

FLUCTUATIONS IN HAEMOGLOBIN LEVELS IN HEMODIALYSIS PATIENTS RECEIVING ERYTHROPOIETIN-STIMULATING AGENTS: FACTORS ASSOCIATED AND CLINICAL CONSEQUENCES

Principal Investigator:

Dr Filippo Aucella, Director, Department of Nephrology and Dialysis, “Casa Sollievo della Sofferenza” Hospital, 71013 San Giovanni Rotondo, (FG) Italy

Co-investigators:

Prof. Loreto Gesualdo, Nephrology Unit, University of Foggia, Italy

Prof. Carlo Manno, DETO, Nephrology Unit, University of Bari, Italy

Dr. Antonio Santoro, Nephrology and Dialysis Unit, Malpighi Hospital, Bologna, Italy

Prof. Mario Bonomini Mario, Nephrology Unit, University of Chieti, Italy

Dr. Salvatore Di Paolo, Nephrology and Dialysis Unit, Barletta, Italy

Dr. Luigi Morrone, Nephrology and Dialysis Unit, Benevento, Italy

Statistical Analysis:

Dr.ssa Diletta Torres, DETO, Nephrology Unit, University of Bari, Italy

Group of Evidence Based Nephrology (EBM) - SIN

Key words: erythropoietin, anemia, haemoglobin cycling, haemodialysis.

Background: Haemoglobin (Hb) cycling is a commonly occurring phenomenon in haemodialysis patients receiving erythropoietin-stimulating agents (ESA). The Hb cycling is defined as a series of measured haemoglobin levels in an individual patient that oscillate over time, in which levels decrease or increase over time. The oscillation has arbitrarily been characterized as >1.5 g/dl from an equilibrium point with reversion back to the same point over a period of at least eight weeks (1). More than 90% of stable haemodialysis patients demonstrate at least one cycle (2).

The etiology is supposed to be multifactorial; factors associated with fluctuations in haemoglobin are changes in ESA dose, different type of ESA agents, changes or initiation of intravenous iron and hospitalization. Thus, other less well-characterized factors may also influence haemoglobin cycling including nutrition status, inflammation status and/or osteodistrophy. This phenomenon may complicate the clinical management of haemodialysis patients, with many economic resources expended trying to reach and maintain the target levels recommended by Guidelines.

Recent studies suggest that haemoglobin cycling is closely associated with frequent ESA dose changes, and it is also associated with hospitalization and iron treatment practices (3).

In a retrospective analysis we analysed data recorded in the SIGANA (Sistema Informatizzato Globale per l'Assistenza Nefrologica Avanzata) database including 21 Italian haemodialysis centres and 1526 patients; all patients treated with ESAs with at least 6 Hb measurements were enrolled. Based on Fishbane's definition of cycling (>1.5 g/dl in Hb levels in 8 weeks of follow-up), this was found in about 62% of patients.

The phenomenon of haemoglobin cycling may have an adverse impact on patients outcome (4-5) and determines a continuous fluctuation in oxygen delivery to vital organs. Repeated episodes of relative ischemia may result in organ damage. Some authors demonstrated an association between haemoglobin variability and all-cause mortality among chronic dialysis patients (6-8). The causal nature of this association has been difficult to ascertain because of potential time-dependent confounding, moreover most of the published studies on this topic are retrospective cohort studies requiring complicated statistical analysis to obtain unbiased results (9).

This is the first prospective cohort study designed in a wide Italian population of dialysis patients.

The purposes of the present study are:

- to describe the haemoglobin cycling, according to Fishbane (defined as cycle with amplitude > 1.5 mg/dl and lasting more than 8 weeks) (2), and to evaluate haemoglobin cycling and time out of target on adverse outcome in a wide population of Italian haemodialysis patients;
- to identify etiologic factors;
- to verify differences between different ESA agents and different way of administration;
- to suggest good clinical practice in administering ESA agents in haemodialysis patients;
- to evaluate the impact of haemoglobin cycling on all-cause mortality, cardiovascular mortality, hospitalization and quality of life (SF-36 adapted to dialysis patients);
- costs/efficacy analysis of ESA therapy and haemoglobin cycling.

Methods:

Study design: prospective cohort study.

Patients: we will enrol all haemodialysis patients aged 18-80 years in haemodialysis from at least 6 months, treated in the participating units. All patients will be treated according to the same Guidelines (10-12) to achieve and maintain the suggested target haemoglobin level (11-12 g/dl).

The following data will be collected:

- gender, date of birth, baseline nephropathy (EDTA code), comorbidity (Charlson index);
- type of haemodialysis;
- number of hospitalization, day of hospitalization, causes;
- haemoglobin levels (every 2 weeks);
- iron, transferrin saturation, iron deposits levels (every 3 months);
- calcium, phosphorus (monthly) and parathyroid hormone (every 6 months);
- albumin (every 6 months);
- Kt/v (monthly);
- C reactive protein (every 3 months);
- ESA type, dose, way of administration, change of dose during the follow-up;
- Iron therapy (type, dose and way of administration);
- other concomitant therapies.

Outcomes:**Primary outcome:**

- all-cause mortality (defined by ICD9 codes);

Secondary outcomes:

- fluctuation patterns will be compared between different type of ESA agents and different schedule of administration up to month 12
- cardiovascular mortality (defined by ICD9);
- hospitalizations (causes and duration);
- quality of life (SF-36 adapted questionnaire).

Subgroup analyses:- diabetic patients;

- resistant ESA patients; (patients with adequate iron stores that remain anemic when receiving doses higher than 30.000 U/week (400-600 U/kg/week for a medium weight of 50-70 kg) or 150 mcg/week can be conventionally considered resistant)- patients with and without concomitant therapies.

Power of the study:

We test the null hypothesis that the hazard rate, which is assumed to be constant across all study intervals, is identical in the two groups (Hb cycling versus no-Hb cycling), in the ESA treated patients.

Study design. This hypothesis will be tested in a study in which subjects are entered and then followed until either (a) the terminal event occurs, or (b) they drop out of the study, or (c) the study ends and the patient is censored while still being actively followed.

The study design calls for an accrual period of 3 months followed by a 12 months period for the Hb cycling observation and a follow-up period of 36 months to determine survival rate.

Effect size. Computation of power is based on a hazard ratio for survival of 1.30 in cycling and non cycling patients, which is assumed to be constant across intervals. Specifically, this is equivalent to median survival times of 46,8 months for the no-cycling group versus 36,0 months for the cycling group. It is also equivalent to a cumulative survival at 36 months of 0,587 for the non cycling group vs 0,50 for the cycling group. This effect was selected as both clinically relevant and reasonable, in the sense that an effect of this magnitude could be anticipated in this field of research. **Sample size.** Subjects will be entered into the study at the rate of 104 per months for 12 months yielding a total of 1250 subjects. Expectedly, 500 (40%) will be in the no cycling group and 750 (60%) in the cycling group.

Attrition. The computation assumes an attrition rate of 0,01 per month. This means that 1% of the subjects who enter (for example) the second month of the study will drop out of the study during that month. This attrition (or drop-out) rate is separate from the censoring of subjects that takes place when the study ends. Subjects changing the type of ESA during the study will be dropped from the statistical analysis because they introduce a bias in Hb stability; the estimated number should not exceed 5%.

Alpha and Tails. The criterion for significance (alpha) has been set at 0,05. The test is 2-tailed, which means that an effect in either direction will be interpreted.

Power. For this study design, sample size, attrition rate, alpha and tails, and the population effect size described above, the study will have power of 80 % to yield a statistically significant result.

Study phases:

- 1) Enrolment: 3 months
 - 2) Observation of 12 months to identify Hb cycling population
 - 2) Follow-up: 36 months to determine survival rate;
- For a total duration of 51 months.

Expected results:

- definition of frequency and duration of haemoglobin cycling;
- impact of haemoglobin cycling on morbidity, all-cause and cardiovascular mortality.
- different pattern of cycling in different ESA types and administration ways.

Budget

| <i>Name</i> | <i>Subtotal</i> |
|-------------------------------|-----------------|
| Clinical Monitor salary | 90.000,00 |
| Monitor trips | 40.000,00 |
| Ethical Committee | 15.000,00 |
| Investigator meeting (no. 3) | 60.000,00 |
| Data management | 80.000,00 |
| Newletters (every six months) | 20.000,00 |
| Statistical analysis | 50.000,00 |
| Software Updates | 50.000,00 |

| | |
|--------------|-------------------------|
| TOTAL | Euros 415.000,00 |
|--------------|-------------------------|

REFERENCES

1. Berns JS, Elzein H, Lynn RI, Fishbane S, Meisels IS, DeOreo PB. Hemoglobin variability in epoetin-treated hemodialysis patients. *Kidney Int* 2003; 64:1514–1521.
2. S. Fishbane, J S. Berns Evidence and implications of haemoglobin cycling in anaemia management *Nephrology Dialysis Transplantation* 2007; 22: 2129-2132.
3. Fishbane S, Berns JS. Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. *Kidney Int* 2005; 68:1337–1343.
4. Gilbertson DT, Ebben JP, Foley RN, et al. Hemoglobin level variability: associations with mortality. *Clin J Am Soc Nephrol* 2008; 3: 133-8.
5. Ebben JP, Gilbertson DT, Foley RN, Collins AJ. Hemoglobin level variability: associations with comorbidity, intercurrent events, and hospitalizations. *Clin J Am Soc Nephrol* 2006; 1:1205–1210.
6. Lacson E Jr, Ofsthun N, Lazarus JM. Effect of variability in anemia management on hemoglobin outcomes in ESRD. *Am J Kidney Dis* 2003; 41:111–124.
7. Yang W, Israni RK, Brunelli SM et al. Hemoglobin variability and mortality in ESRD. *J Am Soc Nephrol* 2007; 18: 3164-3170.
8. Gilbertson DT, Ebben JP, Foley RN, et al. Hemoglobin level variability: associations with mortality. *Clin J Am Soc Nephrol* 2008; 3: 133-138.
9. Brunelli SM, Joffe MM, Israni RK, Yang W, Fishbane S, Berns JS, Feldman H. *Clin J Am Soc Nephrol* 2008; 3: 777-782.
10. Triolo G. Italian Society of Nephrology. Guidelines for the treatment of anemia in chronic renal failure. *G Ital Nefrol* 2003; 20 (Suppl 24): S61-S82.
11. Canavese C, Strippoli M, Bonomini M, Triolo G. Haemoglobin targets for chronic kidney disease: guideline from the Italian Society of Nephrology. *G Ital Nefrol* 2007; 24 (Suppl 37): 99-106.
12. KDOQI. KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. *Am J Kidney Dis* 2007; 50:471-530.

Principal Investigator



Dr. Filippo Aucella

Direttore Struttura Complessa di Nefrologia e Dialisi,

Ospedale “Casa Sollievo della Sofferenza” IRCCS

71013 San Giovanni Rotondo (FG) Italy

☎ +39.0882.410208 📠 +39.0882.410208 ✉ faucell@alice.it;

f.aucella@operapadrepio.it