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PREVENTT Trial: A Snapshot of Preoperative Anaemia in the United Kingdom

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Abstract

Preoperative anaemia is a recognised risk factor for major surgery. Approximately 30% of all preoperative patients are anaemic, and despite the risks it is often overlooked and unmanaged for reasons of insufficient time for intervention from referral to surgery or lack of management protocols. Screening data from a multicentre trial currently being undertaken and recruiting preoperative patients in the United Kingdom was used to assess these challenges. Results showed that between September 2013 and June 2015 screening data had been returned on 4979 patients, of those 415 (8.3%) met eligibility criteria. Of the ineligible patients 5 codes provided nearly 90% of the total exclusions for the trial: 44.9% due to Hb out of range for inclusion (either <90 g/L or >120 g/L); 17.7% not having major open surgery; 11% having laparoscopic surgery; 10.7% unable to randomise 10-42 days before surgery; 4.9% no Hb within 28 days. At least 18% of the patients screened were anaemic. Furthermore, up to half of reported screened patients were potentially anaemic, yet significant numbers of patients did not have adequate time for trial intervention or were without recent haemoglobin measurements. Rapid management of patients from referral to surgery is welcome, but can be a barrier to pre-optimisation of patients, which may reduce the benefit seen. Despite a significant prevalence of preoperative anaemia, current preoperative pathways inadequately facilitate its management for every patient.

Introduction

Preoperative anaemia is a common condition and present in up to 30-60% of patients presenting for elective major surgery across Europe [1-4]. The surgical population may develop anaemia preoperatively from acute or chronic blood loss, nutritional iron deficiency (ID), renal insufficiency, malignancy or chronic inflammatory disease, and is a well-established independent risk factor for increased morbidity and mortality in major surgery [5].

In the perioperative period, anaemia can significantly impact on the already strained effects of undergoing surgery, and has been shown to be a major predictor for blood transfusion, which in itself is associated with a poorer outcome [6]. For these reasons, the first step to be taken in elective major surgery should be the preoperative identification and management of anaemia early enough to implement appropriate treatment. However, there is finite research, sufficiently powered or designed with robust patient primary outcomes, to investigate the impact of managing anaemia and optimising patients in the preoperative period. In addition, limited data exists focusing on how preoperative care can reduce morbidity, mortality and improve quality of life (QoL) in relation to giving intravenous (IV) iron therapy in the preoperative period. Screening data from the multicentre PREVENTT (Preoperative intravenous iron to treat anaemia in major surgery) trial currently recruiting preoperative patients in the National Health Service (NHS), was undertaken to assess preoperative anaemia management. The purpose of the analysis assists to identify challenges to recruitment and possible areas for change to the trial protocols and potentially to clinical practice in the area of preoperative anaemia and major surgery.

Methods

PREVENTT is a phase III randomised control trial and is an ongoing NIHR-funded study recruiting patients across the United Kingdom. The aim is to compare the use of IV ferric carboxymaltose (dose 1000 mg) or placebo 10-42 days before surgery [7]. To be eligible for the study patients must have anaemia, as per the World Health Organisation (WHO) definition of insufficient red blood cell (RBC) mass to meet the body's physiological needs with a haemoglobin (Hb) concentration of <130 g/L for men and <120 g/L for non-pregnant women and be scheduled to be undergoing elective, major open abdominal surgery [8].

Co-primary outcomes to be investigated are the risk of blood transfusion (receiving any volume of one unit of packed red blood cells or any other blood component) or death, from randomisation until 30 days following the index operation and the blood transfusion rate (including repeat transfusions, defined as number of blood transfusions divided by the total patient time at risk). Secondary endpoints will include, but not exhaustive, post-operative recovery, length of hospital stay, health care utilisation and cost analysis. The complete list of the outcomes is detailed in the study protocol [7].

All active sites were required to send monthly screening logs to the Clinical Trials Unit at the Clinical Trials Unit until November 2014. From that point on, screening data was collected from all new sites for their first six months of recruitment, and from all sites in May and June 2015 for monitoring and assessment. The data represents all screening data until April 2015, and does not represent the entire screening population of the trial. One of four 24 exclusion codes for the trial has

been assigned to ineligible patients (Table 1). The anticipated closure of this study is March 2017.

Code		Code	
1	Patient is under 18 years of age	13	Chronic liver disease and/or screening alanine transaminase (ALT) or aspartate transaminase (AST) above three times the upper limit of the normal range
2	Patient not undergoing elective major open surgery (where major surgery is defined as an operation of anticipated duration of more than one hour where all or part of an abdominal organ is to be removed)	14	Patient has received erythropoietin i.v. therapy or blood transfusion in the previous 12 weeks
3	Screening haemoglobin less than 90 (9.0) or greater than 120 g/L (12.0 g/dl) within 4 weeks of randomisation	15	Immunosuppressive therapy (for organ transplantation) or renal dialysis (current or planned within the next 12 months)
4	Randomisation and administration of study drug cannot be completed between 10-42 days before planned operation	16	Patients with severe asthma or allergy
5	Positive pregnancy tests for women of childbearing potential (within last 7 days) or patient does not agree to use an effective form of contraception until 6 weeks post treatment	17	Unfit for elective surgery
6	Laboratory data used for determination of eligibility at the baseline visit is older than four weeks	18	Pregnancy or lactation
7	Patients undergoing laparoscopic surgery	19	Inability to fully comprehend and/or perform study procedures in the investigator's opinion
8	Body weight under 50 kg	20	Patient involvement in another IMP trial within the previous 4 weeks, prior to randomisation or involvement in another IMP trial, following randomisation, that may impact on the results of the PREVENTT trial
9	Known history of acquired iron overload, or family history of haemochromatosis or thalassemia or TSAT >50%	21	Patient did not wish to participate in the study
10	Known reason for anaemia (e.g. B12 or folate deficiency or haemoglobinopathy)	22	Clinical decision (please provide details in comments box or screening log)
11	Known hypersensitivity to ferric carboxymaltose (Ferinject ®) or its excipients	23	Research staff not available
12	Temperature >37.5°C or patient on non-prophylactic antibiotics	24	Other reason (please provide details in comments box on screening log)

Table 1: Exclusion Codes.

Results

A total of 4979 patients screening data across 30 sites were returned by the end of June 2015 (Table 2). From this population, 415 patients met eligibility criteria, although by the end of June 2015 only 40% of these participated in the trial. A total of 234 patients were eligible for recruitment but not entered, with 74% of those refusing enrolment.

Five exclusion codes provided over 90% of the total exclusions for the trial (Table 3). Of the 24 exclusion codes provided, codes 22 (Clinical Decision) and 24 (Other reason), which allow investigators to submit a free text answer as a reason for exclusion, made up 0.6% and 6.2% of these, respectively.

The clinical reasons for exclusion were due to multiple co-morbidities, geographical distance from participating hospital, surgery or referral to another health facility, inoperable disease, and patients lacking capacity or deemed too high risk for involvement in trial, and change in management plan for underlying disease.

During analysis, 174 exclusions were due to patient refusal to participate in the study. The reasons for refusal are represented in Table 4. At least 931 (19.7%) patients screened had anaemia, comprising of 415 (8.3%) eligible and 516 (10.7%) with insufficient time to be randomised.

	All patients
	(n=4979)
Met eligibility criteria	415 (8.3%)
Participated in trial	167 (3.4%)
Eligible but not participated	213 (4.7%)
Refused enrolment	174 (3.5%)

Table 2: Results of eligible screening population.

Exclusion Code	Number of Ineligible
3: Screening haemoglobin <90 g/L or >120 g/L	2161 (44.9%)
2: Patient not undergoing elective major open surgery	854 (17.7%)
7: Patient undergoing laparoscopic surgery	530 (11.0%)
4: Randomisation and administration of study drug cannot be completed between 10-42 days before planned operation	516 (10.7%)
6: Laboratory data used for determination of eligibility at the baseline visit is older than four weeks	238 (5.9%)
14: Patient has received erythropoietin i.v. therapy or blood transfusion in the previous 12 weeks	85 (1.7%)
17: Unfit for elective surgery	62 (1.2%)
20: Involvement in another IMP trial	38 (0.8%)
19: Not competent	35 (0.7%)
08: Body weight <50 kg	29 (0.6%)

Table 3: Common causes for exclusion from trial.

Reason	Number
Declined/Refused	54 (35.3%)
Felt they had too much already with surgery/diagnosis/illness	21 (13.7)
Does not want placebo	11 (7.1%)
Does not want to return to hospital / too far	10 (6.5%)
Does not want to be involved in research or uninterested	6 (3.9%)
Does not want to make extra visit	6 (3.9%)
Unable to take time off work	3 (2.0%)
Fear of side effects	3 (2.0%)
Family advised against enrolment	2 (1.3%)
Unsure if going ahead with operation	2 (1.3%)
Unable to contact	2 (1.3%)
Patient felt 'too old' to partake / dementia	2 (1.3%)
Fear of side effects + too much paperwork	1 (0.7%)
Declined + Now having operation overseas	1 (0.7%)
Did not want infusion	1 (0.7%)
Declined due to anxiety about study	1 (0.7%)
Initially agreed then changed their mind	1 (0.7%)
Declined after reading PIS	1 (0.7%)
Needle phobia or Previous experience with cannulas	1 (0.7%)
Did not want extra tests	1 (0.7%)
Other commitments	1 (0.7%)
Language barrier to understanding	1 (0.7%)
No reason provided by site	22 (14.4%)

Table 4: Reasons for patient refusal.

Discussion

Preoperative anaemia is a risk factor in surgery and is correlated to increased post-operative morbidity, mortality and decreased quality of life. In context of an aging population, with often preexisting comorbid conditions such as diabetes, hypertension and asthma, even the mildest forms of iron deficiency anaemia could drive the vulnerability of a patients' surgical risk even further. Where rapid correction is required in urgent and elective patients, the parenteral route is appealing. In the context of newer formulations, intravenous iron is a safe intervention with minimal side effects [9]. Intravenous iron is highly efficacious to increase Hb levels and correct anaemia. However, data linking this to increased patients' welfare reduce perioperative complications, length of hospital stay and patient outcomes are lacking. This is being tested in the ongoing UK NIHR clinical trial PREVENTT [7].

Since recruitment commenced in September 2013, the sites involved have screened a large cohort of patients undergoing surgery thus far. Recruitment for PREVENTT has been challenging, with only 3.2% of all patients screened recruited. If all patients who had declined were enrolled into the trial, this would be doubled. Analysis of the reasons given for declining to participate included, patient's refusal to enrol as they wanted to have the IV iron, not wishing to have additional tests and language barriers. However, half of patients or sites did not provide any more detail for the reason for refusal.

Five principal reasons for non-eligibility account for the majority of excluded patients, and these are in keeping with the reports from investigating sites, and the efforts made by the project management group and trial steering committee to amend the study protocol to reduce these barriers to recruitment. These amendments comprised of increasing eligibility Hb from 120 g/L to 130 g/L for men, broadening the definition of major surgery to no longer state 'removal of all or part of an organ', and to reduce time between enrolment and surgery from 14 to 10 days.

There is significant variation between sites in terms of their surgical populations, and pathways. Additionally, the reporting of screening can be varied between sites, for example, many sites do not report the majority of laparoscopic cases as screened exclusions, when these are in much greater numbers at many sites than the screening logs would imply.

As clinical care, including surgical specialities, is increasingly reorganised to create higher volume centres to improve outcomes, referrals of patients between hospitals has increased. Many patients have become ineligible due to the poor sharing of clinical data between hospitals and NHS trusts. Patients referred to tertiary hospitals are often screened without any clinical data available, including laboratory results. This is a common criticism in clinical management of patients being seen away from their local hospital, and is challenging to research teams. Referring hospitals should be encouraged to send recent clinical results to other centres, and research teams should try to liaise with the referring hospital to obtain these results.

Between 18% and up to half of reported screened patients were potentially anaemic. This reflects the high burden of anaemia within the surgical population and is in keeping with previous population studies of surgical patients across Europe (on average 30% of surgical patients, rising to up to 70% of colorectal patients) [4]. However, pre-operative pathways do not adequately allow for the recognition, diagnosis and treatment of anaemia. Over 11% of patients were not eligible because there was insufficient time to administer the trial intervention up to 10 days before surgery. Intravenous iron can be used throughout the preoperative period but, ideally, treatment should take place 10 days pre-operatively to allow total erythroid cell maturation and Hb accumulation. This has been a common observation from participating sites. Whilst the swift management of patients with malignancy from referral to surgery is welcomed to improve outcomes, it can be a barrier to pre-optimisation of patients, which may reduce the benefit seen.

Conclusion

Timely referral, with early routine laboratory investigations to allow a thoroughly informed pre-assessment of patients to take place, even in short timeframes, benefits patients in many ways. They can be better prepared physically and psychologically for their treatment, which can improve self-rehabilitation post-operatively; modifiable risk factors can be identified and treatment plans put into place. Furthermore, robust post-operative care and rehabilitation can be planned based upon newly identified needs. This is a corner stone of the concept of perioperative medicine and of enhanced recovery after surgery into which pre-operative anaemia management should be incorporated.

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