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Original Article

Improved management of intradialytic hypotension (IDH) using vitamin E-bonded polysulfone membrane dialyzer

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ABSTRACT: Background: *Intradialytic hypotension (IDH) is a common clinical trait in hemodialysis (HD) which is caused by poor biocompatibility of the dialyzer membrane. Aiming to improve IDH, vitamin E-bonded polysulfone dialyzer (VPS-H) was evaluated in a pilot study.* Methods: *Eight IDH patients on standard HD were switched from their conventional high-flux dialyzers to VPS-H, and intradialytic blood pressure (BP) was monitored regularly for 10 months.* Results: *The results showed that hypotension of systolic BP (SBP), diastolic BP (DBP) and pulse pressure (PP) during the session were improved after changing the dialyzer. Notably, almost all the values recorded from 120 minutes into the session until the end of the treatment in the period between the second and tenth month after treatment were significantly different from the corresponding baseline values. Moreover, after 8 to 10 months, the SBP prior to a dialysis session was significantly reduced compared with baseline values. On the other hand, the pulse rate showed no difference throughout the study period.* Conclusions: *This study provides early evidence of the beneficial role that vitamin E-bonded dialyzers may have in preventing IDH. Larger controlled trials are needed to confirm this original finding. (Int J Artif Organs 2010; 33: 147-53)*

KEY WORDS: Hemodialysis, Intradialytic hypotension, Vitamin E-bonded dialyzer, Nitric oxides

INTRODUCTION

Hemodialysis (HD) treatment is commonly associated with poor control of the patient's blood pressure (BP), which is a major comorbidity in this maintenance therapy (1-3). In particular, a considerable number of HD patients show intradialytic hypotension (IDH). Excessive ultrafiltration with inadequate vascular refilling may play a major role in IDH. Consequently, IDH is usually managed by administering saline or by reducing the ultrafiltration flow from the dialyzer. In severe cases, pharmacological therapy with vasopressors is prescribed for recovery.

However, IHD has a clear multifactorial origin and so far the exact underlying mechanisms of this complication remain largely unknown and are a matter of investigation (4-6). Intradialytic oxidative stress, which is a consequence of bioincompatible dialyzer treatments, has been suggested to have a cause-effect relationship with IDH (7, 8). As a result of oxidative stress, the sympathetic and autonomic nervous systems are activated, lowering BP and leading to hypotension in patients who have a predisposition to develop IDH. Moreover, changes in the blood levels of nitric oxide-related molecules (NOx) are thought to be associated with BP alterations during HD (9–14). NOx are L-arginine derivatives, which have been implicated in mediating a broad spectrum of activities which participate in BP control, including vessel smooth muscle relaxation and endothelial protection, regulation of myocyte proliferation

and cytotoxic reactions, inhibition of platelet aggregation and adhesion, and neuronal transmission (15).

One of the most successful strategies to reduce oxidative stress during HD treatments is the use of biocompatible vitamin E-bonded dialyzers (16-24). Vitamin E-bonded dialyzers are expected to have anti-oxidative properties due to the well documented *in vitro* and *in vivo* antioxidant function of vitamin E and may, therefore, reduce oxidative stress during dialysis treatment. Accordingly, repeated clinical reports have shown improved oxidative stress markers in patients treated with these dialyzer membranes (22-25). It is important to note that these results were obtained using the first generation of vitamin E-bonded dialyzers that were based on a cellulosic membrane technology. This cellulosic nature was a limiting factor to biocompatibility for the first generation of vitamin E-bonded dialyzers. Therefore, due to the superior biocompatibility of synthetic materials (26), a polysulfone-based vitamin E-bonded membrane dialyzer (VPS-H) with anti-oxidant function was developed (27) and introduced to the clinical practice of HD therapy. The first studies on this new generation of synthetic membranes confirmed the value of vitamin E as a biocompatible modifier of this membrane dialyzer and proved the superiority of synthetic materials with respect to cellulosic vitamin E-bonded dialyzers in reducing LDL oxidation during HD treatment (28).

Therefore, this enhanced control of intradialysis oxidative stress suggests that BP fluctuations and IDH could be affected by the use of these synthetic vitamin E-bonded dialyzers. On this basis, we preliminarily investigated whether long-term treatment with vitamin E-bonded polysulfone membrane dialyzers could improve BP control and thus prevent IDH in maintenance HD patients.

SUBJECTS AND METHODS

Subjects

The inclusion criteria for this study were patients with end-stage renal disease (ESRD) undergoing HD treatment three times a week with high-flux dialyzers at our clinical site for more than 3 months; and a ratio of systolic blood pressure (SBP) at the beginning to the minimum value during a dialysis session of lower than 0.7. Patients with liver disease, malignancy, mental retardation, and those who were pregnant were excluded. Consequently, 8 patients were evaluated for this study after obtaining informed consent.

Device

Enrolled patients continued dialysis treatment with a conventional high-flux dialyzer for one month to obtain baseline evaluation data. The dialyzer was then changed to a high-flux Vitamin E bonded polysulfone hollow fiber membrane dialyzer (27) named VPS-H (Asahi Kasei Kuraray Medical, Tokyo, Japan).

Dialysis

The dialysis sessions were performed three times a week for 4 hours at a blood flow rate of approximately 200 ml/min according to the Japanese dialysis standard. Central supplied dialysate (LYMPACK TA3, Nipro, Gunma, Japan or Hysorb-D, Ajinomoto, Chuo-ku, Japan), with sodium, calcium and acetate concentrations of approximately 140, 3 and 10 mEq/L, respectively, was used at a flow rate of approximately 500 ml/min during the entire study period. The water for preparation of the dialysate was purified using a reverse osmotic filter, an ultrafiltrate filter and an endotoxin cut filter. The dialysate supplied to the dialysis machine was monitored for its endotoxin (ET) level using a limulus test once monthly. The monitoring results showed that the ET levels remained less than 0.001 EU/L (undetectable level) during the study period. The dialysis machines used were NCU-7 (Nipro, Japan) or DCS-27 (Nikkiso, Tokyo, Japan). Conditions such as the blood and dialysate flow rates, session times, and medication including erythropoiesis-stimulating agent (ESA) were unchanged during the study. Other parameters such as effective surface area of dialyzers, target dry weight of the treatments, ultrafiltration volumes and so on, were kept constant as much as possible when the dialyzers were changed from conventional dialyzers to VPS-H.

BP measurement

The SBP and diastolic blood pressure (DBP) were monitored by an automated BP recording system and 8 measurements were recorded during each dialysis session at the following intervals: pre-dialysis, 15, 30, 60, 120, 180 and 210 minutes after starting the dialysis, and finally at the end of the dialysis session. Pulse pressure (PP) was

calculated as the difference between SBP and DBP. During the study, these BP measurements were taken at baseline, and at 3, 6, 8 and 10 months. These BP data at each time point were obtained from the recordings of 5 sessions performed at mid- and end-week, while start-of-week records were excluded to unify the measurement condition; the start of week treatment was performed after two days off dialysis while mid- and end-week measurements were performed after one day off dialysis.

Plasma NOx analysis

The total amount of NOx in the patient's plasma was analyzed using a NOx analysis system ENO-20 (Eicom, Kyoto, Japan) together with a diazo coupling method and high-performance liquid chromatography (29). The analyses were performed at baseline, and at 1, 2 and 6 months. Mid-week session blood samples were collected from the arterial circuit at pre-dialysis, 60, 120 and 180 minutes after starting the dialysis and at the end of the dialysis session.

Statistics

Data were calculated as mean ± S.D. and treatment effect was assessed for significance using repeated measures-ANOVA followed by host-hoc test. Statistical significance was defined as $p< 0.05$.

RESULTS

Baseline assessment

Baseline parameters of the 8 patients enrolled in the study are shown in Table I. At this time-point in the study, IDH was observed for all patients except patient No. 7. For this patient, according to the inclusion criteria at the time of enrolment, the ratio of starting SBP relative to the minimum value during the dialysis session was <70%. However, at the baseline evaluation this ratio was 74.1%, which was considered sufficient to keep this patient in the study. At inclusion and up to the baseline evaluation the patients were maintained on their treatment with the high-flux dialyzers described in Table I. These included polysulfone (n=3), polymethylmethacrylate (n=2) and cellulose triacetate (n=3) dialyzers. Then their dialyzers were changed from the conventional ones to VPS-H with the same effective surface area of dialyzer to within 0.1 m^2. The blood access for all patients was arterio-venous fistula and there were no problems with the condition of blood flow during the study period.

SBP change

Table II shows the changes in SBP, DBP and PP during the HD sessions before and after changing the baseline

TABLE I - BASELINE CHARACTERISTICS OF THE PATIENTS

Patient No.	Age (Year)	Gender	Duration (Year)	Body weight (Kg)	Primary cause[a]	Previous dialyzer	Membrane material[b]	SBP Pre (mmHg)[c]	SBP reduction (%)[d]	Minimum[e]
1	64	M	14	64.5	CGN	FB-210F	CTA	165.2 ± 19.3	69.6 ± 13.8	End
2	43	F	9	55.5	DMN	BG-1.6U	PMMA	158.0 ± 24.8	63.9 ± 25.4	End
3	78	F	2	50.5	DMN	BG-1.3U	PMMA	152.8 ± 19.1	60.4 ± 5.3	End
4	62	M	4	47.5	FGS	FB-130U	CTA	162.2 ± 7.0	62.5 ± 12.8	End
5	58	F	9	74.5	DMN	APS-15SA	PS	181.6 ± 17.0	68.3 ± 12.3	End
6	70	F	7	42.0	DMN	APS-15SA	PS	193.6 ± 18.6	64.3 ± 12.9	120 min
7	83	M	5	50.0	IgAN	FB-150U	CTA	136.0 ± 3.8	74.1 ± 11.5	End
8	71	M	19	64.5	CGN	PS-1.6UW	PS	158.2 ± 12.5	65.7 ± 10.6	End
Average[f]	66.1 ± 12.5	-	8.6 ± 5.6	56.1 ± 10.8	-	-	-	163.4 ± 17.6	66.1 ± 4.4	-

[a] CGN = chronic glomerulonephritis; DMN = diabetic nephropathy; FGS = focal glomerular sclerosis; IgAN = IgA nephropathy.
[b] CTA = cellulose triacetate,; PMMA = polymethylmethacrylate; PS = polysulfone.
[c] Values are indicated as the mean ± S.D. of 5 sessions taken from mid- and end-week values at the baseline.
[d] Minimum % value during the session, converted by adjusting the Pre-value (before the session) to 100%.
[e] The term shows the minimum SBP point during the session. End = end of session; 120 min = 120 minutes after the beginning of the session.
[f] Values indicate the average of the 8 patients (mean values for SBP Pre and SBP reduction) with standard deviation.

TABLE II - CHANGE IN SBP, DBP AND PP

Month	Time course after dialysis session begins							
	Pre[a]	15 min	30 min	60 min	120 min	180 min	210 min	End[b]
(A) SBP								
Base	163.5±22.4	150.8±22.3 (92.6)	148.9±25.0 (91.6)	142.4±22.9 (87.6)	127.9±21.1 (78.9)	117.1±16.8 (72.6)	115.2±17.1 (71.3)	111.7±25.9 (68.8)
1	162.1±19.4	150.2±22.6 (92.7)	145.5±19.5 (90.1)	138.5±23.0 (85.5)	131.1±22.0 (81.2)	121.5±22.6 (75.1)	120.9±25.3 (74.2)	121.8±21.8 (75.5)
2	161.0±20.3	153.7±22.6 (95.7)	149.6±19.5 (90.6)	151.1±21.0 (94.5)*	143.2±16.2 (89.6)**	129.5±18.1 (80.9)**	125.7±19.4 (78.5)*	121.1±20.7 (74.5)
4	153.6±24.8	152.5±28.4 (98.6)*	146.2±30.1 (95.0)	144.6±26.3 (93.9)	139.3±28.6 (90.5)**	126.2±25.1 (82.4)*	121.6±22.8 (79.8)*	120.7±23.7 (79.0)
6	158.4±21.1	148.8±23.9 (94.1)	142.9±21.5 (90.7)	145.6±21.4 (92.3)	139.5±19.7 (88.5)**	131.8±20.4 (84.0)**	125.4±21.9 (80.0)*	124.2±23.4 (77.0)*
8	148.4±24.2	146.1±29.3 (99.0)	144.6±25.6 (98.3)	144.3±29.4 (98.0)*	139.9±24.1 (95.4)**	131.1±23.9 (89.8)**	126.5±23.0 (87.0)*	132.2±23.8 (91.1)**
10	151.9±28.5	142.1±30.5 (94.5)	135.9±27.5 (90.5)	142.8±19.2 (95.9)	138.4±21.9 (93.2)*	130.8±18.1 (88.3)**	124.2±22.5 (84.3)*	129.4±26.2 (87.7)**
(B) DBP								
Base	81.9±12.7	79.1±11.2 (96.6)	77.1±15.4 (94.3)	76.0±12.7 (93.2)	69.7±12.7 (86.4)	65.7± 9.6 (81.8)	66.3± 8.9 (82.5)	63.5±11.0 (79.7)
1	82.5±13.3	76.7±11.5 (93.8)	76.5±10.9 (93.6)	74.7±12.6 (91.3)	70.4±13.1 (85.9)	65.7±11.8 (81.1)	66.4±11.4 (80.7)	67.8±11.3 (83.6)
2	82.5±14.4	79.9±11.2 (99.1)	77.6±12.0 (96.1)	78.3±11.0 (97.2)	75.3±10.4 (94.0)*	70.9± 9.4 (88.5)*	69.9± 8.4 (87.7)	66.7±11.0 (84.1)
4	79.7±10.4	78.8±13.8 (98.4)	77.3±13.0 (96.5)	76.2±13.1 (95.5)	73.2±11.7 (92.1)	69.0±12.0 (86.7)	67.4± 9.9 (84.7)	68.7±12.8 (84.4)
6	77.2±14.7	78.4±12.1 (103.1)	76.0±12.0 (100.2)	77.9±11.7 (102.8)*	75.5±11.5 (100.2)*	71.6±12.1 (94.3)**	70.1±12.8 (93.4)*	68.6±15.5 (90.3)
8	76.8±16.6	76.6±15.8 (101.0)	76.2±14.5 (101.3)	74.6±15.8 (98.0)	75.5±15.8 (99.6)**	69.0±16.3 (91.0)	69.1±14.3 (91.4)	72.7±14.1 (94.7)**
10	74.9±15.4	75.1±13.5 (103.0)	73.1±12.8 (100.0)	75.2±11.7 (102.7)	73.2±15.5 (99.3)	69.3±13.4 (94.2)*	68.9±13.3 (94.3)	71.1±13.7 (96.8)**
(C) PP								
Base	81.6±18.3	71.7±15.4 (90.8)	71.8±13.3 (91.1)	66.4±14.7 (83.7)	58.1±14.9 (72.3)	51.4±13.9 (64.3)	48.9±16.4 (61.3)	48.2±19.1 (59.3)
1	79.6±16.1	73.5±16.0 (93.7)	69.0±13.3 (88.8)	63.8±14.5 (81.6)	60.7±14.9 (77.8)	55.8±16.6 (70.8)	54.5±19.3 (66.9)	54.1±16.7 (69.2)
2	78.5±18.0	73.8±15.5 (96.9)	72.0±11.4 (94.5)	72.9±15.0 (96.4)*	67.9±13.4 (89.2)**	58.6±15.9 (76.4)**	55.8±17.9 (72.3)*	54.4±16.0 (71.8)*
4	73.9±20.6	73.8±18.7 (100.3)	68.7±20.5 (94.4)	66.9±21.2 (94.2)	66.1±22.2 (91.0)**	57.1±19.1 (80.2)	54.2±17.7 (75.8)	52.0±17.1 (68.6)
6	81.2±19.6	70.4±15.2 (88.5)	66.9±13.5 (85.3)	67.7±13.4 (86.4)	64.0±15.5 (80.5)*	60.2±13.9 (77.3)**	55.3±14.2 (70.9)	55.6±13.7 (71.5)
8	71.6±17.0	69.5±16.1 (101.6)	68.5±14.0 (100.7)	69.7±16.2 (102.8)	64.4±11.5 (94.8)*	62.1±15.1 (91.3)**	57.5±13.8 (84.7)*	59.6±14.9 (90.3)**
10	77.0±21.6	67.1±21.7 (90.1)	62.9±18.4 (84.5)*	67.6±10.7 (92.9)	65.3±11.3 (89.4)*	61.5±11.4 (85.7)**	55.3±15.2 (77.9)	58.3±20.7 (81.7)*

Values are indicated in mmHg as the mean ± S.D. of 5 sessions taken from mid- and end-week values of 8 patients each. Values in parentheses are ratios calculated by converting the Pre-values to 100% for each patient and then averaging. (A), (B) and (C) correspond to SBP, DBP and PP, respectively.
[a] Measured before dialysis session
[b] Measured at the end of dialysis session
* $P<0.05$ versus Baseline ; ** $P<0.01$ versus Baseline

conventional dialyzers to VPS-H. Following the change to VPS-H dialyzers, the value of SBP steadily decreased throughout the period of VPS-H usage as shown in Table II (A). The difference from baseline to 10 months after switching was evaluated using repeated ANOVA measurements by defining the pre-dialysis SBP values as covariant. The result showed the existence of statistical significance, and then each datum was tested using a post-hoc method to evaluate significance from the baseline. It was consequently found that SBP values had not changed at 1 month, however, a considerable reduction was found to occur from the second month and at all subsequent months of the study; the values recorded at 120, 180 and 210 minutes during 4, 6, 8 and 10 months after VPS-H treatment were significantly different from the corresponding baseline values. Figure 1 illustrates the change in SBP for baseline, 4 and 10 months after the switch to VPS-H dialyzer after normalization of SBP values by adjusting the pre-HD value to 100%. The figure clearly reveals the effect of VPS-H in improving IDH. Moreover, pre-dialysis SBP values showed a reduction from the baseline at 4, 8 and 10 months after VPS-H treatment (Fig. 2). The difference was significant when the pre-dialysis SBP values were analyzed by repeated ANOVA measurements.

DBP, PP and Pulse Rate (PR) changes

As compared to SBP, the improvements on DBP induced by changing the dialyzer to VPS-H were much less evident (Tab. II (B)). However, all the values recorded at 120, 180

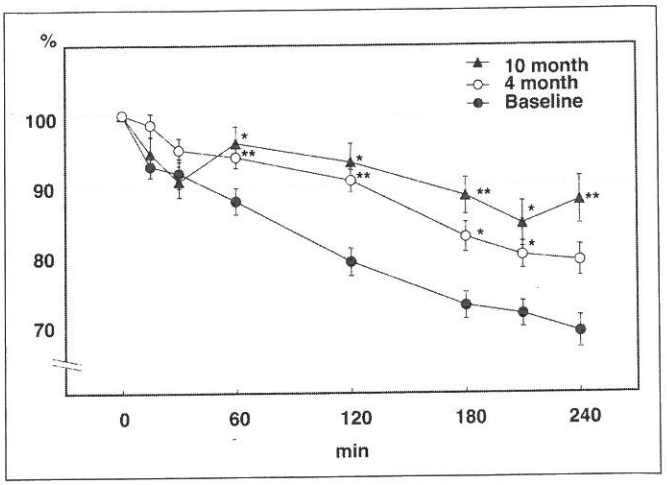

Fig. 1 - *SBP change during session as a result of replacing the conventional dialyzer and introducing VPS-H. Values are a %, converted by adjusting the Pre-value to 100%. Closed circles (•) represent the baseline, open circles (○) represent the period 4 months later, and closed triangles (▲) represent the period 10 months later. Bars indicate the standard error for each data point with n=40 (5 data points for 8 patients). Single asterisks (*) show P<0.05 and double asterisks (**) show P<0.01, versus the baseline.*

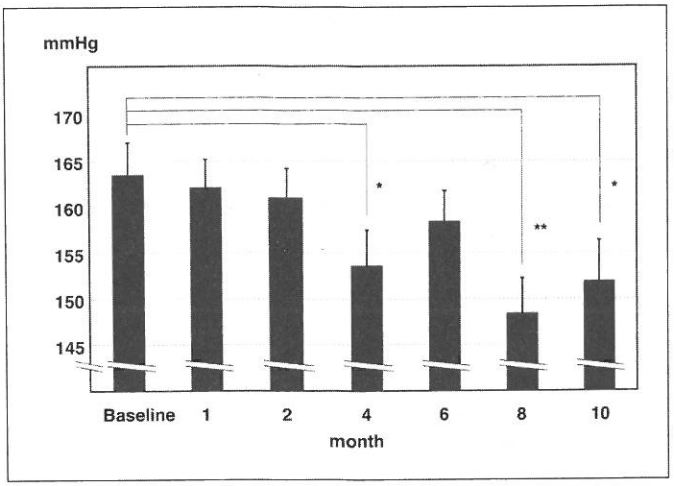

Fig. 2 - *SBP change before the dialysis session. Mean value of SBP measured before 5 dialysis sessions taken from mid- and end-week values for each of the 8 patients. Bars indicate the standard error for each data point with n=40 (5 data points for 8 patients). Single asterisks (*) show P<0.05 and double asterisks (**) show P<0.01, versus the baseline.*

and 210 minutes and the end of HD at 6, 8 and 10 months were significantly different from the corresponding baseline values when the values were normalized by adjusting the pre-HD value to 100%. Consequently, the decrease in PP showed an improvement at 2 to 10 months at several data points, with statistical significance as shown in Table II (C). Once the values were normalized by adjusting the Pre-value to 100%, these differences became more pronounced and the majority of the data showed statistically significant differences. In contrast to BP, PR values did not change during the longitudinal evaluation in all the 8 patients included in this study (data not shown).

Plasma NOx levels, small molecule removal and hemoglobin (Hb) level

Plasma NOx levels were monitored at baseline and after replacing the conventional dialyzer with VPS-H. Pre-dialysis NOx level decreased from 100 ± 67 nM at baseline to 73 ± 58 nM after 2 months of treatment by VPS-H. At the 6-month evaluation, NOx returned to baseline levels (95 ± 80 nM). At all the time points in the study NOx levels at pre-HD were not statistically different from the baseline evaluation. Regarding the NOx level during HD therapy, almost all cases decreased as was apparent by the removal of small molecules through dialysis, except some cases which showed an increase during HD treatment. However, after changing to VPS-H, there was a trend toward a smaller intra-HD fluctuation as the longitudinal observation proceeded to completion (data not shown). The removal of small molecules such as urea, creatinine, and phosphate produced no significant changes in the comparison between conventional dialyzers used at baseline and VPS-H (data not shown). Moreover, there was no significant change in Hb levels or in the dose of erythrocyte-stimulating agents during the study period.

DISCUSSION

This is the first report to show that the VPS-H has the potential to alleviate IDH, which is further evidence of the advantage that these dialyzers may bring in the clinical practice of HD therapy (28). The results showed an improvement in IDH just 2 months after the shift to VPS-H and the improvement continued throughout the longitudinal evaluation with a curve of intra-HD SBP values that suggested a stabilization of BP control during mid- to long-term treatment. Moreover, pre-HD SBP values were significantly reduced after 8 and 10 months, which may account for a

partial recovery in the physiological mechanisms of vascular relaxation. In this respect, this study failed to show that BP control and IDH improvement were significantly correlated with NOx levels. Available methods to measure NOx in plasma are, however, of limited precision and sensitivity and thus other studies are needed to better define the actual effect of these membranes on NOx and particularly on the bioactive fraction of vasorelaxing NO that is available in the circulation as a consequence of VPS-H therapy. However, our results are compatible with a lower intra-HD fluctuation of plasma NOx during the 10 months of VPS-H treatment.

Although biochemical events lying behind the VPS-H induced improvement of IDH remain unknown, the antioxidant activity of these dialyzer membranes demonstrated either in *in vitro* (27) and *in vivo* (28) experiments is of great interest. The clinical value of this pilot observation needs to be confirmed by other trials with larger numbers of patients and with control group comparison design.

In conclusion, vitamin E-bonded membrane dialyzers have the potential to improve IDH of maintenance HD patients. The antioxidant and biocompatibility properties of this membrane are the most likely explanations for this preliminary but original evidence, which will be evaluated in future studies.

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Conflict of interest statement: M. Aritomi and M. Koremoto are employees of Asahi Kasei Kuraray Medical Co., Ltd. There is no conflict of interest for the other authors.

Meeting presentation: Preliminary results of this study were presented at the 22nd High-performance membrane Kenkyu-kai in March 2007 in Tokyo, Japan.

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