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Colloids in Dialytic Refractory Hypotension

Guy Rostoker

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1.Introduction

1.1. Definition and epidemiology of dialytic hypotension

Intradialytic hypotension is the most common complication of hemodialysis, occurring in up to 33% of patients. There are two main clinical patterns of dialysis-associated hypotension : the first is episodic hypotension (defined by a sudden drop of systolic blood pressure below 100 mmHg or at least 30 mmHg with accompanying clinical symptoms), that typically occurs during the later stages of dialysis sessions and is generally favored by excessive weight gain ; the second is chronic persistent hypotension, which affects about 10% of long-term dialysis patients [1, 2], most of whom experience frequent episodes of hypotension during dialysis sessions, whereas some patients have permanent hypotension with low predialysis systolic pressure, often less than 100 mmHg [3, 4]. Intradialytic hypotension not only causes discomfort and has a negative impact on health-related quality of life but it may also adversely affect the outcome of chronic hemodialysis, reducing patients' life expectancy and favoring underdialysis [5-10]. According to recent data, low pre-dialytic systolic and diastolic pressures, like low post-dialytic systolic pressure and the occurrence of hypotensive episodes during dialysis sessions, are associated with a significantly increased risk of death [5-9]. Moreover, a recent Japanese study has shown a link between dialysis-related hypotension and the occurrence of progressive frontal lobe atrophy [10]. The incidence of intradialytic hypotension is expected to grow with the increasing number of elderly and diabetic patients and patients with cardiovascular disease who are now starting hemodialysis, together with the use of long-term dialysis in an increasing number of hemodialyzed patients. In addition, dialysis treatment time has had a tendency to decrease over the last two decades and all these situations are known to be risk factors for this phenomenon [2,3].

1.2. Etiology and pathogenesis of dialytic hypotension

Several factors contribute to dialytic hypotension. These include too rapid fluid removal in an attempt to reach dry weight, a rapid reduction in plasma osmolality which causes extracellular water to move into cells, high interdialytic weight gain, anemia, poor nutritional status with hypoalbuminemia, autonomic neuropathy, anephric status, reduced pressor response to vasopressor agents, reduced cardiac reserve, increased arterial stiffness, impaired venous compliance, use of acetate rather than bicarbonate as a dialysate buffer, ingestion of a meal immediately before or during the dialysis session, use of low sodium or high magnesium concentrations in the dialysate, and intake before the dialysis session of anti-hypertensive medications that can impair cardiovascular stability (especially nitrate derivatives) [1-4, 11,12]. In a recent cross-sectionnal study of a cohort of 72 hemodialysis patients, 36 of whom suffered from dialysis-related chronic hypotension, cardiac diastolic dysfunction was found to be associated with dialysis hypotension [13]. The excessive release of several endogenous vasodilators such as nitric oxide, adrenomedullin and adenosine, has been implicated in the pathogenesis of dialytic hypotension, together with an imbalance in the synthesis of the endogenous vasoconstrictors endothelin and vasopressin [14-17]. The immediate cause of intradialytic hypotension is acute central hypovolemia [2,4]. Frank hypotension occurs when cardiovascular mechanisms do not adequately compensate for the blood volume reduction resulting from the imbalance between the ultrafiltration rate and the plasma-refilling rate [12].

2. Management and prevention of dialytic hypotension

Management of intradialytic hypotension involves treating the acute episode and applying measures to prevent future episodes [4,11,18]. The acute management of intradialytic hypotension includes the following measures : reducing or halting ultrafiltration, use of the Trendelenburg position and often a reduction in the blood flow rate and use of volume expanders, regardless of the underlying mechanism [4,11,18]. Normal saline is the most widely used volume expander and has been advocated as first-line therapy for intradialytic hypotension [4,11,18]. Commonly used second and third-line fluids are hypertonic saline, dextran, hydroxyethyl starch (HES), mannitol, albumin and gelatin solutions [4,11,18,19]. Standard measures to prevent or alleviate intradialytic hypotension include accurate setting of the dry weight, avoidance of modifiable factors known to favor this phenomenon (e.g. excessively rapid fluid removal in an attempt to reach dry weight, anemia, poor nutritional status with hypoalbuminemia, ingestion of a meal immediately before or during the dialysis session, and intake before the dialysis session of anti-hypertensive medications) that can impair cardiovascular stability, adjustment of the dialysate sodium and/or calcium concentration and temperature, use of initial ultrafiltration followed by standard (or isovolemic) dialysis, use of sodium, and ultrafiltration modeling [1-4,14]. Among resistant patients, the most effective strategies to prevent intradialytic hypotension are to increase the dialysis time

(for example by using either short daily hemodialysis sessions or frequent nocturnal hemodialysis) or to switch to peritoneal dialysis [1-4,14].

3. Use of colloids in refractory dialytic hypotension

Recent studies have shown that human albumin is safe in intensive care units and can also be useful in this setting in patients with acute renal failure secondary to sepsis or associated with profound hypoalbuminemia [20]. As central hypovolemia is the initiating factor in the pathogenesis of dialytic hypotension [2, 12], recent studies have hypothesized and analyzed the potential benefit of systematic infusion of colloids -- 20% albumin or 4% gelatin -- during dialysis sessions in hypotension-prone patients unresponsive to usual preventive measures [21, 22]. Until recently, few studies have evaluated colloids and especially albumin as a priming fluid for hemodialysis in septic patients or as preventive or curative therapy for hypotension-prone dialysis patients. Jardin and coworkers showed that infusion of 300 ml of 17.5% albumin as a priming fluid at the start of the dialysis session resulted in better ultrafiltration and hemodynamic stability than saline infusion in patients with sepsis-induced anuric acute renal failure ; these authors also showed that hypovolemia (as reflected indirectly by reduced left ventricular filling pressure), reduced cardiac output and the decline in mean arterial pressure were better corrected by 17.5% albumin than by saline [23]. McLigeyo first reported an improvement in hemodynamic parameters in four hemodialysis patients with chronic persistent hypotension receiving systematic infusions of 100 ml of 25% albumin [24]. More recently, Van der Sande and coworkers showed in nine cardiac-compromised hypotension-prone dialysis patients that 100 ml of 20% albumin and 100 ml of hydroxyethyl starch preserved systolic blood pressure and relative blood volume better than 33 ml of 3% saline during a hypotensive episode [25]. However, the side effects of hydroxyethyl starch (prolonged bleeding time, deposition of HES in various tissues and especially the liver) preclude its use in this setting and it is now forbidden in France and in numerous countries in dialysis patients [26, 27].

We recently conducted a single blind prospective cross-over study of systematic infusion of 200 ml of 20% albumin as compared to 200 ml of 4% gelatin in 10 patients on long-term bicarbonate hemodialysis with refractory permanent hypotension (despite cool dialysate associated with sodium and ultrafiltration profiling, at an ideal dry weight assessed by echocardiography) ; the study lasted 20 weeks [21]. We analyzed the effect of albumin and gelatin infusions on systolic and diastolic pressure and the number of hypotensive episodes by using the n-of-1 trial methodology and the Wilcoxon matched-pairs signed-ranks test [21]. Statistical analysis of individual data showed that 20% albumin increased systolic pressure in 6 patients ($p < 0.05$ Wilcoxon test) whereas 4% gelatin improved systolic pressure in only 2 patients ($p < 0.05$ Wilcoxon test) [21].

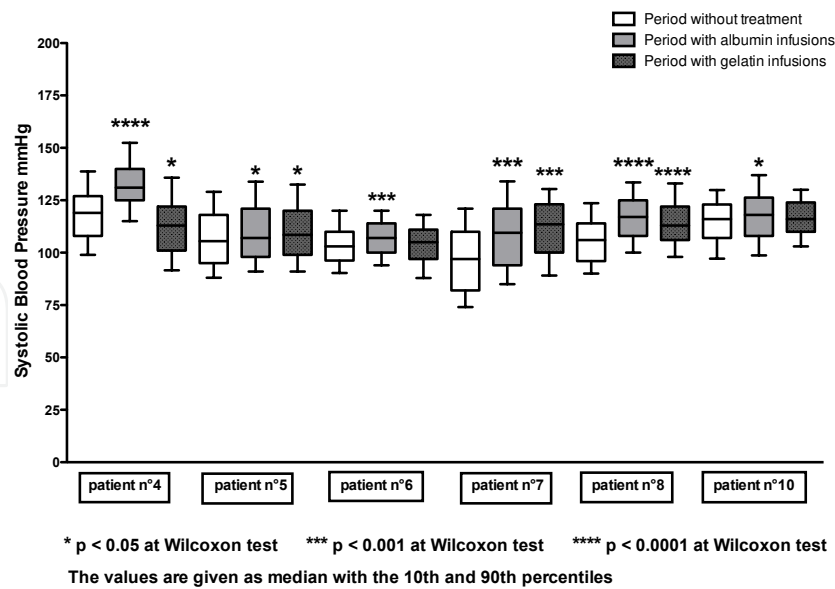


Figure 1. Evolution of systolic blood pressure with 20% albumin and 4% gelatin infusions in improved patients according to Rostoker G, et al. A pilot study of routine colloid infusion in hypotension-prone dialysis patients unresponsive to preventive measures. J Nephrol 2011; 24(02) : 208-217; *p<0.05 at Wilcoxon test, ***p<0.001 at Wilcoxon test, ****p<0.0001 at Wilcoxon test; The values are given as median with the 10th and 90th percentiles

Albumin infusions increased diastolic pressure in 4 patients (p< 0.05 Wilcoxon test) whereas gelatin improved diastolic pressure in only 1 patient (p< 0.05 Wilcoxon test) [21].

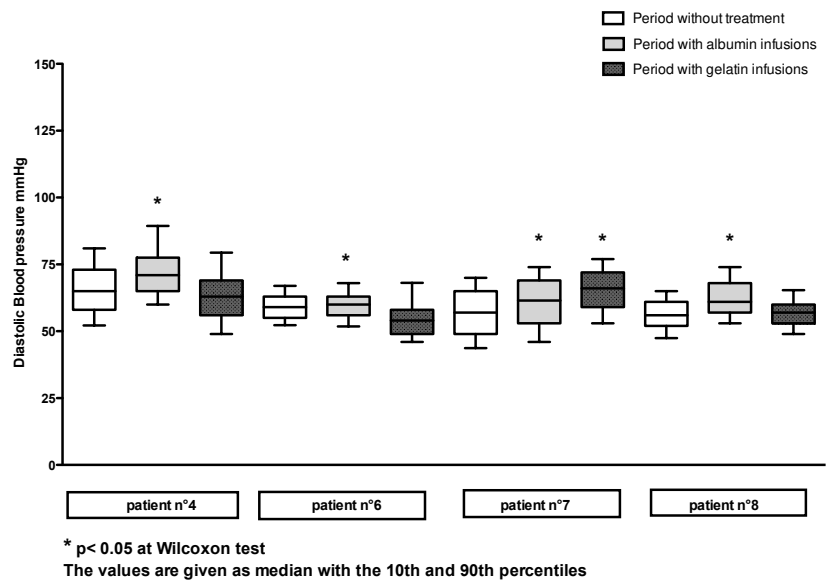


Figure 2. Evolution of diastolic blood pressure with 20% albumin and 4% gelatin infusions in improved patients according to Rostoker G, et al. A pilot study of routine colloid infusion in hypotension-prone dialysis patients unresponsive to preventive measures. J Nephrol 2011; 24(02): 208-217; *p<0.05 at Wilcoxon test; The values are given as median with the 10th and 90th percentiles

The median number of hypotensive episodes (systolic pressure < 100 mmHg) fell significantly in 3 patients during 20% albumin infusion and in 2 patients receiving 4% gelatin ($p < 0.05$, Wilcoxon test) [21]. Dialysis quality assessed by the Kt/V ratio and the relative blood volume reduction were also stable, whereas ionic dialysance at the end of the dialysis session was improved by albumin but not by gelatin ($p < 0.05$, repeated measure ANOVA) [21]. Thus, in this single blind cross-over pilot study using n-of-1 methodology, we found that systematic infusion of 20% albumin or 4% gelatin during hemodialysis sessions improved hemodynamic parameters (systolic blood pressure, diastolic blood pressure and the number of hypotensive episodes) and the ultrafiltration rate in most hypotension-prone patients unresponsive to usual preventive measures [21]. Albumin was proved to be superior to gelatin; however, both colloids were ineffective in some patients, suggesting the need for careful and objective evaluation of these expensive therapeutics on an individual level [21].

4. Hemodynamic mechanisms of action of colloids in refractory dialytic hypotension

In hemodialysis sessions, during ultrafiltration, the refilling rate is dependent on colloid osmotic pressure [28]. Therefore, systematic infusion of 20% albumin during the dialysis session and, to a lesser extent, 4% gelatin, would be expected to increase colloid osmotic pressure, enhance plasma refilling and thus prevent an abrupt reduction in blood volume and acute hypovolemia. Albumin has a water binding capacity of 18 ml per gram, and 200 ml of 20% albumin solution binds 720 ml of water for 6-8 hours, whereas 200 ml of 4% gelatin binds only 200 ml of water for 4-5 hours [29, 30]. It is also tempting to postulate that colloids counteract the reduced cardiac preload with both atrial and ventricular underfilling as recently shown by Graziani and coworkers at the end of the ultrafiltration session in the subset of patients with severe dialysis-related hypotension [31]. Finally, systematic infusion of colloids could improve cardiac output in patients with diastolic dysfunction: the German nephrologic school postulated in the late 1980s, and demonstrated in the early 1990s, that left-ventricular hypertrophy was a risk factor for dialysis-related hypotension due to diastolic dysfunction [32-35]. In contrast to German nephrologists, we found no relationship between diastolic dysfunction and left ventricular mass [13]. The latter finding might be related to changes in the epidemiology of dialysis over the last two decades: patients in the eighties had left ventricular hypertrophy related to both hypertension and uremic fibrosing cardiomyopathy, promoted by a long history of chronic dialysis with cuprophane membranes, while dialysis patients are now older and have diabetes or cardiovascular diseases (especially ischemic cardiopathy), which are known to cause left ventricular diastolic dysfunction and diastolic heart failure [13]. In patients with a very long dialysis vintage left ventricular enlargement is attributable to chronic volume and flow overload associated with anemia, presence of arteriovenous fistulas, sodium, water and uremic toxins retention [36]. Several mechanisms are involved in the pathophysiology of dialytic hypotension secondary to cardiac diastolic dysfunction: first, diastolic dysfunction in hemodialysis patients induces

filling disturbances in diastole leading to systolic dysfunction especially a fall in stroke volume during hypohydration induced by rapid ultrafiltration or when plasma refilling compensatory mechanisms are deficient resulting in central hypovolemia and abrupt hypotension: central hypovolemia in such cases could be counteracted by infusions of colloids [37,38]. Second, these hearts have a limited ability to utilize the Franck-Starling mechanism during exercise or its counterpart such as a dialysis session. Such limited preload reserve especially if coupled with chronotropic incompetence seen with advancing age limits cardiac output during exercise and dialysis sessions ; this leads to lactate accumulation and functional abnormalities of the myocardium [37,38]. Third, a substantial number of patients who have left ventricular hypertrophy with high wall thickness and a small end diastolic volume exhibit a low stroke volume and depressed cardiac output [35].

5. Modulation of oxidative stress and microinflammatory status by colloids in refractory dialytic hypotension

Data on the association between inflammatory status and dialysis hypotension are scarce: Tomita and coworkers have shown in nine patients with a history of intradialytic hypotension when compared with eight patients without dialysis associated hypotension a correlation between the levels of CRP and IL6 and the maximum percent change in mean arterial pressure over multiple dialysis sessions suggesting that dialysis hypotension may trigger inflammation [39]. This is consistent with the finding of Bergamini et al who found a significant release of TNF-alpha during hypotension episodes [40]. We recently hypothesized that frequent hypotension episodes may induce a noxious inflammatory response mediated by oxidative stress induced by ischemia-reperfusion phenomenon [22]. In a prospective cross-over study (lasting 20 weeks) of routine infusion of 200 ml of 20% albumin versus 200 ml of 4% gelatin in 10 patients with refractory intradialytic hypotension, we analyzed the effect of 20% albumin and 4% gelatin on microinflammatory status, oxidative stress, serum nitrite and nitrate levels by analysis of variance [22]. A significant decrease in serum ceruloplasmin and serum C3 was observed during the albumin period ($p < 0.05$, repeated measure ANOVA) [22]. A significant decrease in serum hydrogen peroxide was seen during albumin and gelatin administration ($p < 0.01$, repeated measure ANOVA) and a dramatic decrease in serum lipid peroxides was observed during the albumin period only ($p < 0.01$, Friedman test) [22].

Serum lactoferrin, serum proinflammatory cytokines and serum nitrite and nitrate levels remained stable during the different periods of this pilot trial [22]. These results strongly suggest that the improvement in microinflammatory status observed in hypotension prone dialysis patients may be related to the decrease in ischemia-reperfusion of noble organs by infusions of colloids together with a specific reduction of oxidative stress by 20% albumin.

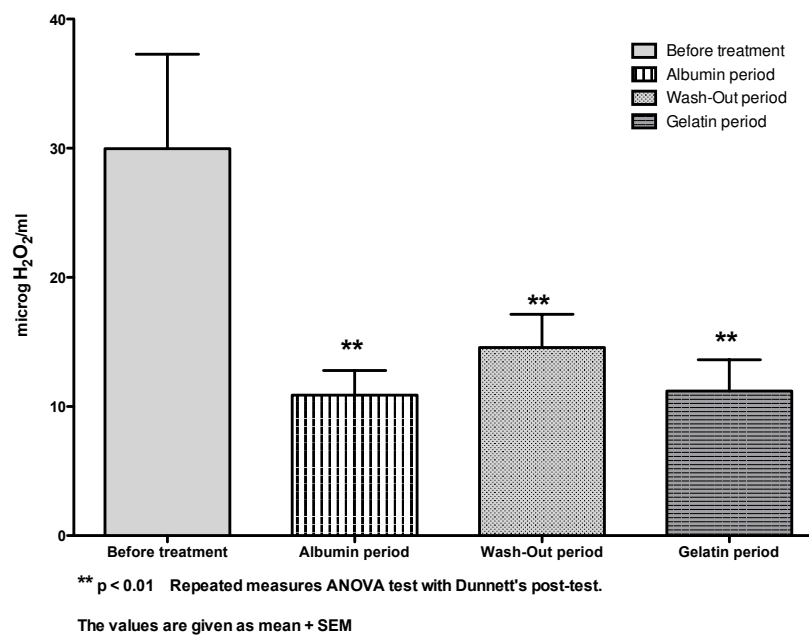


Figure 3. Concentration of serum hydrogen peroxide in patients with refractory dialytic hypotension treated by systematic infusion of colloids during dialysis sessions, according to Rostoker G et al Modulation of oxydative stress and microinflammatory status by colloids in refractory dialytic hypotension. BMC Nephrol 2011; oct 20; 12 (1): 58; **p<0.01 Repeated measures ANOVA test with Dunnett's post-test

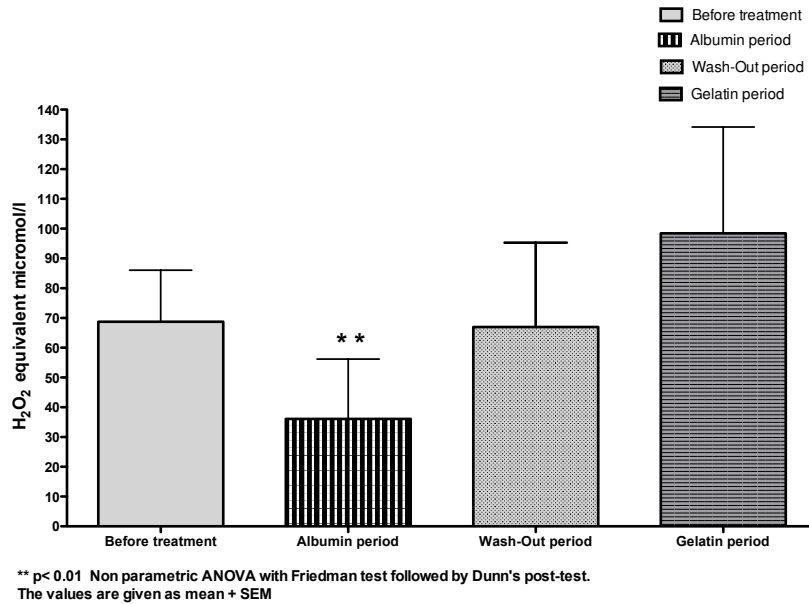


Figure 4. Concentration of serum lipid peroxides in patients with refractory dialytic hypotension treated by systematic infusion of colloids during dialysis sessions, according to Rostoker G et al Modulation of oxydative stress and microinflammatory status by colloids in refractory dialytic hypotension. BMC Nephrol 2011; Oct 20; 12 (1): 58 ; **p<0.01 Non parametric ANOVA with Friedman test followed by Dunn's post-test.; The values are given as mean + SEM

6. Anti-inflammatory mechanisms of action of colloids in refractory dialytic hypotension

In the aforementioned pilot study, C3 and ceruloplasmin were significantly lowered during the albumin period but not during the gelatin period [22]. This is consistent with recent studies using experimental models of hemorrhagic shock, which indicated that the type of resuscitation fluid greatly influences proinflammatory responses and especially neutrophil activation and nuclear factor-Kappa B gene transcription; albumin was found to be the least proinflammatory fluid [41, 42]. Conversely, ex-vivo data suggest that uremia may also increase vascular permeability [43] which may be acutely raised during dialysis-associated hypotension via released mediators such as adenosine aimed to preserve perfusion of the noble organs [17]; in this setting, albumin may itself influence vascular integrity by binding to the interstitial matrix and sub-endothelium and by altering the permeability of these layers to large molecules and solutes; these effects may be mediated by the binding of arachidonic acid to albumin and by polynitroxylated albumin, which inhibits xanthine-oxidase-mediated adhesion of human neutrophils to endothelial cells [44].

In this trial, serum hydrogen peroxide levels were significantly lowered during both the albumin and the gelatin periods, suggesting that the improvement in hemodynamic parameters by colloids reduces oxidative stress related to the ischemia-reperfusion of noble organs that occurs during dialytic hypotension [22,45]. Besides this classical ischemia-reperfusion mechanism, by analogy with heart failure, it was hypothesized that entry of bacterial endotoxin during dialysis sessions might be the result of intermittent underperfusion of the intestine during dialysis-associated hypotension episodes leading to cardiac stunning and oxidative stress [46,47,48]; thus in this setting, colloids may improve both systemic and intestinal perfusion and reduce gut ischemia [22,46,47,48]. In the latter pilot study, serum lipid peroxide levels were also significantly reduced only during the albumin period. This is consistent with data showing that human serum albumin and bovine serum albumin provide protection from lipid peroxidation propagated by inorganic reactive oxygen species generated from xanthine oxidase/hypoxanthine in artificial systems [49] and that persistent hypoalbuminemia in hemodialysis patients is associated with peroxidation of erythrocyte membranes [50]. Moreover, albumin is the major extracellular source of reduced sulphydryl groups, termed thiols which are avid scavengers of reactive oxygen and nitrogen species; in this way albumin influences redox balance [51, 52]. All these data also strongly suggest that dialytic hypotension may contribute by different ways to the overproduction of reactive oxygen species seen in end-stage renal failure patients, a multifactorial process mainly related to uremia per-se, the hemoincompatibility of the dialysis system and trace amounts of endotoxin in the dialysate, gut ischemia and that colloids may in different mechanisms counteract it [22, 53].

7. Conclusions

Recent studies have shown that systematic infusions of 20% albumin and 4% gelatin during hemodialysis sessions improve hemodynamic parameters and ultrafiltration rate in most hypotension prone dialysis patients unresponsive to the usual preventive manoeuvres. An improvement in microinflammatory status was observed in parallel, which might be related to the decrease in both ischemia-reperfusion of noble organs, gut ischemia and oxidative stress. Hyperoncotic 20% albumin was found to have greater anti-inflammatory and anti-oxidative properties than 4% gelatin. Moreover, in the case of a new and expensive therapy such as 20% albumin (cost of 200 ml 20% albumin : 80 Euros as compared to 4 Euros for 200 ml 4% gelatin, in France), n-of-1 trials can furnish powerful evidence for provision on an individual basis, allaying managerial and medical fears as to the cost of frequently ineffective therapies being applied to an expanding at-risk population. From a pragmatic point of view, we advise practitioners to initiate first gelatin which is much less expensive when a treatment of systematic infusion of colloids is scheduled during dialysis sessions. Owing to its high cost, hyperoncotic albumin should be considered as a second-line therapy. Further well-designed controlled trials with a sufficient number of patients, of hyperoncotic 20% albumin and 4% gelatin in hypotension-prone dialysis patients are warranted to assess the benefit of colloids infusions in dialytic refractory hypotension.

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