

Uses and adverse effects of Erythropoietin

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Dear Jonathan,

Please would you see this pleasant 45 year old man who is a Jehovah's witness.

His Hb is 12.0g/dl.

He has recurrent GI stromal tumour in his abdomen.

I plan to remove the tumour surgically.

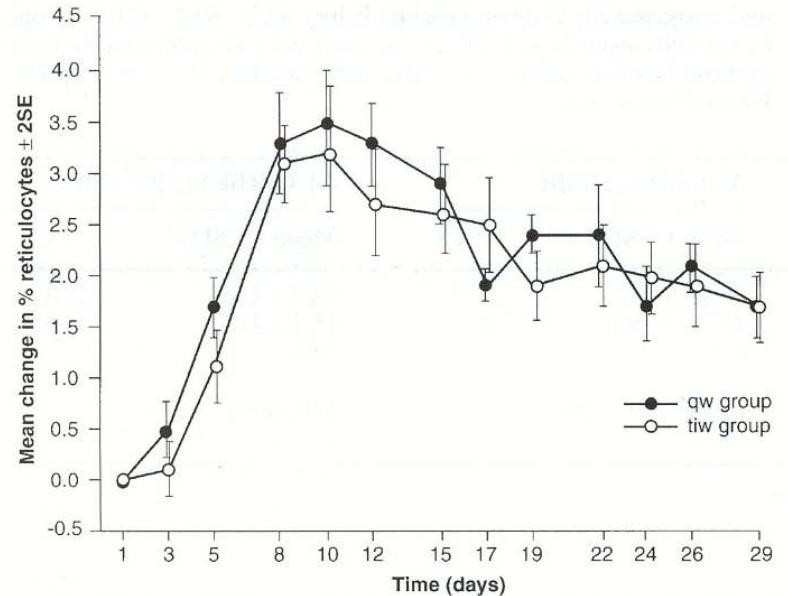
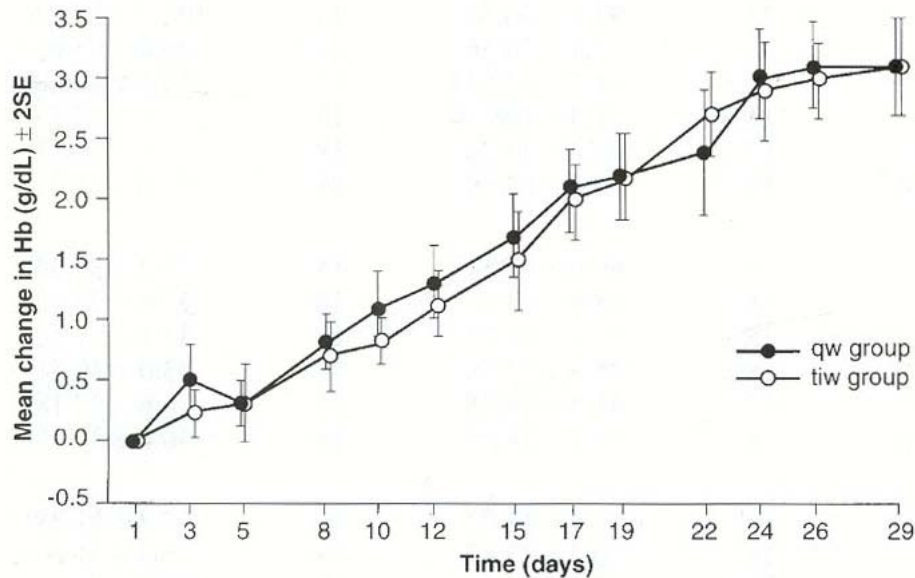
I would be grateful for your advice.

Yours sincerely

Mr Haveago

Effect of Epo in healthy volunteers

Cheung et al Eur J Clin Pharmacol 2001;57:411-8



Hip and Knee surgery: Epo day -10 to +5
Faris et al. J Bone Joint Surgery 1996;78-A:62-72

Treatment group	n	% transfused	Mean units transfused
Epo 300 IU/Kg/day	54	17%	0.37
Epo 100 IU/Kg/day	64	25%	0.58
Placebo	67	54%	1.42

Epo 300 iu/kg/day x 15 days = Eu 3150

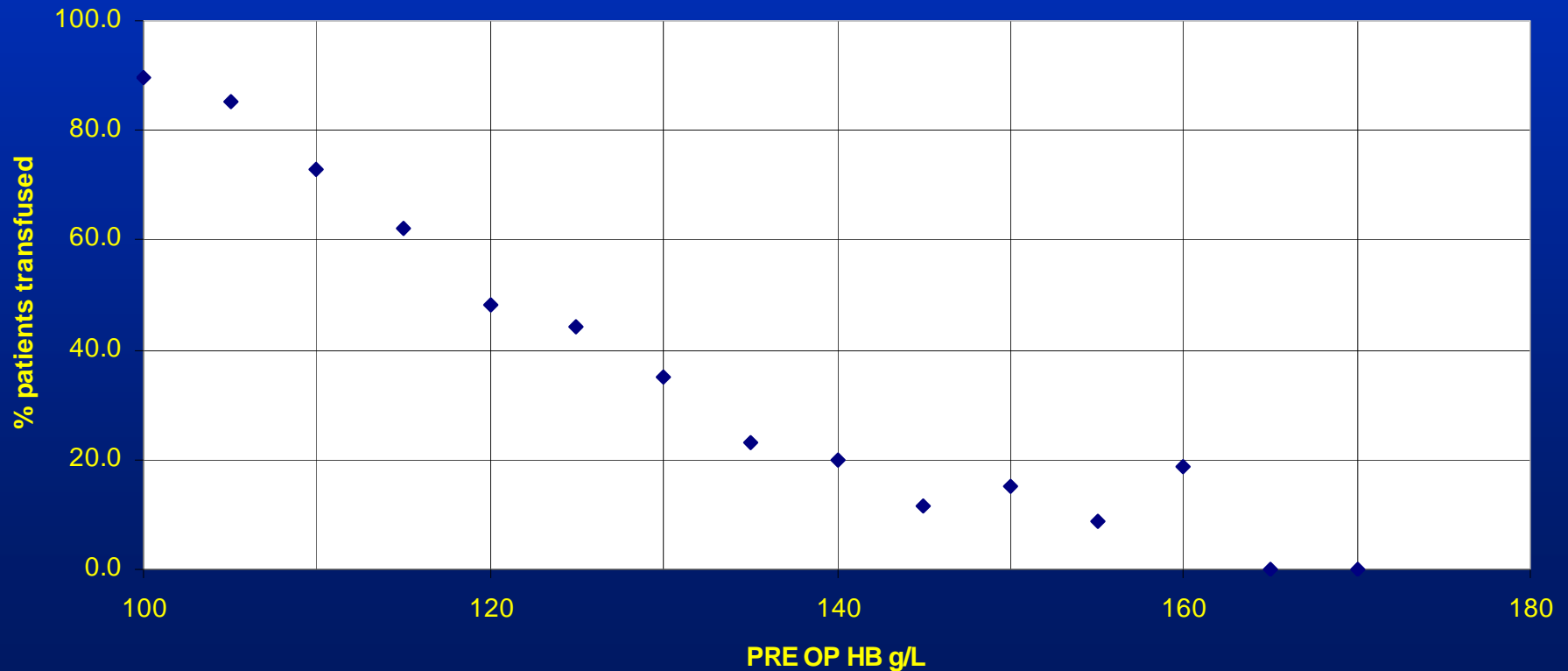
Epo 100 iu/kg/day x 15 days = Eu 1050

One unit red cells = Eu 220

THR at Freeman Hospital:

Pre-op Hb versus likelihood of transfusion

% TRANSFUSED PTS VERSUS PRE-OP hb



Karkouti et al.

Can J Anaesth 2005, 52: 362-8

1. Only 2-3% of major joint replacement patients in N America receive pre-operative Epo

Reasons : Cost and inconvenience

2. Targeted pre-op Epo for 2-3 weeks can reduce transfusion requirements and is economically more attractive.

Average 76000 iu epo ~ Euro 750

Local protocol

Selection of patients:

- Religious objections to transfusion
- Age Younger
- Likely survival Long term
- Likely need for transfusion High (>30%)

Local protocol

- $15 - \text{Hb in g/dl} = \text{number of weeks treatment}$
- Use once weekly epo or darbepoietin
- Monitor weekly
- Give oral iron or iv iron
- Eg: Hb 12g/dl, = 3 weeks Epo = Euro 750

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Cancer, Hb and response to DXT

Grogan et al. Cancer 1999; 86:1528-36

605 women with cervical cancer from 7 centres

Pre-treatment Hb does not correlate with outcome

Hb *during* DXT correlates with outcome

Anaemic patients transfused prior to DXT did as well as non-anaemic patients

Patients who became anaemic during treatment did as badly as those anaemic and not transfused

But see : Santin et al Gynecol Obstet Invest. 2003;56:28-34.

Epo in Cancer

Many prospective randomised studies of short term outcome

- Improved Hb
- Reduced transfusion rates
- Improved Quality of life (QoL)

Several retrospective trials looking at long term outcome

- Improved response to treatment and survival compared to historical controls

Erythropoietin in Cancer

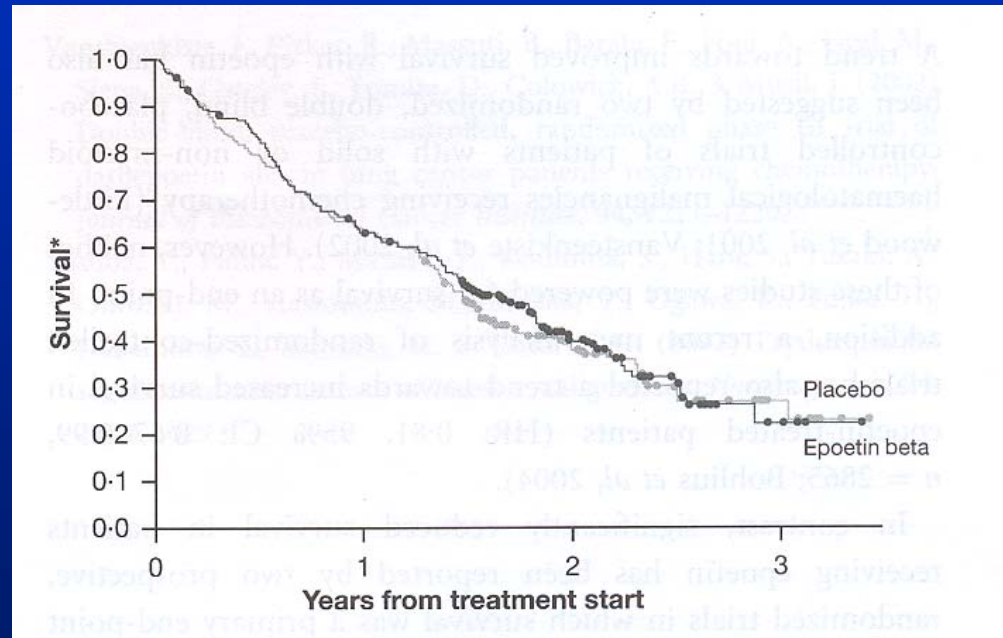
Prospective randomised trials

1. Osterborg *et al* Myeloma and NHL *B J Haem.* 2005; 129: 206-9
2. Littlewood *et al* Haem & non-haem cancer *J Clin Oncol* 2001; 19: 2865-74

Osterborg et al. BJHaem. 2005; 129: 206-9

Myeloma and NHL

Epo x 16 weeks or placebo



Erythropoietin in Cancer

Prospective randomised trials with survival as an outcome

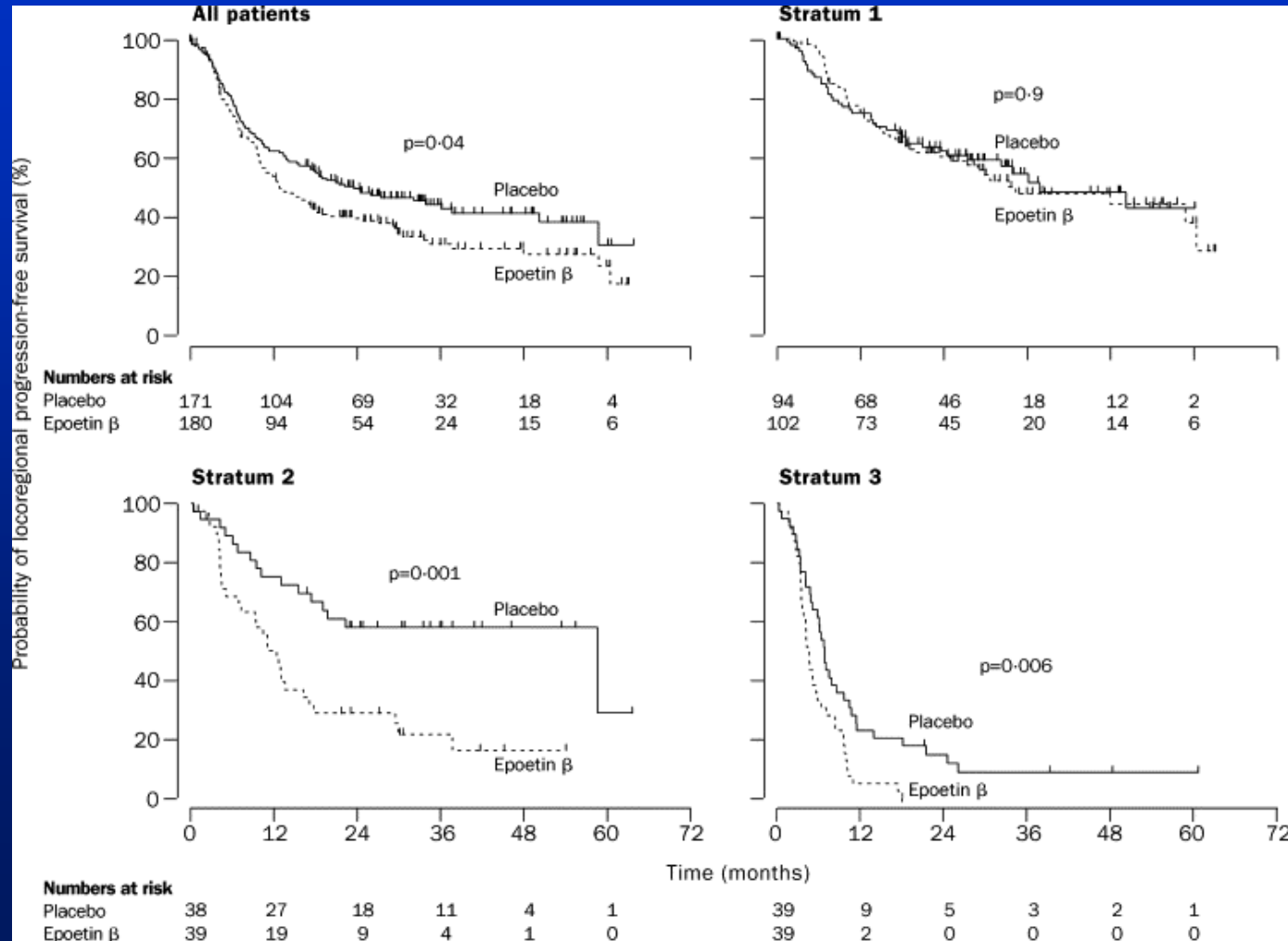
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| 1. Osterborg <i>et al</i> | Myeloma and NHL | <i>B J Haem.</i> 2005; 129: 206-9 |
| 2. Littlewood <i>et al</i> | Haem & non-haem cancer | <i>J Clin Oncol</i> 2001; 19: 2865-74 |
| 3. Henke <i>et al.</i> | Head and neck cancer | <i>Lancet</i> 2003; 362: 1255-60 |
| 4. Leyland-Jones | Breast cancer | <i>J Clin Oncol</i> 2005; 23: 5960-72 |
| 5. DAHANCA | Head and neck cancer | Available at www.DAHANCA.dk |
| 6. GOG-191 | Cervical cancer | <i>Gynecologic Oncology</i> ; 108: 317-25 |
| 7. Prepare study | Breast Cancer | FDA notified of results |

Henke et al. Lancet 2003; 362; 1255-60.

stratum 1: Surgical excision + DXT

stratum 2: Incomplete surgical excision + DXT

stratum 3: DXT alone



“Breast cancer trial with erythropoietin terminated unexpectedly”

Leyland-Jones B Lancet Oncology 2003; 4:459-460.

- Trial closed early
- Poorer outcome in treatment arm
- Possible imbalance in randomisation

Best trial of Epo in Ca breast

Leyland-Jones et al. J Clin Oncol 2005; 25: 5960-72

Subjects: 939 patients stage 4 disease, first line chemotherapy

Intervention: Epo or placebo to keep Hb at 12-14g/dl

Primary outcome : Overall survival at 12 months

Result: 71% vs 76 % in favour of placebo. $P = 0.01$

Primary cause of death	Placebo		Epo
Disease progression	22%	vs	27 %
Chemo toxicity	0.2%	vs	1.7%
Thrombo-embolism	0.6%	vs	1.3%

DAHANCA 10 trial

- 484 patients with Head and neck cancer
- Radiation treatment
- Randomised to Epo (darbopoietin) or placebo
- Primary outcome was 'loco-regional failure'
- Epo arm had 10% higher failure. $p = 0.01$

FDA warning Jan 3rd 2008

GOG-191 study in Ca Cervix

(Thomas et al. Gynecologic Oncology; 108: 317-25)

Prepare study in Breast Ca

‘Both the PREPARE study in breast cancer and the GOG-191 study in cervical cancer showed higher rates of death and or tumor progression in patients who received an ESA compared to patients who did not receive an ESA.’

‘The GOG-191 study stopped enrolling patients because of a higher rate of potentially life-threatening blood clots occurring in the patients who received an ESA.’

Why might Epo be detrimental to survival?

- Epo receptors have been reportedly found in many tissues
- Epo is anti apoptotic
 - I.e. It reduces cell death
 - Eg. Epo reduces ischaemic brain damage in animals and ?in man
 - Eg. Epo reduces cardiac myocyte death in animals and ? in man
- Some cancers appear to be responsive to Epo in vitro
- Blood vessels feeding cancers may be Epo sensitive

Epo and cancer

Can improve Hb and Qol, and reduce transfusion

Has detrimental effects on some tumours

Breast, Squamous head and neck, Cervical

How do we explain the beneficial effect of high Hb on DXT in Cervical cancer?

?? Due to higher endogenous Epo in anaemic patients having DXT

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Does Epo increase likelihood of thrombosis?

Increased incidence of thrombotic events in renal patients on Epo with Hb > 12g/dl

Is thrombosis related to the effect of a higher Hb?

Or to direct effects of Epo ?

Epo and thrombosis

ITU study: Corwin et al NEJM 2007, 357; 965

Increased thrombosis in Epo arm despite no benefit to Hb

Numerous trials on presurgical Epo showed no convincing evidence of increased thrombosis

Conclusion

There is an increase in thrombosis with higher HB
There may be a direct effect of Epo on thrombosis.
Appropriate prophylaxis is recommended

ITU study Corwin et al
NEJM 2007, 357; 965

1460 patients admitted to ITU, 54% trauma
30,000u Epo weekly for 3 weeks

30 day mortality

	Epo	Placebo	
All pts	8.5%	11.4%	
Trauma	3.5%	6.6%	HR 0.52 (.27-.99)

Conclusion

1. Epo can reduce peri-operative transfusion requirements
2. Cost and inconvenience remain a barrier to widespread use
3. Should not be used routinely for non-haematological cancer
4. Beware increased risk of thrombosis
5. Cardio/neuro protection may be more interesting than erythropoietic effects eg see study by Corwin et al

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The patient received Epo,

had a good Hb response,

survived surgery, lowest Hb =12.8g/dl

remains alive and well.

Thank you for your attention