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COCHRANE COMMENTARIES

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Parenteral versus oral iron therapy for adults and children with chronic kidney disease

What is this review about?

The use of intravenous compared with oral iron supplements in patients with chronic kidney disease (CKD).

What are the findings?

Ferritin (Figure 1: mean difference $243 \mu g/L$) and transferrin saturation levels (mean difference 10%) were significantly increased by intravenous (IV) iron compared with oral iron, while haemoglobin levels were slightly increased (mean difference 0.9 g/dl). The required dose of erythropoiesis stimulating agents (ESA) was significantly reduced in dialysis patients receiving IV iron compared with oral iron (Figure 2). Any change in ESA dose could not be assessed in nondialysis patients due to lack of trial data. All-cause mortality, cardiovascular mortality, quality of life and patients' adherence to oral iron did not differ significantly but were reported in few studies. Gastrointestinal adverse effects were significantly more common with oral iron while hypotensive and allergic reactions were significantly more common with IV iron.

What are the findings based on?

Twenty eight trials (2098 patients) compared IV with oral iron therapy. Seventeen trials included only patients on haemodialysis or peritoneal dialysis. Nine trials included only non-dialysis patients, one trial included both dialysis and non-dialysis patients and one trial included only patients immediately post- transplant. Only one study enrolled children. The duration of follow up varied from 35 days to 26 months. The most common agents used were IV iron sucrose and oral ferrous sulphate. Nineteen trials included patients on ESAs. There was considerable heterogeneity in all analyses. Heterogeneity remained largely unexplained despite extensive investigation using multiple subgroup analyses, but was likely to be related to the large variation in the relative doses of IV and oral iron used across the studies.

Risk of bias assessment showed that randomization sequence generation and allocation concealment were adequately reported in 12 and six trials respectively. Although no trials reported blinding, all studies were considered at low risk of performance and reporting bias as the

	IV	iron		Oral iron				Mean Difference	Mean Difference
Study or Subgroup	Mean [ug/L]	SD [ug/L]	Total	Mean [ug/L]	SD [ug/L]	Total	Weight	IV, Random, 95% CI [ug/L]	IV, Random, 95% CI [ug/L]
Svara 1996 HD	166	123	29	109	114	28	4.6%	57.00 [-4.54, 118.54]	
Li 2008 HD	495.7	315.2	70	400.3	264.1	66	4.2%	95.40 [-2.13, 192.93]	
Michael 2007 HD	80	147	33	-31	130	27	4.5%	111.00 [40.86, 181.14]	
Leehey 2005 CKD	132	162	24	19	162	24	4.3%	113.00 [21.34, 204.66]	
Warady 2002 HD	259.1	163.1	17	122	118.8	18	4.2%	137.10 [42.11, 232.09]	
Aggarwal 2003 CKD	266.98	58.84	20	104.35	25.28	20	4.8%	162.63 [134.56, 190.70]	-
Fudin 1998 HD	393.5	249.3	20	229.7	113.6	10	3.8%	163.80 [33.82, 293.78]	
Li 2008 PD	466.7	85.3	26	299.4	83.2	20	4.7%	167.30 [118.26, 216.34]	-
Agarwal 2006 CKD	232	160.8	36	55.9	236.2	39	4.3%	176.10 [85.25, 266.95]	
Van Wyck 2005 CKD	323	178.5	72	132	90.31	72	4.7%	191.00 [144.79, 237.21]	-
Lye 2000 HD	432	288	30	231	204	30	3.9%	201.00 [74.71, 327.29]	
Wang 2003 HD	496	306	21	279	206	22	3.5%	217.00 [60.35, 373.65]	
Broumand 1998 HD	779	205	9	546.5	139	8	3.4%	232.50 [67.53, 397.47]	
Souza 1997 HD	245	133	8	2.3	77.2	11	4.2%	242.70 [139.86, 345.54]	
McMahon 2009 CKD	412	206	39	153	88	38	4.5%	259.00 [188.55, 329.45]	
Macdougall 1999 HD,PD	432	202	41	140	91	35	4.5%	292.00 [223.21, 360.79]	
Charytan 2005 CKD	288	150	39	-5.1	151	44	4.6%	293.10 [228.24, 357.96]	-
Hussain 1998 HD	671	388	10	367	238	10	2.1%	304.00 [21.88, 586.12]	
Provenzano 2009 HD	601.79	282.95	114	289.3	165.76	116	4.6%	312.49 [252.43, 372.55]	-
Macdougall 1996 HD,PD,CKD	490	276	9	165	95	11	3.1%	325.00 [136.15, 513.85]	
Erten 1998 HD	573	246.7	26	247.4	187.7	22	3.9%	325.60 [202.54, 448.66]	
Spinowitz 2008 CKD	555.7	320	228	160.8	161	76	4.6%	394.90 [339.80, 450.00]	-
Kotaki 1997 HD	750	147	15	255	64	16	4.4%	495.00 [414.27, 575.73]	-
Fishbane 1995 HD	753.9	135	20	157.3	87	32	4.6%	596.60 [530.20, 663.00]	-
Total (95% CI)			956			795	100.0%	243.25 [188.74, 297.75]	♦
Heterogeneity: Tau ² = 15848.34; Chi ² = 303.54, df = 23 (P < 0.00001); l ² = 92%									
Test for overall effect: Z = 8.75 (P	Favours oral iron Favours IV iron								

Fig. 1 End of treatment or change in ferritin levels in patients with CKD treated with IV or oral iron.

	Г	0	Oral iron			Std. Mean Difference	Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Li 2008 HD	4,500	1,049	70	6,140	1,014	66	12.8%	-1.58 [-1.97, -1.19]	-
Fishbane 1995 HD	4,050	2,455	20	7,563	2,138	32	11.1%	-1.53 [-2.17, -0.89]	
Li 2008 PD	6,100	1,043	26	7,635	1,024	26	11.3%	-1.46 [-2.08, -0.85]	
Hussain 1998 HD	3,400	1,356	10	4,600	1,356	10	9.0%	-0.85 [-1.77, 0.08]	
Warady 2002 HD	-76.3	104.7	17	-30.9	77.7	18	10.8%	-0.48 [-1.16, 0.19]	
Macdougall 1996 HD,PD,CKD	1,202	229	12	1,294	314	13	9.9%	-0.32 [-1.11, 0.47]	
Macdougall 1999 HD,PD	74	36	41	84	53	35	12.4%	-0.22 [-0.67, 0.23]	
Michael 2007 HD	-28.4	103.6	33	-12.6	79.7	27	12.0%	-0.17 [-0.68, 0.34]	
Kotaki 1997 HD	3,760	1,762	15	4,025	2,168	16	10.6%	-0.13 [-0.84, 0.58]	
Total (95% CI)			244			243	100.0%	-0.76 [-1.22, -0.30]	•
Heterogeneity: Tau ² = 0.39; Chi ² = 42.96, df = 8 (P < 0.00001); l ² = 81%									-4 -2 0 2 4
Test for overall effect. $Z = 3.25$ (P	= 0.001)							Favours IV iron Favours oral iron

Fig. 2 End of treatment or change in ESA dose in dialysis patients treated with IV or oral iron.

primary outcome was laboratory based and unlikely to be influenced by lack of blinding. Reporting of outcome data was complete in 12 studies and 12 studies reported all relevant outcomes. In particular only 50% trials reported on adverse effects. Twelve trials reported receiving support from pharmacological sponsors.

Implications for practice

• Compared with oral iron, IV iron results in higher levels of ferritin and transferrin saturation with a small increase in haemoglobin

• IV iron results in lower doses of ESA compared with oral iron therapy in dialysis patients. Data are not available for non-dialysis patients.

• IV iron is associated with a lower risk of gastrointestinal adverse effects but a higher risk of allergic and hypotensive reactions.

• Study data are inadequate to determine whether mortality and quality of life differ with IV compared with oral iron supplements.

Clinical perspective

This review supports the current use of IV iron in-centre haemodialysis patients to increase iron stores and probably reduce ESA dose and associated cost although there are limited data on all-cause mortality, cardiovascular mortality and morbidity, adverse effects and quality of life. However the trials do not provide sufficient evidence to determine if the benefits exceed the harms in patients with CKD who are receiving peritoneal dialysis or who are not yet requiring dialysis. Further large trials comparing IV with oral iron in these patient groups are required to assess patient-centred outcomes, ESA dose as well as laboratory outcomes to determine if the benefits of IV therapy outweigh the disadvantages including additional clinic visits for treatment.

Citation

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