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CLINICAL STUDY

Effects of vitamin E-coated dialyzer on oxidative stress and inflammation status in hemodialysis patients: a systematic review and meta-analysis

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Abstract

Background: Vitamin E-coated dialyzer may have an effect on oxidative stress and inflammation status in hemodialysis (HD) patients. Therefore, we performed a systematic review to assess the anti-oxidation and anti-inflammatory effects of vitamin E-coated dialyzer in HD patients. *Methods*: The randomized controlled trials (RCTs) and quasi-RCTs of vitamin E-coated dialyzer versus conventional dialyzer for HD patients were searched from multiple databases. We screened relevant studies according to predefined inclusion criteria and performed meta-analyses using RevMan 5.1 software. *Results*: Meta-analysis showed vitamin E-coated dialyzer therapy could significantly decrease the serum thiobarbituric acid reacting substances (TBARS) (SMD, −0.95; 95% CI, −1.28 to −0.61; $p<0.00001$), oxLDL (SMD, −0.61; 95% CI, −1.04 to −0.19; $p=0.005$), interleukin-6 (IL-6) (SMD, −0.65; 95% CI, −0.97 to −0.32; $p<0.0001$) and C-reactive protein (CRP) levels (SMD, −0.46; 95% CI, −0.87 to −0.05; $p=0.03$) compared with that of the control group. However, vitamin E-coated dialyzer did not result in increasing the total antioxidant status (TAS) (SMD, 0.23; 95% CI, −0.16 to 0.61; $p=0.25$) and the fractional clearance of urea index (Kt/v) levels (MD, −0.07; 95% CI, −0.14 to 0.00; $p=0.06$), in addition, there was no significant difference in plasma superoxide dismutase (SOD) level compared with that of the conventional dialyzer & oral vitamin E group (SMD, 0.28; 95% CI, −0.20 to 0.75; $p=0.26$). *Conclusions*: Vitamin E-coated dialyzer can reduce the oxidative stress and inflammation status reflected by the decreasing of serum TBARS, oxLDL, CRP, and IL-6 levels, and this new dialyzer does not affect the dialysis adequacy.

Keywords

Hemodialysis, inflammation, oxidative stress and meta-analysis, vitamin E-coated dialyzer

History

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Introduction

End-stage renal disease (ESRD) is a major health problem worldwide. Hemodialysis (HD), introduced in the late 1950s, offers effective treatment and has increased the survival time of ESRD patients.[1] In recent years, remarkable advances in the dialysis treatment have been achieved. However, the complications associated with prolonged HD have become a serious obstacle. Among these complications the most frequent are infections, cardiovascular diseases, beta-2 microglobulin-amyloidosis and protein malnutrition.[2,3] Since the uremic inflammation, oxidative stress and their relation to cardiovascular diseases were reported firstly by Stenvinkel et al.[4] in the late 1990s, an increasing number of studies have discovered that oxidative stress and microinflammation are principal causes of dialysis-related complications and are important contributors to morbidity and mortality of ESRD in this population.[5–8] It has been demonstrated that the chronic inflammation and oxidative stress status in HD patients can be evaluated by the circulating biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6) or malondialdehyde (MDA).[9–11] And a recently study performed by Kitabayashi et al.[12] has shown that the elevated serum oxidized low density lipoprotein (oxLDL) levels are associated with the development of atherosclerosis in patients undergoing hemodialysis.

Recently, a new dialyzer was developed by Terumo Corporation, with the double goals of increasing membrane biocompatibility and increasing antioxidant capacity.[13] Previous researches suggested a beneficial effect of this new dialyzer on reactive oxygen species (ROS) production compared to conventional membranes.[14,15] The vitamin E-coated membrane also reduces the release of proinflammatory cytokines and provides good control of leukocyte activation.[16] In 2006, a meta-analysis by Sosa et al.[17] concluded that vitamin E-coated dialyzer treatment was associated with a significant decrease of lipid peroxidation biomarkers in plasma, but that research lacked large sample, and randomized trial, which caused low reliability of

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experimental result.[17] This systematic review of available randomized controlled trials (RCTs) and quasi-RCTs aims at assessing the effect of vitamin E-coated dialyzer on chronic inflammation, oxidative stress status in HD patients, in addition, the dialysis adequacy of this new dialyzer is also discussed.

Materials and methods

Inclusion criteria

Types of studies

Randomized controlled trials (RCTs) and quasi-RCTs (e.g. controlled observational study) comparing vitamin E-coated dialyzer with conventional unmodified dialyzer in English or Chinese with available data for one of our prescribed outcomes.

Type of participants

Any patient maintained on hemodialysis for ESRD, while the patients with active infectious disease, active liver or immune disease, or cancer were excluded.

Type of interventions

Comparisons of any (or several) conventional membranes dialyzer with vitamin E-coated membranes dialyzer for chronic hemodialysis.

Type of outcome measures

Oxidative stress parameters: serum MDA, TBARS, oxLDL, plasma superoxide dismutase (SOD), total antioxidant status (TAS); inflammatory parameters: serum CRP, IL-6; dialysis adequacy: fractional clearance of urea (Kt/V).

Search strategy

We performed literature search on PUBMED, SCOPUS, and Cochrane Central Register of Controlled Trials (CCRCT). China National Knowledge Infrastructure Database (CNKI) and China Biology Medicine Database (CBM) (all to December 2013) restricted to English and Chinese language to identify eligible studies. The following search terms were used: hemodialysis, dialysis, renal dialysis, renal replacement therapy, dialyzer, Vitamins, Vitamin E, tocopherol, alpha-tocopherol, beta-tocopherol, antioxidants, inflammation, oxidative stress, CRP, IL-6, MDA, TBARS and so on. In addition, the reference lists of all included studies were checked in order to identify the potentially relevant trials, while the unpublished studies were excluded.

Study selection

We included parallel RCTs or quasi-RCTs and the first period of crossover RCTs or quasi-RCTs on examining the effect of vitamin E-coated dialyzer on markers of oxidative stress and inflammation. Two of the authors (Yang SK and Xu XX) independently screened the titles and abstracts of all identified studies, and excluded clearly irrelevant studies. The full-text articles were retrieved for comprehensive review and were independently examined. Then we excluded studies that did not report oxidative stress or inflammation parameter. The reasons for study exclusion were presented in Figure 1.

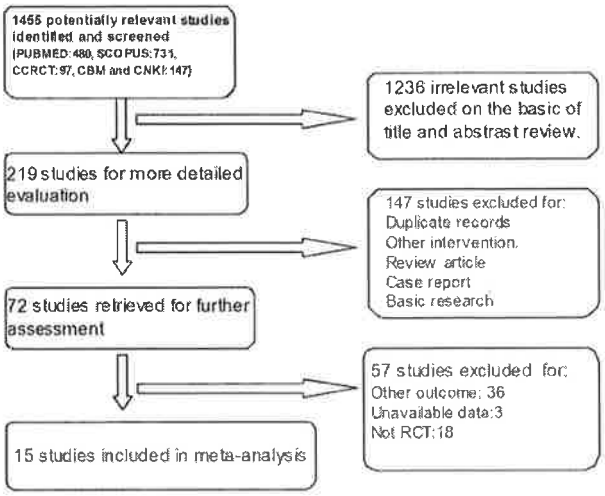

Figure 1. Flow diagram of study selection: vitamin E-coated dialyzer for HD patients. Note: CCCRT, Cochrane Central Register of Controlled Trials; CBM, China Biology Medicine Database; CNKI, China National Knowledge Infrastructure Database.

Data extraction and management

The following data were extracted independently by two authors (Yang SK and Xu B): sample size, percentage of men and female, mean age, mean duration of dialysis, characteristics of the dialysis treatment, study results, and outcome data from studies. We sent emails to study authors in order to seek the required information in cases of missing data.[18] Then the data were entered into RevMan 5.1[19] by Yang SK and Xu XX independently.

Study quality assessment

Study quality was assessed, using the Jadad composite scale by two authors (Yang SK and Xu XX) independently.[20,21] This was a five-point scale included three items directly related to systematic bias: blinding, randomization, and description of withdrawal and dropouts. This tool allows for a range of 0–5 points and studies were decided as low quality if the score was ≤ 2 (high risk of bias), and high quality if the score was ≥ 3.[21,22]

Statistical analysis

Using the data derived from included trials, as different units of measurement were used in different trials, we used standardized mean difference (SMD) with their confidence intervals of 95% (95% CI) to report continuous outcomes, and mean difference (MD) was used to report continuous outcomes using the same unit. The existence of statistical heterogeneity among effect sizes of individual studies was assessed using the χ^2 test, it was considered that there was heterogeneity when $p < 0.1$ or $I^2 > 50\%$.[23,24] We used fixed-effects mode to perform pooled analysis if there was no heterogeneity among studies, however, if there was statistical heterogeneity, the random-effects model was used.

Results

Study selection

Our electronic search identified 1455 studies, of which 1236 studies irrelevant to this review were excluded after title and abstract review. Full-texts of the remaining 219 articles were retrieved for further review. Among them, non-RCTs, review, and the trials concerning other effect of vitamin E-coated dialyzer were excluded. At last, 15 eligibility citations,[18,25–38] including 13 in English and 2 in Chinese, were included in this meta-analysis (Figure 1).

Study characteristics and quality assessment

As shown in Table 1, 15 studies involved a total of 503 HD patients were included in this meta-analysis, among them, 223 were treated with vitamin E-coated dialyzer and 280 were treated with conventional dialyzer. Of these 15 included studies, six studies[18,25,29,31,32,36] compared vitamin E-coated dialyzer to polysulfone dialyzer while four studies[27,30,35,36] compared to cellulose membrane dialyzer, the comparison between vitamin E-coated dialyzer and conventional dialyzer combined with oral vitamin E or intravenously vitamin C were conducted in four studies.[27,35,37,38] Mean age of study participants ranged from 52.8 to 72.3 years, with study duration of 1–8 months. The Jadad score of included study were listed in Table 1 and most trials were of low quality, only three studies explained the randomization method which was computer-generated[25,31] or randomized by drawing numbers.[27] Two trials reported the withdrawals and dropouts.[25,28] The main study limitation was that most studies were not blinded designed, and only one study performed by Panichi et al.[31] was single blinded.

Effect of vitamin E-coated dialyzer on oxidative stress markers

The effect of vitamin E-coated dialyzer on MDA was assessed in three trials,[29,35,36] and two studies reported thiobarbituric acid reacting substances (TBARS),[27,28] as MDA belongs to TBARS category, the pooled analysis on TBARS and MDA was performed together. Based on the results of meta-analysis, a significant decrease in serum TBARS level was observed in the vitamin E-coated dialyzer treatment group (SMD, −0.95; 95% CI, −1.28 to −0.61; $p<0.00001$; Figure 2). Four studies reported the total antioxidant status (TAS) as mean and standard deviation,[18,27,28,36] the fixed model was performed for meta-analysis. The results showed that vitamin E-coated dialyzer therapy did not result in a significant increase in TAS level (SMD, 0.23; 95% CI, −0.16 to 0.61; $p=0.25$; Figure 3), and we performed subgroup analysis stratified by the study duration and dialyzer membranes biocompatibility, however, the results showed that there was no difference on serum TBARS and TAS levels among trials of different duration or different membranes biocompatibility (Table 2).

Two studies were analyzed under a fixed-effects mode,[28,29] the analysis showed that vitamin E-coated dialyzer therapy resulted in a significant reduction in serum oxLDL level (SMD, −0.61; 95% CI, −1.04 to −0.19; $p=0.005$; Figure 2), with minimal heterogeneity ($p=0.40$; $I^2=0\%$). Akiyama and Zhao et al.[35,37] reported the change of plasma superoxide dismutase (SOD) between vitamin E-coated dialyzer and oral vitamin E supplementation therapy, the pooled result showed that there was no significant difference in plasma SOD level compared with that of the conventional dialyzer & oral vitamin E group (SMD, 0.28; 95% CI, −0.20 to 0.75; $p=0.26$; Figure 3).

Effect of vitamin E-coated dialyzer on inflammatory markers

Four primary studies reported changes in CRP.[18,28,30,31] The pooled analysis included three studies showed that conversion from conventional dialyzer to vitamin E-coated dialyzer treatment resulted in a significant decrease in serum CRP level (SMD, −0.46; 95% CI, −0.87 to −0.05; $p=0.03$; Figure 4). Two studies performed by Mandolfo and Panichi[18,31] has investigated the different effect on serum CRP between vitamin E-coated dialyzer and polysulfone dialyzer, the subgroup analysis showed that serum CRP level was also decreased significantly (SMD, −0.51; 95% CI, −0.96 to −0.06; $p=0.03$; Table 2). In the study performed by Kirmizis et al.[28] serum CRP data were reported as median and range, it showed that serum CRP level was significantly decreased from 4.2 (3.5–18.3 mg/L) to 3.0 mg/L (3.0–12.4 mg/L) during 6 months in the vitamin E-coated dialyzer treatment group ($p=0.004$) and remained stable in control group.

Five included studies reported changes in IL-6.[18,25,28,30,31] Four studies were included in pooled analysis, the result showed that vitamin E-coated dialyzer therapy could significantly decrease serum IL-6 level compared with that of controls (SMD, −0.65; 95% CI, −0.97 to −0.32; $p<0.0001$; Figure 4). The subgroup analysis showed that vitamin E-coated dialyzer therapy could also decrease serum IL-6 level significantly compared with that of the biocompatible membranes (polysulfone) dialyzer group (SMD, −0.64; 95% CI, −1.10 to −0.18; $p=0.006$; Table 2). One study performed by Andrulli et al.[25] reported IL-6 value as median and range, Andrulli et al.[25] found that IL-6 levels was decreased from 8.4 (4.15–22.5 pg/mL) to 6.2 pg/mL (1.5–10.3 pg/mL) during 8 months in the vitamin E-coated dialyzer treatment group ($p=0.006$).

Effect of vitamin E-coated dialyzer on dialysis adequacy

Four studies involving 73 patients reported fractional clearance of urea (Kt/V) index as a measure of dialysis adequacy.[18,26,29,33] All the patients received bicarbonate dialysis thrice weekly for a mean time of 4 h. These four studies were included into meta-analysis, the result showed that Kt/V index had no significant difference between patients treated with vitamin E-coated dialyzer and conventional dialyzer (MD, −0.07; 95% CI, −0.14 to 0.00; $p=0.06$; Figure 5), with minimal heterogeneity ($p=0.85$; $I^2=0\%$; Figure 5).

Publication bias

We used funnel plots to assess the publication bias, as shown in Figure 6, most funnel plots of the outcomes such as

Table 1. Characteristic of included studies.

Author, year, country	Study design	No. of patients	Mean age (years)	Gender (M/F)	Dialytic age (years)	Study duration (months)	Intervention	Jadad score
Andrulli 2010[25], Italy	Not blind, Parallel	E:10[a] C:10	E:67 (58–76)[b] C:72 (59–74)[b]	E:5/5 C:5/5	E:3.5 (2.0–9.7)[b] C:3.3 (1.8–6.1)[b]	8	E: Vit E-coated PSM dialyzer C: PSM dialyzer	3
Akiyama 2005[37], Japan	Not blind, Parallel	E:15 C:16	E:60.9 ± 11.4 C:59.6 ± 13.8	E:8/7 C:8/8	E:7.0 ± 6.7 C:10.6 ± 9.4	6	E: Vit E-coated dialyzer C: Cuprammonium dialyzer + Vit E 600 mg/day PO	2
Clermont 2001[26], France	Not blind, Crossover	E:6 C:10	61.6 ± 4.0 61.6 ± 4.0	11/5 11/5	NR NR	1	E: Vit E-coated dialyzer C: synthetic hollow fiber dialyzer	2
Eiselt 2001[27], Czech	Not blind, Parallel	E:6 C1:6 C2:6	NR	NR	NR	1	E: Vit E-coated CLSM dialyzer C1: CLSM dialyzer C2: CLSM dialyzer + Vit C 500 mg/HD IV	3
Kirmizis 2011[28], Greece	Not blind, Parallel	E:37[c] C:25	E:55.0 ± 16.0 C:62.0 ± 13.0	E:19/16 C:12/13	E:84 ± 58 months C:65 ± 41 months	6	E: Vit E-coated dialyzer C: CLSM, PSM, haemophane membrane dialyzer	2
Mandolfo 2012[18], Italy	Not blind, Crossover	E:8 C:8	72.3 ± 8.9	NR	45.5 ± 40.8 months	6	E: Vit E-bonded PSM dialyzer C: PSM dialyzer	2
Morimoto 2005[29], Japan	Not blind, Crossover	E:16 C:15	E:69.4 ± 10.6 C:69.0 ± 12.2	E:8/8 C:7/8	E:77.8 ± 65.1 months C:73.9 ± 58.3 months	6	E: Vit E-coated PSM dialyzer C: PSM dialyzer	2
Nakamura 2003[30], Japan	Not blind, Parallel	E:7 C:12	E:54.0 ± 5.2 C:54.5 ± 5.0	E:5/2 C:8/4	E:5.0 ± 2.2 C:4.5 ± 2.0	10 weeks	E: Vit E-coated dialyzer C: CLSM dialyzer	2
Panichi 2011[31], Italy	Single blind, Crossover	E:31 C:31	E:68 ± 13 C:63 ± 11	E:16/15 C:18/13	48 ± 27 months	6	E: Vit E-coated PSM dialyzer C: PSM dialyzer	3
Tarng 2000[32], Taiwan	Not blind, Crossover	E:24 C:20	E:60 ± 15 C:61 ± 14	E:8/16 C:9/11	E:26 ± 20 months C:29 ± 18 months	6	E: Vit E-coated dialyzer C: PSM dialyzer	2
Tsuruoka 2002[33], Japan	Not blind, Crossover	E:5 C:5	55 ± 6	4/6	9.5 ± 2.9	3	E: Vit E-coated dialyzer C: hemophane membranes dialyzer	2
Usberti 2002[34], Italy	Not blind, Parallel	E:9 C:18	E:63.0 ± 11.0 C:64.0 ± 15.0	NR	E:90 ± 75 months C:99 ± 86 months	3	E: Vit E-coated dialyzer C: CLSM and PSM dialyzer	2
Wang 2012[36], China	Not blind, Parallel	E:10 C1:10 C2:10	E:56.9 ± 16.5 C1:52.8 ± 15.3 C2:57.4 ± 17.7	E:5/5 C1:6/4 C2:3/7	E:13.5 ± 5.3 months C1:12.1 ± 4.3 months C2:10.3 ± 3.3 months	1	E: Vit E-coated dialyzer C1: CLSM dialyzer C2: PSM dialyzer	2
Yang 2006[38], Taiwan	Not blind, Parallel	E:20 C1:20 C2:20	NR	NR	12 ± 2 months	2	E: Vit E-bonded dialyzers C1: Conventional dialyzers C2: Conventional dialyzers + Vit C 1000 mg/HD IV	2
Zhao 2004[35], China	Not blind, Parallel	E:19 C1:19 C2:19	E:56.0 ± 9.5 C1:52.9 ± 13.1 C2:58.8 ± 9.2	E:12/7 C1:12/7 C2:13/6	NR	1	E: Vit E-coated dialyzer C1: CLSM dialyzer C2: CLSM dialyzer + Vit E 400 mg/day PO	2

Note: PSM, polysulfone membrane; CLSM, cellulose membrane; Vit, Vitamin; NR, not reported; PO, take orally; IV, intravenous injection; E, vitamin E-coated dialyzer group; C, conventional dialyzer group.
[a]Nine patients in vitamin E-coated dialyzer treatment group completed the study.
[b]Values were reported as median (range).
[c]Thirty-five patients in vitamin E-coated dialyzer treatment group completed the study.

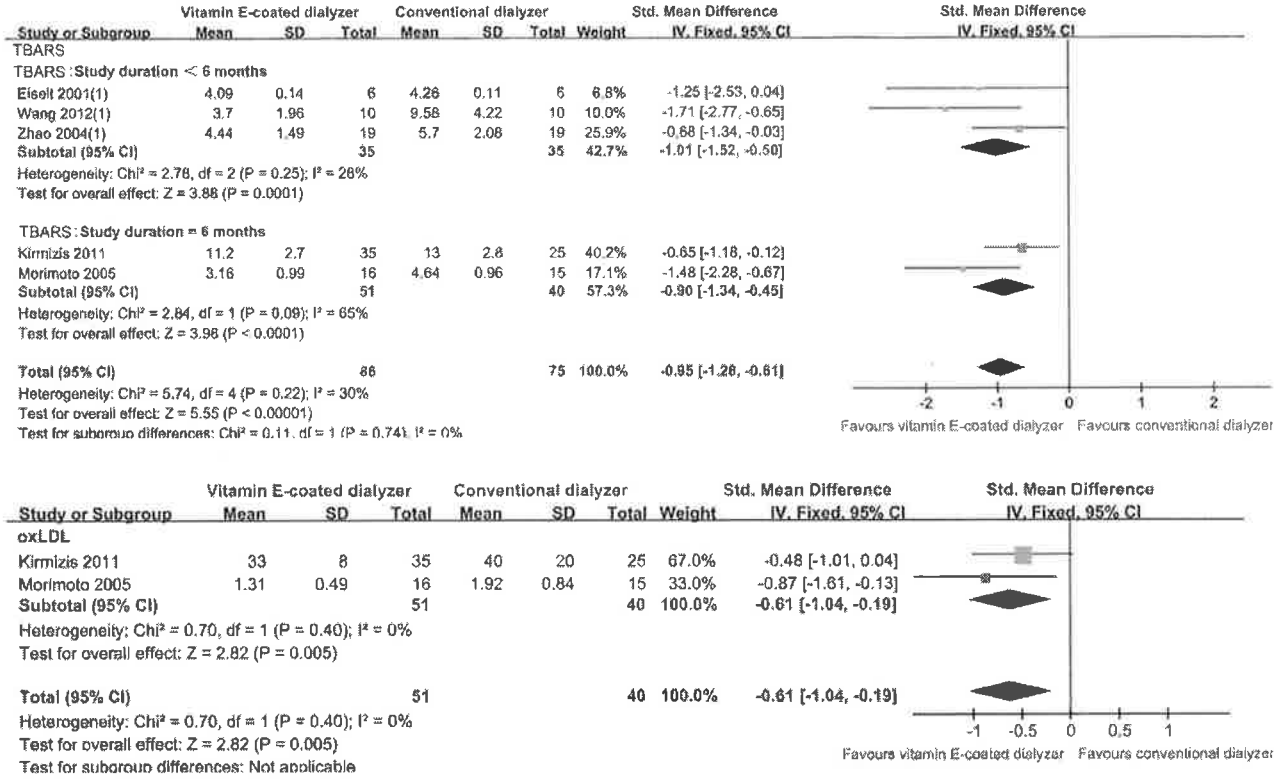

Figure 2. Forest plot of studies comparing the effect of vitamin E-coated dialyzer versus conventional dialyzer on serum TBARS and oxLDL in HD patients.

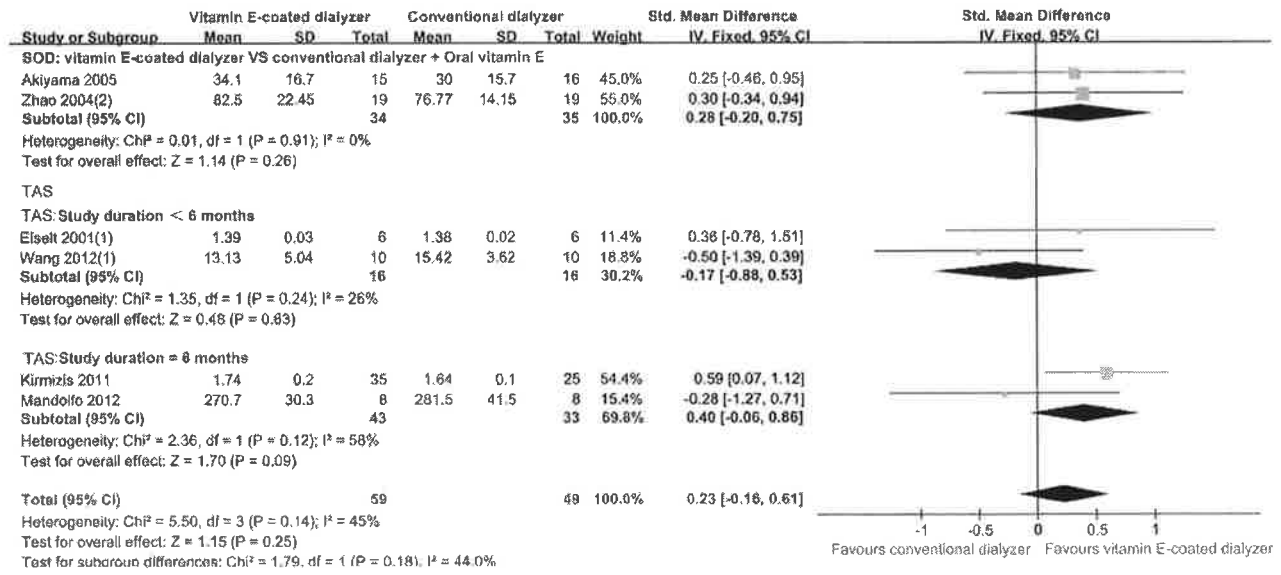

Figure 3. Forest plot of studies comparing the effect of vitamin E-coated dialyzer versus conventional dialyzer on serum SOD and TAS in HD patients.

TBARS, TAS, oxLDL, SOD were symmetric. However, there were some key outcomes such as serum CRP, IL-6 and Kt/v was asymmetric, which suggested that there might be publication bias among these studies.

Discussion

It is now accepted that oxidative stress and chronic inflammation are important contributors to morbidity and mortality of ESRD in HD patients. The objective of this systematic review was to examine whether vitamin E-coated dialyzer had an effect on oxidative stress and chronic inflammation status in maintenance HD patients. The main finding based on this systematic review is that vitamin E-coated dialyzer can reduce the oxidative stress and chronic inflammation status reflected by the decreasing of the levels of serum TBARS, oxLDL, CRP

Table 2. Summary effect of vitamin E-coated dialyzer on maintenance hemodialysis patients.

Outcome variables	No. study	No. patient	Mean net change (95% CI)	p Value	Assessment of heterogeneity: I^2 index (%)	Assessment of heterogeneity: Q-statistic p Value	Publication bias: Funnel plots
Oxidative stress markers							
TBARS (total)	5	161	−0.95 (−1.28, −0.61)	$p<0.00001$	30	0.22	Symmetric
TBARS (study duration <6 months)	3	70	−1.01 (−1.52, −0.50)	0.0001	28	0.25	–
TBARS (study duration = 6 months)	2	91	−0.90 (−1.34, −0.45)	$p<0.0001$	65	0.09	–
TBARS (VEM dialyzer vs. BCM dialyzer)	2	51	−1.46 (−2.09, −0.83)	$p<0.00001$	0	0.94	–
TBARS (VEM dialyzer vs. BICM dialyzer)	3	70	−1.01 (−1.52, −0.50)	0.0001	28	0.25	–
oxLDL	2	91	−0.61 (−1.04, −0.19)	0.005	0	0.4	Symmetric
SOD	2	69	0.28 (−0.20, 0.75)	0.26	0	0.91	Symmetric
TAS (total)	4	108	0.23 (−0.16, 0.61)	0.25	45	0.14	Symmetric
TAS (study duration < 6 months)	2	32	−0.17 (−0.88, 0.53)	0.63	26	0.24	–
TAS (study duration = 6 months)	2	76	0.40 (−0.06, 0.86)	0.09	58	0.12	–
TAS (VEM dialyzer vs. BCM dialyzer)	2	36	−0.14 (−0.80, 0.51)	0.67	0	0.71	–
TAS (VEM dialyzer vs. BICM dialyzer)	2	32	−0.17 (−0.88, 0.53)	0.63	27	0.24	–
Inflammatory markers							
CRP (total)	3	97	−0.46 (−0.87, −0.05)	0.03	0	0.87	Asymmetric
CRP (VEM dialyzer vs. BCM dialyzer)	2	78	−0.51 (−0.96, −0.06)	0.03	0	0.94	–
CRP (VEM dialyzer vs. BICM dialyzer)	1	19	–	–	–	–	–
IL6 (total)	4	157	−0.65 (−0.97, −0.32)	$p<0.0001$	0	0.48	Asymmetric
IL6 (VEM dialyzer vs. BCM dialyzer)	2	78	−0.64 (−1.10, −0.18)	0.006	57	0.13	–
IL6 (VEM dialyzer vs. BICM dialyzer)	1	19	–	–	–	–	–
Dialysis adequacy markers							
Kt/v	4	73	−0.07 (−0.14, 0.00)	0.06	0	0.85	Asymmetric

Note: [1]VEM, vitamin E-coated membranes; BCM, biocompatible membranes; VEM, vitamin E-coated membranes; BICM, bioincompatible membranes.

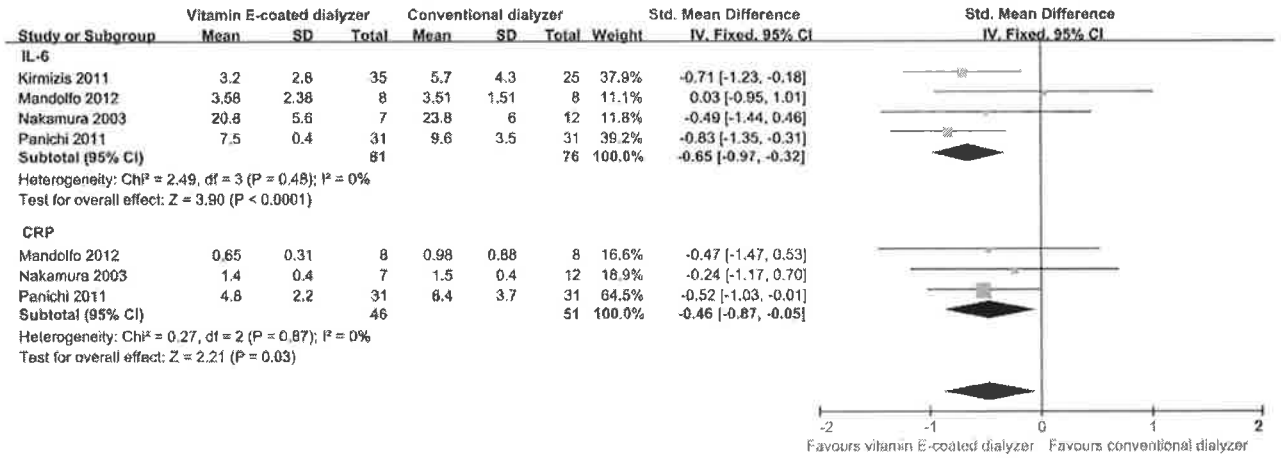

Figure 4. Forest plot of studies comparing the effect of vitamin E-coated dialyzer versus conventional dialyzer on serum IL-6 and CRP in HD patients.

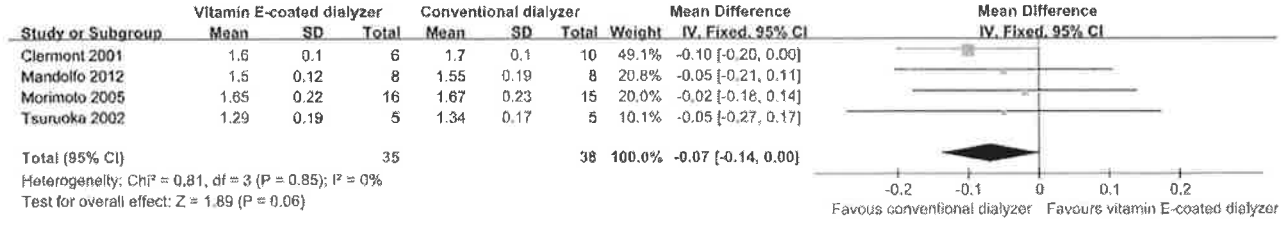

Figure 5. Forest plot of studies comparing the effect of vitamin E-coated dialyzer versus conventional dialyzer on Kt/v in dialysis HD patients.

and IL6, and this new type of dialyzer does not affect dialysis adequacy.

Increased oxidative stress in hemodialysis patients appears to be for two main reasons: first, an increased free radicals production during hemodialysis for the using of bio-incompatible membranes (e.g. cellulose-derived dialysis membranes); second, a net losses of many soluble antioxidants, such as hydrosoluble vitamin C and urate.[7,39,40]

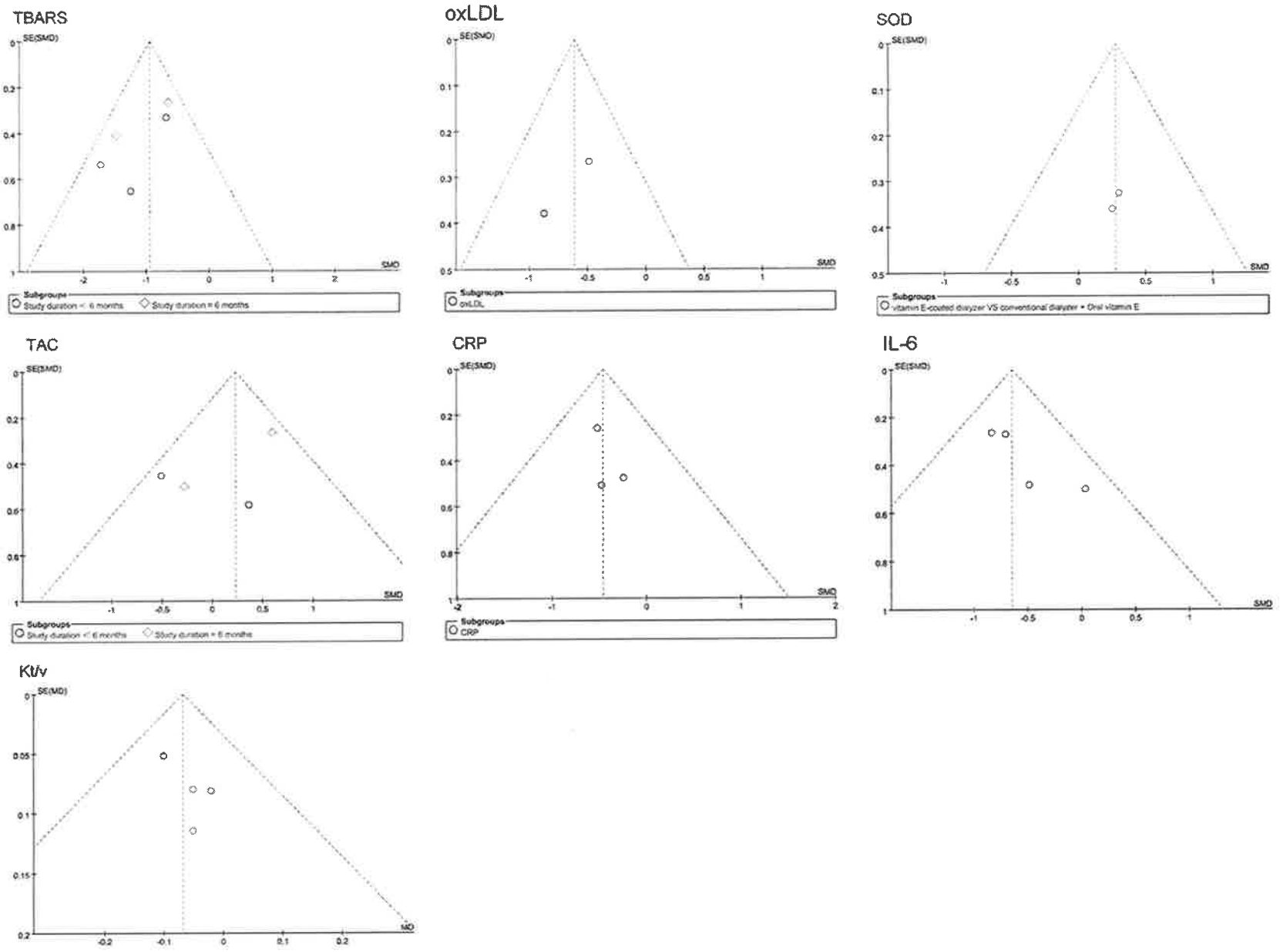

Figure 6. Funnel plots with mean differences (MD) or standardized mean difference (SMD) for studies included in this meta-analysis comparing vitamin E-coated dialyzer with conventional dialyzer for the treatment of HD patients.

In this meta-analysis, We have performed subgroup analysis stratified by the biocompatible character of the controlled dialyzer, but the results showed that there was no difference on serum oxidative stress and inflammation parameters among trials of different biocompatible character (shown in Table 2). It indicates that vitamin E-coated dialyzer may has better anti-inflammatory and anti-oxidation effects compared with conventional dialyzer regardless of the controlled dialyzer membranes biocompatibility. The concept that hemodialysis evokes chronic inflammation is based on the finding that dialysis causes the release of inflammatory cytokines (e.g. TNF-α, IL-1 and IL-6).[41] In addition, recent studies have also indicated that there was a positive correlation between the levels of oxidative stress and inflammatory biomarkers in HD patients.[42]

It was postulated that the antioxidant capacity of HD patients is reduced,[43] yet the exact mechanism of this remains unclear. Our meta-analysis found that the vitamin E-coated dialyzer treatment did not have a significant increase in TAS level compared with that of the ordinary membrane dialyzer (SMD, 0.23; 95% CI, −0.16 to 0.61; $p = 0.25$). In agreement with our pooled result, Yang et al.[38] found that intravenous vitamin C could effectively preserve the plasma TAS levels in patients receiving HD, while these patients received vitamin E-coated dialyzer did not seem to have restored plasma TAS levels. And a recent research performed by Antoniadi et al.[44] showed that prolonged oral vitamin E administration also have a pro-oxidant action under special conditions such as other antioxidants (e.g. vitamin C) are deprived in HD patients, these results indicates that vitamin E-coated dialyzer plus appropriate replacement of ascorbic acid and so on lost during dialysis is likely to be benefit to improve antioxidant capacity in HD patients.

Vitamin E was discovered in 1922 when Evans and Bishop described a ''substance X'' essential for rat fertility.[45] One of the key biological roles of vitamin E was that of a physiological liposoluble antioxidant trapping peroxyl radicals and other reactive species generated during cell metabolism and oxidative stress.[46] In 1990, cellulose-based vitamin E-coated dialyzer was developed by Terumo Corporation under the commercial name Excebrane™. Besides better filtration and biocompatibility, this modified dialyzer has introduced a third function of dialyzer membranes, namely ''antioxidant bioactivity''.[13] In this systematic review, our pooled analysis results have shown that serum CRP, IL-6, TBARS and oxLDL levels are significantly decreased in patients with vitamin E-coated dialyzer treatment ($p = 0.03$, $p < 0.0001$, $p < 0.00001$, $p = 0.005$, respectively). Based on the above findings, we speculated that vitamin E-coated dialyzer therapy might effectively reduce chronic inflammation, oxidative stress status in HD patients. Our meta-analysis also compared the antioxidant ability of vitamin E-coated dialyzer and oral vitamin E supplementation therapy, the pooled result showed that there was no significant difference in plasma SOD level compared with that of the conventional dialyzer and oral vitamin E group ($p = 0.26$), it indicates that simple oral supplement of vitamin E might benefit antioxidant ability, however, as mentioned earlier, Antoniadi et al.,[44] found that prolonged oral vitamin E administration also have a pro-oxidant action in HD patients. The contradicting results of these studies indicate the necessity for more large RCTs to evaluate the exact effects of vitamin E supplementation in HD patients.

The ultimate objective of hemodialysis is to restore the patient's homeostasis and realize a zero sodium and water balance. Dialysis dose is a useful index for assessing treatment delivery. Gotch et al.[47] developed the concept of dialysis quantification based on urea clearances to evaluate the dialysis dose. Despite its limitations, the fractional clearance of urea (Kt/V), is a widely used tool to assess the dialysis efficacy in everyday clinical practice.[48] In this meta-analysis, four trials were included, and 35 patients received Excebrane therapy thrice weekly for a mean time of 4 h, while 38 patients received conventional dialyzer at the same dialysis dose. The result showed that there is no significant difference of Kt/v with vitamin E-coated dialyzer-treated patients compared with conventional dialyzer-treated patients (MD, −0.07; 95% CI, −0.14 to 0.00; $p = 0.06$).

Although this meta-analysis was performed carefully, there are several limitations should be acknowledged. Firstly, the included studies were small-size, and mostly were of low quality, only three studies explained the randomization method, and most studies were not blinded. Secondly, though the included RCTs or quasi-RCTs were similar in baseline characteristics of patients, there were a few heterogeneities in clinical features, such as different types of conventional dialyzer and different study duration. We tried to control some differences by subgroup analysis stratified by the study duration and dialyzer membranes biocompatibility, however, we should note that the accuracy of the pooled analytical results might be influenced in the presence of heterogeneity. Finally, all the included studies reported short-term (<1 year) outcomes of vitamin E-coated dialyzer treatment, therefore long-term efficacy of vitamin E-coated dialyzer need to be proven by further long-term studies. Despite these limitations, this systematic review shows that vitamin E-coated dialyzer can improve the chronic inflammation and oxidative stress status, and does not affect dialysis adequacy. However, because criteria (CRP, TBARS and IL-6) selected are surrogate markers and not hard endpoints of HD patients such as morbidity (e.g. hospitalization) or mortality, this result needs to be confirmed by more high-quality randomized clinical trials. This study provides evidence that further studies need to be conducted in the use of other biocompatible or modified membrane dialyzers, especially antioxidants-coated membrane dialyzers.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. This research was supported by grants from the Creative Research Group Fund of the National Foundation Committee of Natural Sciences of China (81270812).

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