration technique:

Technique	mid dilution	pre and post dilution
Dialyser	Nephros Olpur MD 190 (high flux polyethersulfone membrane, 1,9 m^2; Nephros, New York, USA; Bellco, Mirandola, Italy)	Polyflux 24 S (high flux polyamide membrane, 2,4 m^2; Gambro Lund, Sweden)
Dialysis machine	Bellco Formula (Bellco, Mirandola, Italy)	Gambro AK 200 (Gambro, Lund, Sweden)

About the polyamide membrane dialyser we point out that this dialyser, was chosen for its excellent performances in both pre-dilution and post-dilution techniques.

All the dialysis machines utilized were equipped for on-line preparation of sterile infusion fluid.

Anticoagulation was performed by unchanged adoption of form and dosage of the previous routine heparinization. Four patients received standard heparin as a bolus/continuous infusion and two patients received low molecular weight heparin in single bolus form at the start of the dialysis session.

Measure of treatment efficacy

Treatment efficacy was determined by measuring single pool, variable volume Kt/V for urea and reduction ratios (RR).

Reduction ratios was determined both for small molecular weight solutes like urea (60 D), creatinine (113 D) and phosphorus (96 D), and for middle molecular weight solutes like β2 microglobulin (11,8 kD). Finally we determined clearance rate for albumin (67 kD), too.

For this purpose plasma concentrations were measured in blood samples drawn from the arterial blood line before the start (C_{pre}) and at the end (C_{post}) of each treatment session after reduction of the blood flow to 100 ml/min and dialysate flow turned off for 15 seconds.

Reduction ratio was calculated according to equation 1 [7]:

$RR = (1 - C_{post} / C_{pre}) * 100$ (equation 1)

For middle and large molecular weight solutes C_{post} values were corrected for changes in the extracellular volume [8].

Data analysis

About descriptive and comparative statistical analysis of the results, we point out that the values of each parameter, found before the start and at the end of the first and last dialysis session of the fifth week of each of the three treatment periods, were combined calculating an average data for pre dialysis values and another for post dialysis values. The descriptive statistics, carried out by calculating mean values ± Standard Deviation (SD), and comparative statistical analysis were performed on the outcoming values.

Comparative statistical analyses of within-subject between-treatment differences were assessed using a variance analysis model (ANOVA). A p value of < 0.05 was considered as statistically significant.

Statistical evaluation was performed by means of the SAS software package (version 8.2 for Windows; Cary, NC, USA).

RESULTS

Clinical observations

All patients completed the whole study period, except for a male patient that (during the mid-dilution hemodiafiltration treatment period) after the first five mid-dilution hemodiafiltration sessions presented an intradialytic angor episode, although without any important change of myocardial necrosis markers, nor significant electrocardiogram abnormalities.

This patient underwent shortly after a coronarography that showed no pathological changes. Anyway he decided to drop out of the study.

This episode represented the only adverse event during the study: all the three hemodiafiltration techniques were performed without provoking in the patients any adverse symptoms such as hypotension, headache or other; notably the electrocardiograms showed no changes from baseline, as well as unchanged and stable were the intradialytic blood pressure values.

Treatment efficiency

The results of our study allow only an evaluation of the middle molecules clearance, as small molecules (particularly urea nitrogen) clearance is indissolubly bound to the Kt/V single pool, variable volume, targets chosen for all the three hemodiafiltration techniques in accordance with the study design.

Moreover, we can't forget that we studied a small sample.

Nevertheless, regarding β2 microglobulin removal, we found a statistical significant difference in the post dialysis value, corrected for hemoconcentration, between mid-dilution and pre-dilution hemodiafiltration in favour of mid-dilution hemodiafiltration (6.77 ± 0.83 vs 8.81 ± 1.99 mg/ dl; P-value = 0.0473). The β2 microglobulin reduction ratio with mid-dilution hemodiafiltration was -76.97± 4.13 % compared to -69.31 ± 7.96 % with pre-dilution hemodiafiltration: this difference, however, didn't reach statistical significance (probably due to the small sample size) (Table 1; Figure 1,2).

No statistically significant difference, regarding β2 microglobulin removal, was found between mid-dilution and post-dilution hemodiafiltration, however mid-dilution hemodiafiltration achieved a lower β2 microglobulin post dialysis value compared to post dilution hemodiafiltration (6.77 ± 0.83 vs 7.78 ± 1.33 mg/ dl; P not significant) and a higher β2 microglobulin reduction ratio (-76.97± 4.13 % compared to -72.19 ± 5.69; P not significant) (Chart 1; Figure 1,2).

The Kt/V (Chart 3) and the reduction ratios of small molecules like blood urea nitrogen, creatinine and phosphorus, due to the Kt/V targets chosen, didn't show any statistical difference between treatments.

Our study showed also a higher albumin loss with mid dilution hemodiafiltration in comparison to post-dilution and pre-dilution hemodiafiltration (-2.39 ± 2.00 compared to -1.64 ± 1.08 and -0.96 ± 1.61 as percent of reduction ratio calculated taking account of hemoconcentration, respectively; P not significant) (Table 2).

No statistical difference was found between all the three hemodiafiltration techniques about potassium, magnesium, hematocrit, total protein, calcium, iPTH and the other parameters assessed (ferritin, transferrin, C reactive protein, homocysteine).

DISCUSSION

The results of our study, though is a pilot one with a small sample size, demonstrate, as described in medical literature [9], that β2 microglobulin, as a reference middle molecule involved in dialysis-related amyloidosis, is better removed with mid-dilution hemodiafiltration as compared to post-dilution and pre-dilution hemodiafiltration both performed making use of high substitution fluid rates and large surface hemodiafilters.

This finding is even more significant taking in account that mid-dilution hemodiafiltration was performed using a smaller surface hemodiafilter (1,9 m^2) in comparison to hemodiafilter (2,4 m^2) used in both pre- and post-dilution hemodiafiltration, however mid-dilution hemodiafiltration allows the infusion of much higher substitution fluid volumes in comparison to post-dilution hemodiafiltration (7,9 ± 1,8 vs 4,3 ± 0,7 lt/ h) thereby enhancing convective mass transfer without diluting solutes in blood to an extent found in predilution hemodiafiltration and, as described in medical literature [9], there is a positive linear correlation between clearance and substitution rate for both small and middle molecular weight solutes as β2 microglobulin.

Anyhow to allow a better comparison between the three hemodiafiltration techniques, as suggested in medical literature [9], substitution fluid rate and hemodiafilter surface were chosen near the operational limit of each respective hemodiafiltration mode.

On the other hand, the study design, imposing the goal of the same Kt/V for all the three hemodiafiltration techniques, allowed only an evaluation of the middle molecules clearance making unnecessary to increase the dialysate flow to raise small molecules clearance; for this reason we left dialysate flow unchanged, to the usual values of the clinical practice for all techniques equals 500 ml/ min.

As recommended in literature [9] to achieve comparable small solute clearances in mid-and post-dilution hemodiafiltration it is recommended to set dialysate flows to values of 800 ml/ min.

Table 1: Beta2 microglobulin (mg/dL) – Descriptive Statistics and Statistical analysis.

Dialysis Technique	Descriptive Statistics	Pre	Post	Post corrected	Delta Pre vs Post corrected	RR %
MID	N	5	5	5	5	5
	Mean	29.67	7.76	6.77	-22.90	-76.97
	SD	3.02	0.68	0.83	3.27	4.13
	Median	30.10	7.75	6.93	-23.17	-77.91
	Min	26.55	7.10	5.71	-27.12	-81.19
	Max	33.40	8.80	7.93	-18.62	-70.12
POST	N	5	5	5	5	5
	Mean	28.28	9.09	7.78	-20.50	-72.19
	SD	2.85	1.18	1.33	3.34	5.69
	Median	28.43	8.95	7.55	-20.86	-71.49
	Min	23.80	7.90	6.63	-25.07	-79.07
	Max	31.70	10.80	9.79	-16.25	-65.40
PRE	N	5	5	5	5	5
	Mean	29.03	10.59	8.81	-20.22	-69.31
	SD	4.03	2.27	1.99	4.00	7.96
	Median	27.95	9.15	7.52	-20.56	-73.56
	Min	24.50	8.78	7.18	-24.17	-74.98
	Max	35.30	13.32	11.13	-13.67	-55.79

	ANOVA p-value		
	Post corrected	Delta	RR%
Overall	0.1289	0.4471	0.1799
MID vs POST	0.2930	0.3055	0.2419
MID vs PRE	0.0473	0.2559	0.0720
POST vs PRE	0.2887	0.9044	0.4725

Note: Pre and Post data are mean values within patient of plasma Beta2 microglobulin concentration, found before the start and at the end of the first and last dialysis session during the fifth week of each of the three treatment periods. Post values were corrected for changes in the extracellular volume. Reduction Ratio(RR) was calculated taking into account hemoconcentration.

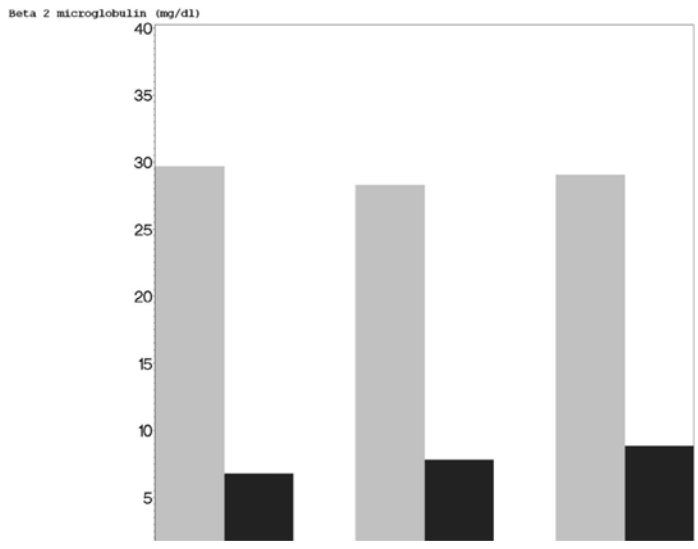

Figure 1: Plasma Beta 2 microglobulin concentration (mg/dl) sampled before and after the execution of each dialysis technique.

However the dialysis dose achieved by mid-dilution hemodiafiltration in our study far exceeded the target dose chosen.

Finally our study showed, confirming medical literature reports [9], that mid-dilution hemodiafiltration leads to an albumin loss greater than what occurred in pre and post-dilution hemodiafiltration techniques.

However, even if our follow up was short, we didn't reported, any malnutrition symptoms, like hypoalbuminemia and weight loss, greater for mid-dilution than pre or post-dilution hemodiafiltration.

Lastly, in contrast to other papers [9,10], mid–dilution hemodiafiltration was performed without provoking any problem with regard to anticoagulation, and tolerability was as good as the other two hemodiafiltraton techniques.

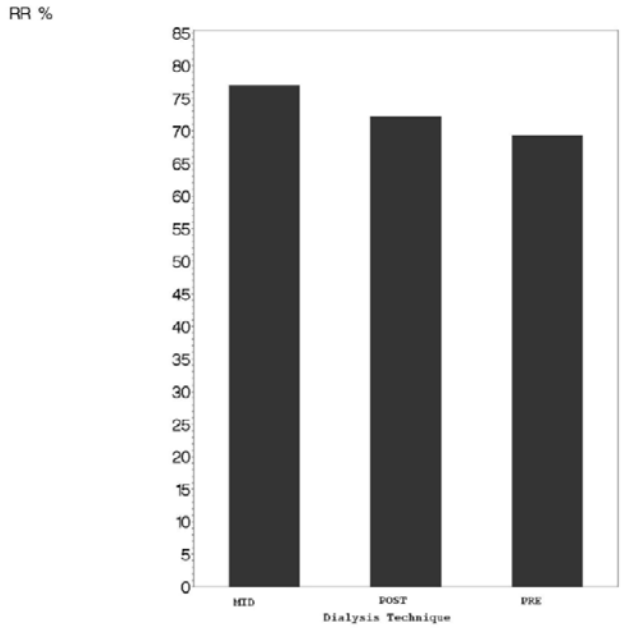

Figure 2: Beta 2 microglobulin reduction ratio (%) performed by each dialysis technique.

Table 2: Plasma Albumin concentration (gr/dL) - Descriptive Statistics and Statistical analysis.

Dialysis Technique	Descriptive Statistics	Pre	Post	Post corrected	Delta Pre vs Post corrected	RR %
MID	N	5	5	5	5	5
	Mean	3.69	4.13	3.60	-0.09	-2.39
	SD	0.39	0.26	0.42	0.07	2.00
	Median	3.65	4.20	3.49	-0.08	-2.07
	Min	3.10	3.75	3.04	-0.16	-4.50
	Max	4.05	4.40	4.07	0.02	0.54
POST	N	5	5	5	5	5
	Mean	3.85	4.44	3.79	-0.06	-1.64
	SD	0.25	0.23	0.26	0.04	1.08
	Median	3.90	4.45	3.79	-0.07	-1.69
	Min	3.50	4.10	3.44	-0.11	-2.74
	Max	4.15	4.75	4.08	0.00	0.11
PRE	N	5	5	5	5	5
	Mean	3.98	4.75	3.94	-0.04	-0.96
	SD	0.22	0.32	0.26	0.06	1.61
	Median	4.05	4.85	3.96	-0.04	-1.09
	Min	3.60	4.30	3.52	-0.11	-2.62
	Max	4.15	5.05	4.15	0.05	1.20

	ANOVA p-value		
	Post corrected	Delta	RR%
Overall	0.2882	0.4648	0.3995
MID vs POST	0.3866	0.5530	0.4712
MID vs PRE	0.1226	0.2254	0.1847
POST vs PRE	0.4605	0.5170	0.5197

Note: Pre and Post data are mean values within patient of plasma Albumin concentration, found before the start and at the end of the first and last dialysis session during the fifth week of each of the three treatment periods. Post values were corrected for changes in the extracellular volume. Reduction Ratio (RR) was calculated taking into account hemoconcentration.

CONCLUSION

Though results are importantly affected by the study design and small sample size, our data show that mid-dilution hemodiafiltration leads to higher β2 microglobulin clearance than pre-dilution hemodiafiltration and to a better trend for the same clearance (even if not statistically significant) in comparison to post-dilution hemodiafiltration.

Mid-dilution hemodiafiltration substantially increase middle

Table 3: Kt/V - Descriptive Statistics and Statistical Analysis.

Dialysis Technique			
Descriptive Statistics	**MID**	**POST**	**PRE**
N	5	5	5
Mean	1.34	1.43	1.37
SD	0.16	0.23	0.28
Median	1.25	1.37	1.21
Min	1.20	1.19	1.17
Max	1.60	1.79	1.85
	ANOVA p-value		
	Overall	0.8223	
	MID vs POST	0.5448	
	MID vs PRE	0.8235	
	POST vs PRE	0.6996	

molecular weight solutes clearance allowing, in comparison with post-dilution hemodiafiltration, the infusion of much higher substitution fluid volumes thereby enhancing convective mass transfer without diluting solutes in blood to an extent found in pre-dilution hemodiafiltration.

According to our study and literature reports [9], we believe therefore that, hemodiafilters' surfaces being equal; mid dilution can assure better performances, with regard to β2 microglobulin clearance, than pre-and post-dilution hemodiafiltration.

Moreover, we point out that mid-dilution hemodiafiltration was well tolerated, as much as pre- and post-dilution hemodiafiltration.

For all these reasons we deem it advisable to publish our pilot study data, even if they are waiting for confirmation from a planned larger clinical trial.

The corresponding author on behalf of all the authors declares that there is any potential conflict of interest that might constitute an embarrassment to any of the authors.

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