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Original Contribution

Can the normobaric oxygen paradox (NOP) increase reticulocyte count after traumatic hip surgery?

Pierre Lafère MD (Staff Anesthesiologist)[a,d], Thomas Schubert MD (Staff Surgeon)[b], David De Bels MD (Assistant Professor of Critical Care Medicine)[c,e,*], Peter Germonpré MD (Head, Center for Hyperbaric Oxygen Therapy)[d,e], Costantino Balestra PhD (Head, Environmental and Occupational Physiology Laboratory)[e,f]

[a]*Department of Anesthesiology, Centre Hospitalier Hornu-Frameries, 7301 Hornu, Belgium*
[b]*Department of Orthopedics and Traumatology, Saint-Pierre Clinic, 1340 Ottignies, Belgium*
[c]*Department of Intensive Care, Brugmann University Hospital, B 1020 Brussels, Belgium*
[d]*Center for Hyperbaric Oxygen Therapy, Queen Astrid Military Hospital, 1120 Brussels, Belgium*
[e]*Environmental and Occupational Physiology Laboratory, Haute Ecole Paul Henri Spaak, 1180 Brussels, Belgium*
[f]*Vice President, Research and Education, Europe Research Division, Divers Alert Network (DAN), 64026 Roseto, Italy*

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Abstract

Study Objective: To determine if the normobaric oxygen paradox (NOP) was effective in increasing reticulocyte count and reducing postoperative requirements for allogeneic red blood cell transfusion after traumatic hip surgery.

Design: Prospective, randomized, double blinded, multi-center study.

Setting: Surgical wards of two academic hospitals.

Patients: 85 ASA physical status 1 and 2 patients undergoing surgery for traumatic hip fracture.

Interventions: Patients were randomly assigned to receive 30 minutes of air [air group (control); n = 40] or 30 minutes of 100% oxygen (O_2 group; n = 14) at 15 L/min every day from the first postoperative day (POD 1) until discharge.

Measurements: Venous blood samples were taken at admission and after surgery on POD 1, POD 3, and POD 7. Hemoglobin (Hb), hematocrit (Hct), reticulocytes, hemodynamic variables, and transfusion requirements were recorded, as were hospital length of stay (LOS) and mortality.

Main Results: Full analysis was obtained for 80 patients. On hospital discharge, the mean increase in reticulocyte count was significantly higher in the O_2 group than the air group. Percent variation also increased: 184.9% ± 41.4% vs 104.7% ± 32.6%, respectively; $P < 0.001$. No difference in Hb or Hct levels was noted at discharge. Allogeneic red blood cell transfusion was 7.5% in the O_2 group versus 35% in the air group ($P = 0.0052$). Hospital LOS was significantly shorter in the O_2 group than the air group (7.2 ± 0.7 days vs 7.8 ± 1.6 days, respectively; $P < 0.05$).

* Correspondence: David De Bels, MD, Intensive Care Unit, Salle 92, Brugmann University Hospital, 4, Place A. Van Gehuchten, B 1020, Brussels, Belgium. Tel.: +32 2 477 92 93; fax: +32 2 477 92 94.
E-mail address: david.debels@chu-brugmann.be (D. De Bels).

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Conclusions: Transient O_2 administration increases reticulocyte count after traumatic hip surgery. Hospital LOS also was shorter in the O_2 group than the control group. Allogeneic red blood cell transfusion was reduced in the O_2 group but it was not due to the NOP mechanism.

1. Introduction

Red blood cell administration is indicated for patients with a symptomatic deficiency of oxygen-carrying capacity. Patients must be evaluated individually to determine the proper transfusion therapy so as to avoid inappropriate transfusion or over- or under-transfusion. Triggers for transfusion should be not only laboratory values but also physiological values and clinical assessment. It is important to ensure that the correct patient receives the correct blood and that blood components are used and handled with care [1,2].

Potential complications from blood transfusion [3,4] have prompted alternative blood management strategies, especially in patients with hip fracture. The unplanned nature of trauma surgery precludes the use of preoperative blood donation [5]; allogeneic blood is often used to maintain adequate O_2 tissue delivery [6].

Balestra et al recently described a hypothetical physiological mechanism, the "normobaric oxygen paradox" (NOP), which may provide a safer alternative to transfusion. This mechanism is based on the regulation of O_2 homeostasis governed by the hypoxia-inducible factor-1 (HIF-1), a transcription factor that regulates the expression of multiple genes involved in erythropoiesis, angiogenesis, cellular energy metabolism, and glucose transport [7,8]. The study showed that, aside from an absolute low level of tissue O_2 tension, transient hyperoxia followed by a return to normoxia acted as an effective trigger for erythropoietin (EPO) production [9]. Although quite new, this work already has been challenged in the literature. Indeed, a short period of normobaric O_2 breathing does not increase the EPO concentration in aerobically fit, healthy men [10], while EPO production triggered by a short-term hyperoxic stimulus is observed only when preceded by the administration of a single dose of N-acetylcysteine [11]. Despite those discrepancies, two clinical studies confirmed the potential of NOP. The first study showed that NOP increased reticulocytes and Hb in healthy young volunteers [12]. The second study showed that in mechanically ventilated heart surgery patients, EPO concentrations increased significantly more if the hyperoxic stimulus was high [13]. Burk reported that the clinical application of NOP appeared to be a completely effective substitute for exogenous EPO to achieve Hb production in the treatment of chemotherapy-induced anemia [14]. Another recent case report has confirmed these findings [15].

The purpose of this experiment was to study whether daily 100% O_2 breathing increased reticulocyte count and Hb levels after posttraumatic hip surgery. Reduction in allogeneic transfusion (namely red blood cell transfusion) requirements and hospital length of stay (LOS) constituted secondary endpoints.

2. Materials and methods

In this randomized, double-blinded, two-center study, 85 ASA physical status 1 and 2 patients (66 women, 19 men) hospitalized for hip fracture were enrolled after study approval by the Academic Ethical Committee of Brussels (no. B200-2010-103) and written, informed consent. Patients at each of the participating hospitals were randomly assigned to receive either 30 minutes of air or 30 minutes of 100% O_2 every day from postoperative day (POD) 1 until discharge. Randomization was computer-generated using GraphPad Statmate version 1.01 software for Windows for each participating hospital (GraphPad Software, San Diego, CA, USA). Subjects breathed the gases via a "non-rebreather" face mask at a 15 L/min rate. Patients, ward physicians, and the medical staff performing the hematological analyses were blinded to the nature of the gas breathed.

Venous blood samples were taken at admission and on POD 1, POD 3, and POD 7. Hematocrit and Hb concentrations were measured using an Advia 2120 Hematology System (Siemens Healthcare Diagnostics, Inc., Deerfield, IL, USA). A fluorescent reticulocyte count was obtained for the nontransfused patients of both groups using a Sysmex XT 2000i (Sysmex Europe GMBH, Norderstedt, Germany). Transfused patients were excluded from the reticulocyte analysis.

Postoperative follow-up was performed by a dedicated ward physician (not the surgeon or anesthesiologist) without changing the standard transfusion policy of the institution. The triggers for transfusion primarily relied on a clinical indication [16,17], defined as recorded rapid blood loss of more than 15% of total blood volume, need for intravenous fluid replacement > 10 mL per kg of patient body weight, or evidence of poor tissue O_2 delivery [18] such as congestive heart failure, angina pectoris, or one of the following criteria:

1) systolic blood pressure (SBP) < 90 mmHg or decrease in SBP > 40 mmHg within 4 hours before transfusion;
2) diastolic blood pressure (DBP) < 40 mmHg or decrease of DBP > 40 mmHg within 4 hours before transfusion;

3) heart rate (HR) above 100 beats per minute (bpm) within 4 hours before transfusion;
4) oxygen saturation via pulse oximetry (SpO_2) < 90%.

An absolute value of Hb triggered a blood transfusion only if Hb levels were below 8.5 g/dL [19,20].

Five patients were excluded from the study, two for insufficient data (one pt each from both groups), two for early discharge on POD 5 (both O_2 group pts), and one patient who died on POD 1 from complications associated with severe liver failure prior to the protocol. Hospital LOS and mortality also were recorded. Comorbidities were compared with the 2004 Belgian population survey [21] to assess the representativeness of our population sample as compared with the global population.

2.1. Statistical analysis

Standard statistical analysis, including mean, standard deviation, and analysis of variance for repeated measures, was performed to test between- and within-subjects effects, using Dunnett's test as a post-test after Kolmogorov Smirnov test for normality (GraphPad Prism version 5.00 for windows; GraphPad Software); between-group comparisons were performed using unpaired t-test or Mann-Whitney test according to normality testing. A threshold of $P < 0.05$ was considered statistically significant.

3. Results

A total of 85 ASA physical status 1 and 2 patients (66 women, 19 men; mean age 81.1 ± 7.9 yrs), hospitalized for hip fracture, were enrolled in the study. As 5 patients were excluded, data from 80 patients (62 women, 18 men) are shown. The two groups were comparable in age, gender ratio, renal function, delay to intervention (defined as the time between day of admission and day of the surgery), operative side, type of intervention, and blood loss (Table 1). No differences in associated comorbidities were found. Moreover, when comparing the proportion of comorbidities in our sample with the 2004 Belgian population survey [21], our population was representative of the global population except for neurological diseases, which were overrepresented in our sample.

Allogeneic red blood cell transfusion requirements were significantly reduced in the O_2 group versus the air group ($P = 0.0052$). A total of 17 patients received a transfusion; all but three of these patients belonged to the air group. Neither baseline Hb value nor intraoperative blood loss predicted the need for postoperative transfusion. Three patients (one in the O_2 group, two in the air group) were transfused due to an absolute Hb value < 8.5 mg/dL. The other 14 patients were transfused according to predefined clinical criteria (Table 2).

Table 1 Study group demographics

	O_2 group (n = 40)	Air group (n = 40)	*P*-value
Gender ratio (F/M)	32/8 (80% F)	30/10 (75% M)	0.79
Age (yrs)	80.4 ± 7.43	81.7 ± 8.41	0.48
Delay to intervention (days)	2.03 ± 1.03	2.28 ± 0.96	0.26
Side ratio (left/right)	19/21	22/18	0.65
Type of intervention			0.61
proximal femoral intramedullary nail	31	28	
hemiarthroplasty	9	12	
Perioperative blood loss (mL)	473 ± 282	424 ± 378	0.38
Renal function			
urea (mg/dL)	52.6 ± 16.5	47.1 ± 21.7	0.10
creatinine (mg/dL)	0.853 ± 0.234	0.763 ± 0.237	0.05
glomerular filtration (mL/min)	88.4 ± 22.1	80.3 ± 24.8	0.05
Associated pathologies			
hypertension	16	19	0.65
neurologic diseases	14	14	1.00
ischemic heart diseases	5	6	1.00
diabetes	8	7	1.00
COPD	4	5	1.00
Transfusion	3/40	14/40	0.0052

The O_2 group received 30 minutes of 100% oxygen at 15 L/min and the air group received 30 minutes of air each day from the first postoperative day to discharge; COPD = chronic obstructive pulmonary disease.

There was a very high and significant increase in reticulocyte count (Fig. 1) and percent variation on POD 7 in the O_2 group (184.9% ± 41.4%) compared with the air group (104.7% ± 32.6%). This difference also was significant when comparing POD 1 with POD 3 ($P < 0.0001$) and in comparison with the air group ($P < 0.001$). Although transfusions may not affect the reticulocyte count per se, it may impact the de novo production.

Hemoglobin (Fig. 2) and Hct (Fig. 3) levels were similar in both groups. Hospital LOS was significantly shorter in the O_2 group than the air group (7.2 ± 0.7 days vs 7.8 ± 1.6 days, respectively; $P < 0.05$). All patients were alive at 6-month follow-up.

4. Discussion

Postoperative anemia is not uncommon in patients undergoing hip fracture surgery. It is associated with allogeneic blood transfusion, a higher mortality rate, increased hospital LOS, and morbidities such as postoperative infections or poorer physical function/recovery [22]. Anemia may be explained by posttraumatic and perioperative blood loss. However, there is evidence that the characteristics

Table 2 Predefined clinical criteria for transfusion of patients

Reason for PRBC transfusion	Patient number	Pretransfus Hb (g/dL)	Transfus (days)	Volume (U)	Admission Hb (g/dL)	Postop Hb (g/dL)	Delay to intervention (days)
Oxygen group							
SBP < 90 mmHg; DBP < 40 mmHg	1	8, 8	4	2	13, 7	9, 7	2
HR > 100 bpm	2	9, 1	3	1	12, 6	9, 2	2
Air group							
SBP < 90 mmHg	3	9, 1	3	2	16, 3	11, 4	4
SBP < 90 mmHg	4	10, 8	3	2	11, 1	10	2
HR > 100 bpm	5	8, 9	2	2	11, 0	8, 9	1
HR > 100 bpm & angina pectoris	6	9, 8	1	4	12, 5	9, 8	1
HR > 100 bpm & angina pectoris	7	9, 1	2	4	14, 9	11, 1	3
SBP < 90 mmHg	8	9, 0	3	2	11, 9	10, 1	2
DBP < 40 mmHg	9	10, 7	3	1	11, 4	10, 6	2
SpO_2 < 90%	10	9, 8	3	2	14, 8	11, 1	0
SBP < 90 mmHg	11	10, 0	3	2	11, 6	13, 4	3
SBP < 90 mmHg	12	8, 7	2	3	14, 4	9, 1	2
SpO_2 < 90% & angina pectoris	13	9, 8	3	3	10, 8	11	2
HR > 100 bpm	14	10, 2	4	1	13, 5	12, 7	1

Patients were transfused according to the predefined clinical criteria, excluding the 3 patients transfused on the basis of a hemoglobin (Hb) value. Each row represents the transfusion trigger for that patient.
PRBC = packed red blood cells, Pretransfus = pretransfusion, Transfus = transfusion, Volume [unit (U); median packed red blood cell (PRBC) unit = 225 mL), Postop = postoperative, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, SpO_2 = oxygen saturation via pulse oximetry.

of postoperative anemia are similar to those of the anemia seen in chronic diseases [23,24]. This type of anemia is characterized by a decrease in plasma iron despite adequate iron stores and a reduction in erythropoiesis. The latter occurs especially in the first week after surgery due to the failure of bone marrow to increase red blood cell production in response to anemia. In one study, it took 4 weeks after major surgery to observe an increased erythropoiesis [25], which was induced by EPO. When perioperative exogenous EPO is used, the first observed change is an increase in reticulocyte production in a dose-dependent manner [26]. However, EPO synthesis assessments are difficult to obtain; it is not so easy to effectively show a significant increase of EPO after a single exposure to normobaric O_2. Several concomitant mechanisms are involved, such as the individual circadian rhythm as well as seasonal rhythms in EPO production [9,10]. Another concern is the effective amount and activity of glutathione of each subject. Indeed, the repletion of glutathione intracellular reserves may modulate EPO production [11,27]. The amount of O_2 received is also an important parameter to take into account, as a too high dose of O_2 will be responsible for a decrease in EPO synthesis [28]. Given those facts, EPO synthesis assessment may be inaccurate. We therefore decided to use (indirect) proof of EPO secretion: an increase in reticulocyte production.

In this context, the major finding of the present study was a significantly increased reticulocyte count in the O_2 group. These results cannot be explained by transfusion; we

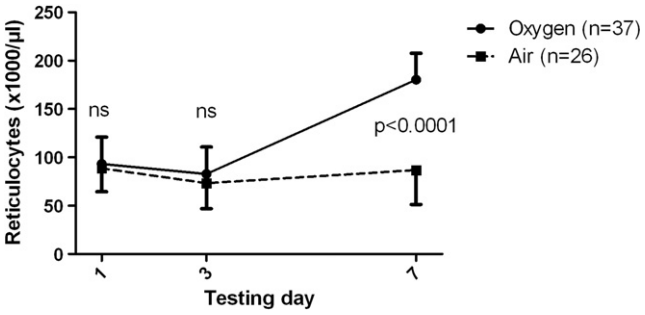

Fig. 1 Time course of reticulocyte count in non-tranfused patients. ns = not significant. ***$P < 0.001$ for between-group comparison.

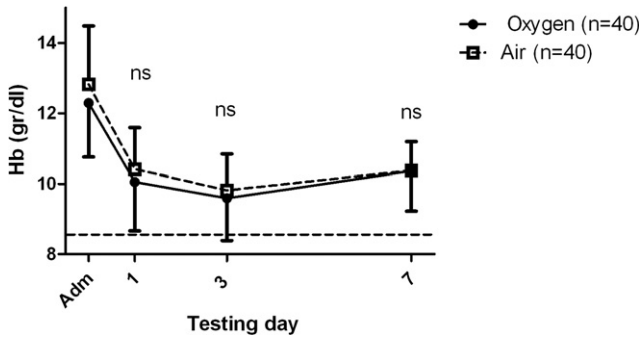

Fig. 2 Time course of hemoglobin (Hb) in all patients. ns = not significant.

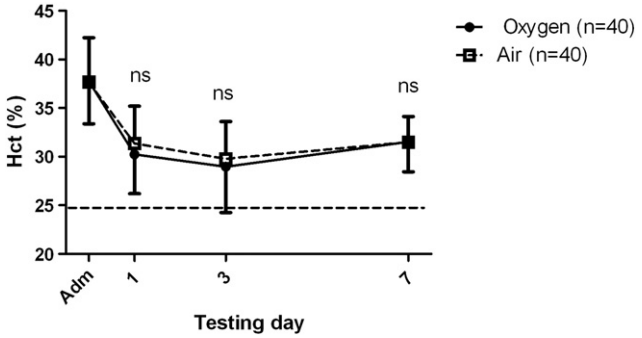

Fig. 3 Time course of hematocrit (Hct) in all patients. ns = not significant.

excluded all transfused patients from this particular analysis since transfusion impairs reticulocyte production [29]. Preoperative and postoperative Hb levels, which were comparable in both groups, were not accountable for these changes. The delay observed in our study (on POD 7), preceding the reticulocyte count increase, was in agreement with previous work suggesting EPO stimulation of the colony-forming unit (CFU-e) in the bone marrow, which requires 4 to 8 days to produce new erythrocytes [30,31]. Although we did not measure EPO concentration itself, it was logical to assume that the decrease in inspired O_2 concentration from 100% to 21% at the end of the O_2 breathing period produced the relative hypoxia, similarly to that which caused the EPO increase in the healthy volunteers studied by Balestra et al [9]. Since renal function, a major determinant in EPO production, was normal and similar in both groups, we suggest that NOP was responsible for the increase in reticulocyte production noted in our O_2 group.

Our second finding was a significant difference in transfusion rate between the two groups. Reticulocytosis cannot be an explanation for the reduced transfusion rate as the increase in reticulocyte production occurred around POD 7, and all transfusions took place between POD 3 and POD 4. The reduced transfusion rate noted in the O_2 group thus could not be attributed to "de novo" production of RBCs. No other potential confounders, such as preoperative use of aspirin or clopidrogel, which might have placed the control group at a higher risk for transfusion, were identified.

To explain the difference in transfusion rate between the two groups, we have to look at the triggers for these transfusions. The institutional transfusion policy, which was adhered to in this study, was based on clinical criteria in all but three patients, whose transfusions were based on absolute Hb values (Table 2) [16,18-20]. All patients were evaluated by the same physician; patient, evaluating physician, and medical staff performing the hematological analyses were all blinded to group assignment.

Despite similar Hb and Hct values, patients in the O_2 group seemed to be in a better clinical state than those in the control group. This finding may have been due to the mechanism behind the NOP hypothesis. Indeed, the protective response against free radicals induced during the brief O_2 treatment was sustained beyond the exposure period. This results in a further decrease in free radical levels [32,33]. The resulting reduced level of free radicals may explain the seemingly better clinical state of patients in the O_2 group. Mild hyperoxia may offer clinical benefits that are responsible for this reduced transfusion need. Pure O_2 breathing induces peripheral vasoconstriction and counteracts hypotension, possibly reducing vasopressor requirements. In animal experiments, a redistribution of cardiac output toward the kidney, liver, and spleen was noted during hyperoxic breathing. Hyperoxia not only reverses anesthesia-related impairment of the host defense but also acts as an antibiotic, as shown in studies in which perioperative hyperoxia significantly reduced wound infections proportionally to tissue O_2 tension [34,35]. Hyperoxia also has been investigated as an inhibitor of cancer cell development, probably through the HIF pathway [36,37].

Erythropoietin induces other physiologic effects, which include Hct-independent/vasoconstriction-dependent hypertension, increased endothelin production, tissue renin upregulation, changes in vascular tissue prostaglandin synthesis, and stimulation of angiogenesis [38-40]. Erythropoietin also has a dominant role in neuroprotection and acts as a neurotrophic factor in the central nervous system [41-45]. It possesses cardioprotective properties at least equal in magnitude to those conferred by ischemic preconditioning [46,47]. All of these mechanisms may be responsible for the better clinical condition of O_2 group patients, resulting in a reduction in allogeneic blood transfusions.

Our last finding was the statistically significant, but clinically insignificant, decrease in hospital LOS in the O_2 group versus the air group.

4.1. Conclusion

This study showed that repeated short bursts of hyperoxia applied with a minimal protocol (30 min per day), effectively stimulated the production of reticulocytes in postoperative conditions. Allogeneic red blood cell transfusion was reduced in the O_2 group but this was not due to the NOP mechanism. These findings should prompt more studies of the clinical impact of repeated perioperative transient hyperoxia.

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