

# Continuous Versus Intermittent Intravenous Iron Administration In Haemodialysis Patients On Erythropoietin: A Randomised Controlled Study

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## Abstract

**Methods:** This randomised controlled study was designed as a pilot study to compare the efficacy and safety outcomes between a reactive protocol of intermittent bolus intravenous iron administration (RPIB) using Ferrum H boluses (200mg-1000mg) and a proactive protocol of continuous intravenous iron administration (PPCI) using the dialysis heparin pump to co-infuse 10mg Ferrum H per dialysis, in haemodialysis patients in a tertiary teaching Renal Unit with more than 300 dialysis patients

**Results:** The PPCI achieved equivalent measured outcomes to RPIB. Fifty stable haemodialysis patients were randomised at a point of stable Hb, iron stores and erythropoietin (EPO) dose. At the end of six months, the total delivered iron dose was not statistically significantly different, although PPCI tended to deliver more intravenous iron (PPCI  $632.3 \pm 82.7$ mg vs RPIB  $411.5 \pm 571.5$ mg/6months). PPCI (n=24) maintained an achieved Hb no different to RPIB (n=26) (PPCI  $12.0 \pm 1.9$  vs RPIB  $12.1 \pm 1.2$  (SD)). The EPO doses were not statistically significantly different. However the EPO dose in PPCI group therapy fell progressively over the 6 months, resulting in a 12% reduction in median EPO dose, compared to the RPIB group which showed a small progressive rise, but this did not reach statistical significance. Iron parameters were not different between the two groups at baseline or at six months although there was a trend to higher TSAT in participants receiving RPIB therapy, which did not reach statistical significance (p=ns) at the end of six months. No participants had to cease RPIB for iron overload.

**Conclusion:** PPCI therapy successfully maintained achieved Hb and iron parameters while allowing a small progressive reduction in EPO dose, compared to RPIB therapy, without the risk of iron overload. The administration of Ferrum H in the heparin infusion proved safe and no adverse reactions were detected (24 patients, > 1848 dialyses).

## Key Words

Iron infusion, haemodialysis, dialysis, erythropoietin

## Introduction

The major factor in the cause of anaemia in haemodialysis patients is erythropoietin deficiency (1998). Erythropoietin replacement therapy (ERT) corrects anaemia but requires parental iron replacement. Iron deficiency is a common cause of erythropoietin resistance despite standard iron protocols (Nissenson & Strobos, 1999). Intravenous iron is required in the majority of haemodialysis patients receiving ERT (Bailie, Johnson, & Mason, 2000). There are two broad categories of intravenous iron therapy in haemodialysis patients. The current standard therapy is a medical order driven, reactive, bolus intravenous iron administration protocol (Stevens, Stigant, & Levin, 2002; Yee & Besarah, 2002). A more recent trend is to consider a protocol driven; nurse initiated proactive continuous intravenous iron administration protocol (Stevens et al., 2002; Yee & Besarah, 2002). Such continuous iron therapy can

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be administered via the dialysis machine heparin pump, as the doses and volumes are small and compatible with heparin infusion.

There is no current evidence to demonstrate the benefits of a proactive protocol of continuous intravenous iron administration (PPCI), in a nurse initiated protocol delivered via the dialysis heparin pump, compared to standard practice. This randomised controlled study has been initiated to investigate whether PPCI differs from a reactive protocol of intermittent intravenous iron bolus administration (RPIB), in terms of achieved Hb level, EPO dose or iron parameters. A further aim of the current study has been to ensure that PPCI can deliver significant iron doses over time without risk of iron overload.

The heparin infusion pump on the haemodialysis machine provides a convenient method by which to deliver low dose intravenous iron therapy, and was first described in a cohort study in 1997. Granolleras et al. (1997) described a continuous intravenous iron administration protocol for patients on regular haemodialysis, utilising a dose of 10mg mixed in the heparin infusion.

## Methods

### Participants

Participants were recruited from three haemodialysis units within a tertiary teaching Renal Unit with more than 300 dialysis patients. Participant recruitment began in August 1, 2003 and ended December 2003. Fifty patients met the inclusion criteria. Criteria for inclusion included patients on haemodialysis for at least 6 months, who were iron replete, with a stable Hb and stable EPO dose and had no background haematological disorder (Table 1). Participants were (i) aged older than 18 years (ii) able to provide informed consent, (iii) iron replete with a serum Ferritin 100 - 650 ug/L or transferrin

saturation 20 - 50%[4], (iv) receiving Heparin via an infusion pump during haemodialysis, (v) with no previous history of reaction to iron polymatose, and (vi) no concurrent sepsis.

Participants were randomized to either continue the established RPIB protocol or to change to a PPCI iron protocol for 6 months. Pre-study measurements on blood parameters were recorded (Table 2). The standard RPIB protocol relied on 3 monthly iron tests to identify absolute or relative iron deficiency and a medical order for intravenous Ferrum H either as 1.0g Ferrum H I.V. or as 200mg Ferrum H I.V. weekly for 3-5 weeks (Bailie et al., 2000; Johnson & Simons, 2004; Stevens et al., 2002; Yee & Besarah, 2002). Following the approval of the project by the Facility Human Ethics Research Committee, the participants were randomised. The randomisation process involved an independent person choosing a sealed envelope containing a randomisation number. The selected number allocated the participant to either the control or the intervention group.

The participants of the intervention group were randomised to receive 10mg

Ferrum H mixed with heparin loaded into the infusion pump each dialysis. The exact amount of heparin required for the dialysis session was drawn into a 30ml syringe. To the heparin, 0.2 ml of Ferrum H (10mg) was added. One Registered Nurse was responsible for the addition of Ferrum H to the heparin infusion each shift. A 1ml syringe was used to measure the Ferrum H volume. A new drawing needle was used for each 0.2 ml of Ferrum H drawn. The volume of the heparin line of the dialysis circuit was not considered in the volume to be infused.

A variety of haemodialysis machines were used to deliver both the RPIB and PPCI protocols across the three haemodialysis units. This included Fresenius 4008®, Cobe C2® and Cobe C3®, Gambro Gambro AK 90®, Gambro AK 95®, Gambro AK 100® and the Gambro Ultra®. The machines used Gambro® circuit lines except for the Fresenius®, which used Fresenius® circuit lines. All machines were calibrated to infuse heparin via a 30ml syringe.

A medical officer ordered all doses of Ferrum H. Administered doses of Ferrum H were signed by the Registered Nurse on the medication chart.

Table 1. The characteristics of the study population

	RPIB	PPCI	p-value for difference
<b>Numbers</b>	26 (52.0%)	24 (48.0%)	-
<b>Gender</b>			0.57
Male (%)	13 (50%)	13 (54.1%)	
Female (%)	13 (50%)	11 (45.9%)	
<b>Ethnic origin</b>			0.51
Caucasian (%)	20 (76.9%)	18 (75.0%)	
Oriental (%)	1 (3.8%)	1 (4.2%)	
Others (%)	4 (15.4%)	1 (4.2%)	
Not stated (%)	1 (3.8%)	4 (16.7%)	
<b>Main cause of the renal disease</b>			0.37
Glomerunephritis	4 (15.4%)	4 (16.7%)	
Pyelonephritis	1 (3.8%)	0	
Diabetic nephritis	4 (15.4%)	8 (33.3%)	
Others	17 (65.4%)	12 (50.0%)	
<b>Age (years)</b>	57.6	64.1	0.10
<b>Height (cms)</b>	162.0	165.5	0.32
<b>Weight (kgs)</b>	75.5	73.8	0.67

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**Table 2. Pre-study measurements**

	RPIB (n=26)	PPCI (n=24)	p-value for difference
Folate (nmol/L)	1263.9	1180.7	0.72
B12 (pmol/L)	274.2	518.3	0.10
Hb (g/dl)	11.4	12.0	0.18
FERRITIN (ng/ml)	307.2	265.6	0.42
T SAT (%)	29.4	26.1	0.12
Platelet	219.3	221.0	0.92
Haemodialysis frequency (Treatment per week)	3.0	3.0	0.30
Duration of Haemodialysis (hrs)	5.0	5.0	0.71
SBP (mmHg)	148.6	152.8	0.52
DBP (mmHg)	80.9	80.2	0.85
Creatine (umol/L)	801.3	686.6	0.08
Urea (mmol/L)	20.5	22.0	0.31
ERT (mean units/week)	7692.3	8708.3	0.45

Participants randomised to PPCI were monitored with iron indices every 3 months to monitor for iron overload (i.e. a Ferritin >800ug/L and/or transferrin saturation >50%). Haemoglobin level was monitored monthly. Adverse events were tracked by the research nurses monthly and recorded files stored in secure filing cabinet.

### Statistical analysis

Data are presented as means. Changes over time and by method in mean Hb, ferritin or transferrin saturation levels were considered using the two-way repeated measures analysis of variance models, executed using SPSS version 10.0. Within group comparisons were made by repeated measures analysis of variance and paired t-test methods. The conventional 95% significance level was chosen (p<0.05).

### Results

No adverse reactions were detected in the PPCI iron group of 24 participants and more than 1848 dialysis episodes. However, one participant withdrew from the study after two weeks complaining of itching during dialysis. This participant had received intravenous Ferrum H previously without any reported adverse events. The participant also had an elevated serum phosphate level

at the time. Despite discussion with the participant's medical consultant, participant and the research staff, the participant withdrew from the study.

During the study period, the mean iron dosage used in the PPCI group was 632.3±82.7mg/6months while the RPIB group received 411.5±571.5mg/6months. This achieved the aim of continuous therapy in delivering higher overall doses of intravenous iron therapy. The analysis failed to detect a statistically significant difference, possibly because of the low numbers and the variability in RPIB dosage (unpaired t test, p=0.067).

The Hb was equally well maintained in the two groups Figure 1, compared to starting Hb (NS, p=0.18) with the Hb concentration increasing by a mean of 0.41g/dl in the PPCI group (Table 3).

There was no statistically significant difference between the two groups in terms of the achieved Ferritin levels and the TSAT levels at 6 months. At most time points the RPIB group had higher measured iron parameters than the PPCI group. No participants achieved TSAT or Ferritin elevated above the higher limit of the recommended therapeutic range (Table 3).

While the mean ERT dose for the two protocols was not significantly different at any timepoint, there was a trend for the mean EPO dosage to fall progressively in the PPCI group during the study while there was a trend for the EPO dose to rise progressively in the intermittent bolus RPIB group (Figure 2).

### Discussion

Continuous heparization and IV iron can be delivered together without pharmacological incompatibility. The six months experience, without attributable adverse incidents reported here, suggest that this method could become an ideal way to deliver IV iron during haemodialysis. The protocol provides a simple and cost effective method, compared to current unit practices.

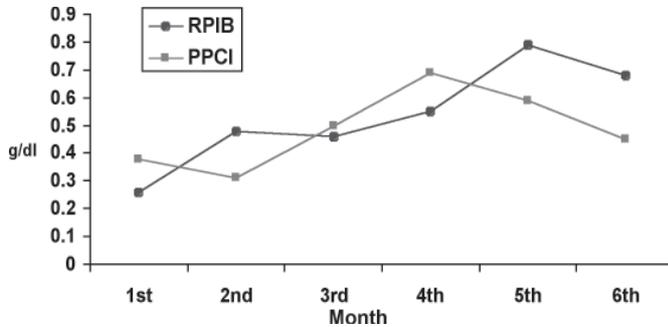
A proactive continuous intravenous iron protocol has certain advantages in clinical therapy. It can deliver a higher iron dose more evenly over time, without resulting in iron overload, and it can ensure optimal EPO efficiency, achieved

**Table 3. Comparison of mean of change of outcomes during 6-month study period**

	RPIB (n=26)	PPCI (n=24)	p-value for difference
Hb (g/dl)	0.54	0.41	0.76, NS
Creatine (umol/L)	22.79	23.82	0.97, NS
Urea (mmol/L)	1.10	-0.04	0.33, NS
ERT (units)	97.44	0	0.81, NS
Ferritin (ng/ml)	32.42	16.06	0.74, NS
T SAT (%)	-0.23	4.89	0.09, NS

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Fig 1. Changes in haemoglobin levels during the study period. The Hb was equally well maintained in the two groups



Hb and measured iron parameters. This randomised controlled study has demonstrated that a proactive, nurse initiated, continuous iron protocol does not differ significantly from a standard, reactive bolus medical order driven protocols in widespread use.

This PPCI protocol requires less medical time and ensures that no patient will receive sub optimal iron therapy. Comparing the costs for ERT (data not presented), there was a saving for ERT in the PPCI iron therapy arm, compared to the RPIB group of \$16,432.90 for the 6-month period. Prior to the study the average use of ERT for the PPCI group was 8708.3 units, which is the same as the mean usage during the 6 months study time. Whilst, the RPIB group increase the usage of ERT from mean of 7692.3 units to 7859.0 units. However,

the mean change of use of ERT was not found to be significantly different between the two groups.

Beside possible savings in the cost of ERT, this protocol eliminates the need for the supply and ongoing maintenance of electronic infusion pumps, as well as the nursing time in locating, setting up and taking down of the separate infusion. The most significant potential saving in nursing time is the reduced need for close vital sign observation of the patient during administration of large bolus iron therapy. Large doses of intravenous iron are also more likely to precipitate hypotension, myalgia, and arthralgia, requiring further intervention (CARI, 2003; Kock & Stein, 1997; MIMS, 2004).

A subsequent study, using a PPCI protocol administering 100mg Ferrum

H monthly, will be undertaken in a larger number of participants, to better document the potential cost savings involved with proactive continuous intravenous iron therapy.

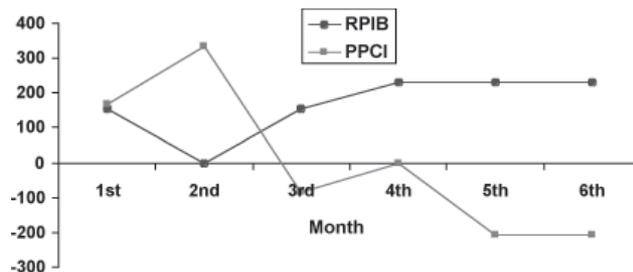
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## References

- Auerback, M., Winchester, J., & Wahab, A. e. a. (1998). A randomized trial of three Iron Dextran infusion methods for anaemia in EPO treated dialysis patients. *American Journal of Kidney Diseases*, 31(1), 81-86.
- Bailie, G., Johnson, C., & Mason, N. (2000). Parenteral iron use in the management of anaemia in end-stage renal disease patients. *American Journal of Kidney Diseases*, 35(1), 1-12.
- CARI. (2003, 27/4/2005). *The Caring for Australians with Renal Impairment (CARI) Guidelines*, from <http://www.kidney.org.au/cari/drafts/iron.jtm>
- Granolleras, C., Zein, A., Oules, R., Branger, B., Fourcade, J., & Shaldon, S. (1997). Continuous administration of intravenous iron during haemodialysis. *Nephrology Dialysis Transplantation*, 12, 1007 - 1008.
- Johnson, C., & Simons, W. (2004). *Dialysis of Drugs*. North Ryde NSW: Williams & Williams.
- Kock, K., & Stein, G. (1997). *Pathogenic & therapeutic aspects of chronic renal failure*. New York: Marcel Dekker Inc.
- MIMS. (2004). *MIMS Annual* (XXXX ed.). Singapore: Tien Wuh Press.
- Nissenson, A., & Strobos, J. (1999). Iron deficiency in patients with renal failure. *Kid Int, Supplement* 69, S18-21.
- Stevens, L., Stigant, C., & Levin, A. (2002). Should haemoglobin be normalized in patients with chronic kidney disease? *Seminar in Dialysis*, 15(1), 8-13.
- Yee, J., & Besarab, A. (2002). Iron sucrose: The oldest iron therapy becomes new. *American Journal of Kidney Diseases*, 40(6), 1111-1120.

Fig. 2 Changes in ERT dosage (units/week) during the study period. While the mean ERT dose for the two protocols was not significantly different at any timepoint, there was a trend for the mean



EPO dosage to fall progressively in the PPCI group during the study while there was a trend for the EPO dose to rise progressively in the intermittent bolus RPIB group.