Factors Affecting Intermittent Infusion Hemodiafiltration

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Keywords

Intermittent infusion hemodiafiltration · Cardiothoracic ratio · Arteriosclerosis obliterans · Valvular heart disease · Dialysis

Abstract

Background: Intermittent infusion hemodiafiltration (I-HDF) has been performed for a number of years since this mode of dialysis became available with dialyzers used in Japan. It has been effective in some cases and ineffective in others. In this study, we analyzed and clarified these differences. **Summary:** We conducted a retrospective study to determine the factors affecting the effectiveness of I-HDF treatment in some patients and ineffectiveness in others and classified the complex causes associated with volume load that were identified. **Key Messages:** Bolus dialysate infusion in I-HDF affects the volume load (preload), and repeated bolus dialysate infusion influences both preload and afterload in patients with valvular heart disease. In this study, I-HDF was effective when brain natriuretic peptide levels, cardiothoracic ratio, and ultrafiltration rate were well controlled and cardiac load was low. I-HDF was shown to be effective in patients who are prone to developing hypotension at the end of a dialysis session. There were several factors, including different types of load, involved in inefficiency of I-HDF.

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Introduction

Various clinical evaluations of intermittent infusion hemodiafiltration (I-HDF) have been made since the procedure was devised in the latter half of the 2000s [1]. At Tajirigaoka Hospital, our experience has been that treatment is effective in some cases and ineffective in others after switching from dialysis mode to I-HDF mode. However, no studies to date have clarified the factors associated with the effectiveness or ineffectiveness of I-HDF. The objective of this study was to analyze and elucidate factors related to these differences.

Materials and Methods

Participants were 43 dialysis patients from Tajirigaoka Hospital. We explained the details of the study to each patient individually, informed them of the research objectives in writing, and explained their right to withdraw their consent at any time. Following these explanations, written informed consent was obtained from each participant. The institutional review board of Tajirigaoka Hospital reviewed and approved the study protocol.

Following the introduction of a new machine at the hospital, the setting was changed from dialysis mode to I-HDF mode, and effectiveness was investigated. I-HDF was performed using the TR-3300M™ online hemodiafiltration machine (Toray Medical Co. Ltd., Tokyo, Japan). I-HDF is used in various conditions in each hospital [2] and at Tajirigaoka Hospital, dialysis was per-

Table 1. Patient background

	All patients			Patients entered into retrospective analysis		
	total (<i>n</i> = 43)	I-HDF effective (<i>n</i> = 20)	I-HDF ineffective (<i>n</i> = 23)	total (<i>n</i> = 36)	I-HDF effective (<i>n</i> = 18)	I-HDF ineffective (<i>n</i> = 18)
Age, years, mean (SD)	69.0 (12.03)	66.6 (12.29)	71.1 (11.94)	68.9 (11.70)	66.9 (10.74)	70.0 (12.58)
Gender, male, <i>n</i> (%)	27 (62.8)	14 (70.0)	13 (56.5)	23 (63.9)	12 (66.7)	11 (61.1)
History of type 2 diabetes, <i>n</i> (%)	20 (46.5)	7 (35.0)	13 (56.5)	16 (44.4)	7 (38.9)	9 (50.0)
More than mild heart valve disease, <i>n</i> (%)	35 (81.4)	12 (60.0)	23 (100.0)	30 (83.3)	12 (66.7)	18 (100.0)
Sever arteriosclerosis obliterans (fontaine classification $\geq$ IIb), <i>n</i> (%)	4 (9.3)	0 (0.0)	4 (17.4)	3 (8.3)	0 (0.0)	3 (16.7)

I-HDF, intermittent infusion hemodiafiltration.

formed for 4 h, and each of the following 3 regimens below was used for 2 months each, for a total period of 6 months: Regimen 1, infusion volume 200 mL, infusion rate 150 mL/min, and total infusion volume of 1,200 mL at 30-min intervals from 60 min after the start of dialysis; Regimen 2, infusion volume 200 mL, infusion rate 150 mL/min, and total infusion volume 2,000 mL at 20-min intervals from 40 min after the start of dialysis; and Regimen 3, infusion volume 100 mL, infusion rate 150 mL/min, and total infusion volume 1,000 mL at 20-min intervals from 40 min after the start of dialysis. Patients were then divided into those for whom I-HDF was effective and those for whom it was ineffective. As the basic condition, the upper limit of the ultrafiltration rate (UFR) was set to 0.89 kg/h (this value does not include the ultrafiltration rate for I-HDF). The standards for determining whether I-HDF initiation was effective or ineffective were investigated by staff completing a form for each patient as follows: 1, individuals who developed adverse reactions during the remaining 30 min of I-HDF; 2, patients for whom I-HDF was deemed effective but in whom other conditions had to be changed (i.e., the dry weight [DW] target was not achieved or time was prolonged to allow for achieving a value within the upper limit of the ultrafiltration rate for I-HDF); 3, patients for whom I-HDF was deemed ineffective for other reasons and the reasons were recorded. In addition, treatment was also considered to be ineffective in patients who may have developed heart failure due to rapid infusion or repeated I-HDF.

When it was difficult to determine whether I-HDF was effective or ineffective even for patients categorized under 1 or 2 above, I-HDF was judged ineffective if rapid infusion was frequently needed in the event of hypotension or if time frequently needed to be prolonged when compared with the previous treatment mode. If I-HDF was determined to be ineffective in any such cases, we returned to the mode of treatment previously used.

For safety, if blood pressure did not return to normal during dialysis and it was deemed risky to continue I-HDF, then I-HDF was terminated immediately and the patient was switched to the mode of treatment used previously. Also, cardiothoracic ratio (CTR) in dialysis patients affects prognosis [3, 4], so I-HDF was terminated if any rapid increase in CTR $\geq$ 5% was noted. I-HDF was also terminated in patients who developed intradia-

lytic hypertension (persistent systolic blood pressure [SBP] $\geq$ 180 mm Hg).

When initiated using the above-mentioned criteria, I-HDF was effective in 20 of the 43 patients and ineffective (terminated) in 23 patients. Then, for 36 patients with a complete set of data for analysis, we divided them into an effective group (*n* = 18) and an ineffective group (*n* = 18) and performed a retrospective comparative analysis of the 2 groups. Intergroup comparison was performed using the *t* test after calculating mean values or percentages, and *p* values <0.05 (two-tailed) were considered significant.

Results

Retrospective Analysis of Effective or Ineffective I-HDF

Table 1 shows the background characteristics of all 43 patients and the 36 patients who were entered into the retrospective analysis. We observed no major differences in patient characteristics between the overall group and the retrospective analysis groups.

A slightly higher number of patients had a history of type II diabetes in the ineffective group than in the effective group. All members of the ineffective group had some form of valvular heart disease graded mild or greater. Severe arteriosclerosis obliterans (ASO) grade IIb or greater according to the Fontaine classification was seen only in the ineffective group. All patients who had ASO also had concomitant cardiovascular disease. Furthermore, most of the patients who complained of symptoms after rapid infusion to treat hypotension likely had developed heart failure, so I-HDF was contraindicated in patients with severe ASO.

Comparing the effective group with ineffective group, we found that the mean CTR 6 months prior to initiation of I-HDF was significantly larger in the ineffective group (51.5% in the effective group vs. 57.5% in the ineffective

Fig. 1. Retrospective analysis of patients treated with I-HDF. **a** CTR at 6 months before I-HDF introduction and during I-HDF treatment. **b** BNP levels at 12 months before I-HDF introduction and during I-HDF treatment. **c** Echocardiographic parameters before I-HDF introduction. **d** Ultrafiltration rate of patients during I-HDF treatment. Eff: patients for whom I-HDF was effective. In-

eff: patients for whom I-HDF was ineffective (both $n = 18$). Data are expressed as the mean (X), median (line), and interquartile range (box). * $p < 0.05$ (Welch t test). ns, not significant; I-HDF, intermittent infusion hemodiafiltration; BNP, brain natriuretic peptide; CTR, cardiothoracic ratio.

group). Mean CTR at 2 months after initiation of I-HDF was again significantly higher in the ineffective group (52.3 vs. 58.4%, respectively; Fig. 1a). Serum levels of brain natriuretic peptide (BNP) 1 year prior to initiation of I-HDF were 371 in the effective group and 601 in ineffective group, but this difference was not significant (Fig. 1b). Serum BNP levels during I-HDF were 470 in the effective group and higher, but not significantly so, at 1,093 in ineffective group. There were no differences between the 2 groups in terms of cardiac output or ejection fraction measured by echocardiography before initiation of I-HDF (Fig. 1c). The UFR (mL/kg/h), not including the ultrafiltration rate for I-HDF, did not differ significantly between the 2 groups (10.72 vs. 11.55 mL/kg/h, respectively; Fig. 1d).

Based on these results, CTR and BNP values before I-HDF introduction were high in the ineffective group and these patients already had high preload or afterload. There were no significant differences in BNP values between the

2 groups, although BNP values were higher in the ineffective group. So, we believe that these cases in the ineffective group had a high risk of developing heart failure. BNP values were elevated in both the effective group and the ineffective group during I-HDF. These show that the ineffective group had extremely high UFR and weight gain.

Classification of Patients Who Developed Heart Failure Due to Volume Overload Following Rapid Infusion

The results obtained from extracting factors associated with ineffective I-HDF suggest some form of volume overload. To extract complex multifactorial involvement, we classified symptoms in 20 patients for whom I-HDF was effective and 23 patients for whom it was ineffective who were prone to developing heart failure due to volume overload after rapid infusion during I-HDF. These were classified as A, B, or C as follows: (A) severe ASO grade IIb or

Fig. 2. Classification of patients for whom I-HDF was ineffective and who are at high risk of developing heart failure by rapid volume load. Patients for whom I-HDF therapy was ineffective ($n = 23$) were classified into groups A, B, or C according to the following risk factors for heart failure: group A, severe ASO (Fontaine classification $\geq$ IIb); group B, more than mild valvular heart disease; and group C, cardiothoracic ratio (CTR) $\geq 55\%$ (male) and $\geq 60\%$ (female), a rapid increase in CTR, or SBP > 180 mm Hg throughout dialysis treatment.

greater according to the Fontaine classification (all the patients also had comorbid cardiovascular disease); (B) any valvular heart disease graded mild or greater; and (C) preload, afterload (increased CTR; $\geq 55\%$ for men and $\geq 60\%$ for women), rapid increase in CTR $\geq 5\%$, and intradialytic hypertension (persistent SBP ≥ 180 mm Hg). We also attempted to use BNP values, but there were large variations between individuals, so this factor was considered unsuitable for classification. Among a total of 23 patients for whom I-HDF was ineffective, 4 patients were classified as A, 23 were classified as B, and 19 were classified as C. All cases were complicated by 2 or more factors (Fig. 2); 4 patients with severe ASO (this classification was commonly associated with cardiovascular complications) were classified as both A and B and 19 patients were classified as both B and C. Also, those patients classified as both B and C developed volume overload (preload), pressure overload (postload), heart failure with large CTR, or pressure overload (postload) due to systolic intradialytic hypertension.

Of the 20 patients for whom I-HDF was effective, none were classified as A, 12 were classified as B, and 2 were classified as C; 7 patients did not fit into any classification. Only 1 case was complicated by 2 or more factors (Fig. 3). There was a major difference between cases for which I-HDF was effective and ineffective in terms of complications by 2 or more factors.

Discussion

The results of this retrospective analysis of cases of effective and noneffective I-HDF revealed that none of the patients had elevated BNP levels before the intro-

Fig. 3. Classification of patients for whom I-HDF was effective and who are at high risk of developing heart failure by rapid volume load. Patients for whom I-HDF therapy was effective ($n = 20$) were classified into group A, B, or C, as described in Fig. 2.

duction of I-HDF in any group. In other words, the results suggest that repeated infusions during I-HDF which contribute to volume overload will ultimately affect preload if patients have comorbid valvular heart disease, which in turn results in high afterload. Patients for whom I-HDF was effective had lower initial load with well-controlled BNP, CTR, and UFR, and I-HDF functioned to serve as an effective preload comparative to the extent of hypotension during dialysis. Patients for whom treatment was ineffective had high baseline CTR and BNP values. If CTR was high, a lower setting for DW was used to decrease CTR, but if this was unsuccessful, multiple types of burden might have been involved.

When we consider the results of the patients who readily developed heart failure due to volume overload as a result of rapid infusion, those who were effectively treated tended to have adequately controlled CTR, DW, and UFR values. However, those that were treated ineffectively were complicated by 2 or more factors and had complex multifactorial involvement, so if they were complicated by 2 or more factors, then initiation of I-HDF was not performed. In many unsuccessful cases, setting a lower DW to decrease CTR resulted in the levels of multiple factors (CTR, BNP, preload, afterload, and blood pressure) simultaneously reverting to their appropriate ranges, enabling I-HDF to be restarted. Nevertheless, caution is required when initiating I-HDF in patients with increased CTR or recalcitrant intradialytic hypertension, so this treatment cannot be recommended in cases such as high-flow shunt, severe aortic valvular stenosis, congestive heart failure, and cardiomyopathy.

Based on the findings from patients for whom I-HDF was ineffective, we created an internal protocol at Tajirigaoka Hospital that evaluates the presence of factors A, B, and C. If one of these factors was present, then I-HDF could be initiated, but if complicated by 2 or more of these factors, I-HDF was not initiated. In addition, the following items were established as criteria for terminating I-HDF after initiation: volume load (preload) increase during initiation of I-HDF, which is defined as rapid increase in CTR or CTR $\geq 55\%$ in men and $\geq 60\%$ in women; and pressure load (afterload) increase during initiation of I-HDF, which is defined as intradialytic hypertension (persistent SBP ≥ 180 mm Hg).

Conclusion

I-HDF is effective in patients who develop intradialytic hypotension as well as in patients with adequately controlled body weight. In patients with high preload/afterload, I-HDF acts as an effective preload if the DW is sufficiently reduced and the CTR is decreased. Patients who are susceptible to overload, such as by rapid infusion, must be identified. These include patients with severe ASO grade IIb or greater according to the Fontaine classification (all the patients also had comorbid cardiovascular disease), high-flow shunts, severe aortic valvular stenosis, congestive heart failure, and cardiomyopathy. Patients for whom I-HDF was ineffective often had increased load, with poor circulation and multifactorial in-

volvement. We have now started applying in clinical practice the protocol we have developed for determining whether I-HDF should be initiated.

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Statement of Ethics

The institutional review board of Tajirigaoka Hospital reviewed and approved the study protocol, and written informed consent was obtained from all participants in the study.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

K.E. designed the study. K.E. and T.O. conducted the study and interpreted the results. K.E. wrote the manuscript. T.O. contributed to the manuscript revision. All authors approved the final version of the manuscript.

References

- 1 Mineshima M, Eguchi K. Development of intermittent infusion hemodiafiltration using ultrapure dialysis fluid with an automated dialysis machine. *Blood Purif*. 2013;35(suppl 1):55–8.
- 2 Koda Y, Aoike I, Hasegawa S, Osawa Y, Nakagawa Y, Iwabuchi F, et al. Feasibility of intermittent back-filtrate infusion hemodiafiltration to reduce intradialytic hypotension in patients with cardiovascular instability: a pilot study. *Clin Exp Nephrol*. 2017 Apr;21(2):324–32.
- 3 Ito K, Ookawara S, Ueda Y, Miyazawa H, Yamada H, Goto S, et al. A higher cardiothoracic ratio is associated with 2-year mortality after hemodialysis initiation. *Nephron Extra*. 2015 Dec;5(3):100–10.
- 4 Yen TH, Lin JL, Lin-Tan DT, Hsu KH. Cardiothoracic ratio, inflammation, malnutrition, and mortality in diabetes patients on maintenance hemodialysis. *Am J Med Sci*. 2009 Jun;337(6):421–8.