Association between haemoglobin concentration and intradialytic hypotension in patients undergoing maintenance haemodialysis: a retrospective cohort study

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ABSTRACT

Objectives Haemoglobin concentration is a potentially modifiable factor that may help lower the risk of intradialytic hypotension (IDH), but its association with IDH is not well understood. This study aimed to clarify the relationship between haemoglobin concentration and IDH.

Design Retrospective cohort study.

Setting We evaluated patients undergoing maintenance haemodialysis in December 2017 at Rakuwakai Otowa Kinen Hospital.

Participants A total of 543 patients were included. We defined exposure according to the following five categories depending on haemoglobin concentrations by 1.0 increments: <9.0, ≥9.0 to <10.0, 10.0 to <11.0, ≥11.0 to <12.0 and ≥12.0 g/dL.

Primary outcome measure The primary outcome of interest was the development of IDH, defined as any nadir <100 mm Hg if the pre-dialysis systolic blood pressure (SBP) was ≥160 mm Hg or any nadir <80 mm Hg if the pre-dialysis SBP was <160 mm Hg (IDHnadir).

Results Overall, IDHnadir occurred in 14.3% (465/3250) of the sessions. With a haemoglobin concentration of ≥10.0 to <11.0 g/dL set as reference, the adjusted ORs for IDHnadir were 0.82 (95% CI, 0.32 to 2.15), 1.16 (95% CI, 0.56 to 2.39), 1.26 (95% CI, 0.68 to 2.36) and 3.01 (95% CI, 1.50 to 6.07) for haemoglobin concentrations of <9.0, ≥9.0 to <10.0, 10.0 to <11.0 and ≥12.0 g/dL, respectively. In the cubic spline analysis, a high haemoglobin concentration was associated with the development of IDHnadir.

Conclusion High haemoglobin concentration is associated with IDH, and thus, the upper limit of haemoglobin concentration should be closely monitored in patients with IDH.

INTRODUCTION

Renal anaemia is a major complication in patients undergoing haemodialysis (HD). Previous studies have shown that anaemia is associated with adverse outcomes such as mortality and cardiovascular events.1–3 Therefore, there have been attempts to improve anaemia using erythropoietin-stimulating agent (ESA) preparations, iron preparations, hypoxia-inducible factor prolyl-hydroxylase inhibitor preparations and red blood cell transfusions.10 However, previous studies have also reported that the disadvantages of higher haemoglobin targets in ESA treatment outweigh their benefits.11–16 Therefore, the optimal haemoglobin concentration target in patients undergoing HD remains controversial. Moreover, it may vary depending on the clinical problem in each case.

Intradialytic hypotension (IDH) is a clinically relevant complication in patients undergoing HD. IDH is associated with high mortality and incidence of cardiovascular events.17–21 However, there is limited evidence to provide a basis for developing the optimal strategy for preventing IDH.22–24 Further, although the haemoglobin concentration is a potentially modifiable risk factor for IDH, its association with IDH is not well understood. Thus, this study aimed to clarify the relationship between the haemoglobin concentration and IDH.

METHODS

Study design and population

This was a retrospective cohort study of patients undergoing maintenance HD in December 2017 at Rakuwakai Otowa Kinen Hospital.

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Hospital, a high-volume dialysis centre in the Yamashina region of Kyoto, Japan. The eligibility criterion was available data on the haemoglobin concentration and other medical information. This study excluded patients with pre-dialysis systolic blood pressure (SBP) <90 mm Hg because these patients were not at risk for IDH. In addition, we disclosed information about the purpose and implementation of the study to patients and informed them that they had the opportunity to refuse to participate in the study.

**Exposure**

The exposure of interest was the haemoglobin concentration measured during the week’s first session. The haemoglobin concentration was divided into five categories by 1.0 g/dL increments (1) <9.0 g/dL, (2) ≥9.0 to <10.0 g/dL, (3) ≥10.0 to <11.0 g/dL, (4) ≥11.0 to <12.0 g/dL and (5) ≥12.0 g/dL. For categorical variable analysis, ≥10.0 to <11.0 g/dL was set as a reference based on a previous study. For continuous variable analysis, a concentration of 10.0 g/dL was set as reference. Given that the haemoglobin concentration was not available in all dialysis sessions, the values obtained from the first session were used in the analysis. Given that our facility conducted blood tests every 2 weeks, we considered the data obtained for 2 weeks (about six HD sessions) as one data set.

**Outcomes**

The primary outcome of interest was the development of IDH, defined as any nadir <100 mm Hg if the pre-dialysis SBP was ≥160 mm Hg or any nadir <90 mm Hg if the pre-dialysis SBP was <160 mm Hg (IDH nadir). Pre-dialysis SBP was measured mainly in the dorsal position after a 30 min period. The haemoglobin concentration was calculated using the following formula:

\[ \text{Hb concentration} = \frac{\text{Hb measured}}{1.05} \]

Therefore, under the assumption that the IDWG dilutes the haemoglobin concentration, the assumed haemoglobin concentration were calculated using a mixed-effects logistic regression model. A random intercept was included to account for repeated measures within the subjects, imposing a compound symmetric covariance structure.

This model was adjusted for age, sex, body mass index (BMI), diabetes as the primary cause of end-stage renal disease (ESRD), HD vintage, vascular access, dialysate temperature, interdialytic weight gain (IDWG), ultrafiltration rate, treatment modality, ischaemic heart disease (IHD), use of antihypertensive drugs, use of antihypotensive drugs, use of iron agents, ESA dose, transferrin saturation (TSAT), ferritin level, serum albumin level, and C reactive protein (CRP) level. These variables were based on a priori clinical judgement and existing studies.

Serum albumin and CRP levels were not available at every dialysis session, and thus, the values obtained from the first session were used in the analysis.

Darbepoetin alfa and epoetin beta pegol doses were converted to ESA doses (IU/week) using the following dose conversion ratio: epoetin: darbepoetin alfa:epoetin beta pegol=200:1:1. Furthermore, we used a restricted cubic spline to analyse the relationship between the haemoglobin concentration as a continuous variable and IDH. As recommended, we used four knots located at the 5th, 55th, 65th and 95th haemoglobin concentrations. Two sensitivity analyses were performed to examine the robustness of the association. In sensitivity analysis 1, unadjusted and adjusted ORs with 95% CIs for IDH nadir according to the categories of haemoglobin concentration were calculated using a logistic regression model in the first session (patient-level).

In sensitivity analysis 2, we conducted the same analysis for the association between the assumed haemoglobin concentration and IDH nadir. A previous study showed that each 1 L of ultrafiltration leads to an increase in the haemoglobin concentration of approximately 0.4 g/dL. Therefore, under the assumption that the IDWG dilutes the haemoglobin concentration, the assumed haemoglobin concentration was calculated using the following formula:

**Table 1** ORs for IDH nadir by haemoglobin concentration categories

| Haemoglobin concentration, g/dL | <9.0 | ≥9.0 to <10.0 | ≥10.0 to <11.0 | ≥11.0 to <12.0 | ≥12 |
|---------------------------------|------|---------------|----------------|----------------|-----|
| Unadjusted OR                   | 1.66 (0.67 to 4.13) | 1.11 (0.51 to 2.39) | 1 (reference) | 1.20 (0.63 to 2.31) | 4.31 (2.12 to 8.75) |
| Adjusted OR                     | 0.82 (0.32 to 2.15) | 1.16 (0.56 to 2.39) | 1 (reference) | 1.26 (0.68 to 2.36) | 3.01 (1.50 to 6.07) |

Note: Bold values indicate statistical significance A haemoglobin concentration of ≥10.0 to <11.0 g/dL was set as the reference. ORs were estimated using a mixed effects logistic regression for the association between haemoglobin concentration and IDH nadir adjusted for age, sex, BMI, diabetes as the primary cause of ESRD, haemodialysis vintage, vascular access, dialysate temperature, IDWG, ultrafiltration rate, treatment modality, IHD, use of antihypertensive drugs, use of antihypotensive drugs, use of iron agents, ESA dose, TSAT, ferritin, serum albumin and CRP. IDH nadir is defined as any nadir <100 mm Hg if the pre-dialysis SBP is ≥160 mm Hg or any nadir <90 mm Hg if the pre-dialysis SBP is <160 mm Hg. CRP, C reactive protein; ESA, erythropoietin-stimulating agent; ESRD, end-stage renal disease; IDH, intradialytic hypotension; IDWG, interdialytic weight gain; IHD, ischaemic heart disease; TSAT, transferrin saturation.
Results

Baseline clinicodemographic patient characteristics

A total of 3250 HD sessions of 543 patients were analysed (online supplemental figure 1). Online supplementary table 1 shows the baseline characteristics in the overall cohort and by haemoglobin concentration categories. The median age was 71.0 years, and 58.4% of the patients were male. The primary cause of ESRD was diabetes in 42.2% of the patients, and 89.3% had an arteriovenous fistula (AVF). The median HD vintage was 5.0 years. A higher proportion of the high haemoglobin concentration group had an AVF and used antihypotensive drugs, and that group received a lower ESA dose and had a higher level of serum albumin.

Association between haemoglobin concentration and IDH nadir

Categorical and continuous variable analyses

IDH nadir occurred in 14.3% (465/3250) of all sessions. Table 1 shows the association between the haemoglobin concentration categories and IDH nadir.

With a haemoglobin concentration of ≥10.0 to <11.0 g/dL as reference, the unadjusted ORs for IDH nadir were 1.66 (95% CI, 0.67 to 4.13), 1.11 (95% CI, 0.51 to 2.39), 1.20 (95% CI, 0.63 to 2.31) and 4.31 (95% CI, 2.12 to 8.75) for haemoglobin concentrations of <9.0, ≥9.0 to <10.0, ≥11.0 to <12.0 and ≥12.0 g/dL, respectively. After adjusting for potential confounders, the adjusted ORs for IDH nadir were 0.82 (95% CI, 0.32 to 2.15), 1.16 (95% CI, 0.56 to 2.39), 1.26 (95% CI, 0.68 to 2.36) and 3.01 (95% CI, 1.50 to 6.07), respectively.

Figure 1 shows the association between haemoglobin concentration as a continuous variable and IDH nadir. Restricted cubic spline analysis revealed that a high haemoglobin concentration was also associated with the development of IDH nadir.

Sensitivity analysis

In sensitivity analysis 1, with a haemoglobin concentration of ≥10.0 to <11.0 g/dL as reference, the adjusted ORs for IDH nadir were 1.04 (95% CI, 0.35 to 3.10), 1.10 (95% CI, 0.46 to 2.63), 1.11 (95% CI, 0.53 to 2.33) and 2.00 (95% CI, 0.93 to 4.28) for haemoglobin concentrations of <9.0, ≥9.0 to <10.0, ≥11.0 to <12.0 and ≥12.0 g/dL, respectively (table 2).

Discussion

Although the haemoglobin concentration is a potentially modifiable risk factor for IDH, its association with IDH is still unclear. This study found that a high haemoglobin concentration is associated with IDH, both in categorical and in continuous variable analyses. Similar results regarding these associations were obtained in the sensitivity analyses.

Patient and public involvement

Neither the patients nor the public were involved in the design, conduct, reporting, or dissemination plans of our research.

Association between haemoglobin concentration and IDH nadir.

Note: Restricted cubic spline plots of the ORs for IDH nadir according to haemoglobin concentration. The horizontal grey line corresponds to a normal reference OR of 1.0. Haemoglobin concentration=10.0 g/dL was used as reference in this study. ORs were estimated using mixed effects logistic regression for the association between haemoglobin concentration and IDH nadir adjusted for age, sex, BMI, diabetes as the primary cause of ESRD, haemodialysis vintage, vascular access, dialysate temperature, IDWG, ultrafiltration rate, treatment modality, IHD, use of antihypertensive drugs, use of antihypotensive drugs, use of iron agents, ESA dose, TSAT, ferritin, serum albumin and CRP. IDH nadir is defined as any nadir <100 mm Hg if the pre-dialysis SBP is ≥160 mm Hg or any nadir <90 mm Hg if the pre-dialysis SBP is <160 mm Hg, BMI, body mass index; CRP, C reactive protein; ESA, erythropoietin-stimulating agents; ESRD, end-stage renal disease; IDH, intradialytic hypotension; IDWG, interdialytic weight gain; IHD, ischaemic heart disease; TSAT, transferrin saturation.
Consistent with previous findings that a high haemoglobin concentration is associated with cardiovascular events, the present study also found that a high haemoglobin concentration is associated with the development of IDH. However, in contrast with previous studies, we found that the risk of IDH was relatively lower in patients with a low haemoglobin concentration. This may be related to the amount of extracellular fluid in blood vessels. The haemoglobin concentration was calculated as the amount of haemoglobin relative to the circulating blood volume. It is assumed that the extracellular fluid volume in the blood vessel is relatively low at a high haemoglobin concentration, and the volume can easily decrease due to ultrafiltration, which may lead to the development of IDH.

The clinical implication of our findings is that regulating the haemoglobin concentration may help to reduce the occurrence of IDH. Previous studies have shown that a high haemoglobin concentration improves the quality of life, while a low haemoglobin concentration is a risk factor for developing cardiovascular events. Therefore, no clinical action should be taken to uniformly lower the haemoglobin concentration. However, the treatment and prevention of IDH is an area where there is very little evidence, and in consideration of other risks, it may help them if dialysis physicians and their patients are facing trouble with IDH.

The major strengths of this study are as follows. First, to the best of our knowledge, this study is the first to reveal the association between a high haemoglobin concentration and IDH. Second, the association between the haemoglobin concentration and IDH was consistent across the various sensitivity analyses, indicating the robustness of the results. Third, the haemoglobin concentration is easily modifiable in clinical practice because it is measured routinely and is a main parameter evaluated by dialysis physicians.

However, this study also has several limitations. First, this was a single-centre study in Japan, and thus, the findings have limited generalisability. Particularly, haemoglobin concentrations in other countries are higher than those in Japan due to differences in the timing of measurements. Therefore, the association between a high haemoglobin concentration and the development of IDH may be a more relevant issue in other countries. Second, there were unknown and unmeasured confounding factors. We lacked information on comorbid conditions other than IHD and diabetes. Therefore, our cohort may have included patients with other malignancies and gastrointestinal bleeding. However, the association

### Table 2 ORs for IDH\textsubscript{nadir} by haemoglobin concentration categories in sensitivity analysis 1

| Haemoglobin concentration, g/dL | Unadjusted OR | Adjusted OR |
|--------------------------------|--------------|-------------|
| <9.0                          | 1.81 (0.76 to 4.31) | 1.04 (0.35 to 3.10) |
| ≥9.0 to <10.0                 | 1.07 (0.48 to 2.42) | 1.10 (0.46 to 2.63) |
| ≥10.0 to <11.0                | 1.13 (0.57 to 2.25) | 1.11 (0.53 to 2.33) |
| ≥11.0 to <12.0                | 2.72 (1.39 to 5.33) | 2.00 (0.93 to 4.28) |
| ≥12                           | 1 (Reference)    | 1 (Reference) |

Note: Bold values indicate statistical significance. A haemoglobin concentration of ≥10.0 to <11.0 g/dL was set as the reference. ORs were estimated using a logistic regression for the association between haemoglobin concentration and IDH\textsubscript{nadir} adjusted for age, sex, BMI, diabetes as the primary cause of ESRD, haemodialysis vintage, vascular access, dialysate temperature, IDWG, ultrafiltration rate, treatment modality, IHD, use of antihypertensive drugs, use of antihypotensive drugs, use of iron agents, ESA dose, TSAT, ferritin, serum albumin and CRP. IDH\textsubscript{nadir} is defined as any nadir <100 mm Hg if the pre-dialysis SBP is ≥160 mm Hg or any nadir <90 mm Hg if the pre-dialysis SBP is <160 mm Hg. BMI, body mass index; CRP, C reactive protein; ESA, erythropoietin-stimulating agent; ESRD, end-stage renal disease; IDH, intradialytic hypotension; IDWG, interdialytic weight gain; IHD, ischaemic heart disease; TSAT, transferrin saturation.
between a low haemoglobin concentration and the development of IDH might be overestimated because total circulating blood volume loss is a risk factor for the development of IDH. Third, baseline data were used to define exposure categories in this cohort. The pre-dialysis haemoglobin concentration may vary for each dialysis session.27 However, the robustness of the results was verified by a sensitivity analysis that considered the pre-dialysis haemoglobin concentration. In future studies, it will be necessary to repeatedly measure the haemoglobin concentration during each HD session. Fourth, we defined IDH as IDH nadir in our study.17 The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines define IDH as a decrease of either SBP ≥20 mm Hg or mean arterial pressure ≥10 mm Hg and associated symptoms, such as cramping, headache, lightheadedness, vomiting or chest pain during HD.35 Similarly, the European Best Practice Guidelines (EBPGs) define IDH as a decrease of ≥20 mm Hg in SBP in combination with clinical events and interventions.36 We were not able to measure the patients' subjective symptoms and obtain detailed information on interventions for blood pressure management due to the retrospective observational nature of the study. However, IDH nadir has been suggested to be related to mortality and cardiovascular events in previous studies and is considered to have a satisfactory criteria-related validity.17 Thus, we believe that it is a clinically relevant and reasonable definition.

In conclusion, a high haemoglobin concentration is associated with IDH, and thus, its upper limit should be monitored in patients with IDH.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the ethical review board of Rakuwakai Otowa Hospital Ethics Committee (approval number: Rakuuto-Rin-21-022). Participants gave informed consent to participate in the study before taking part.

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