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A Review of 'The Implications of Perioperative Blood Transfusion in Patients Undergoing Vascular Surgery'

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Abstract

Introduction: The negative effect of Blood Transfusion (BT) in patients undergoing cardiac surgery has been demonstrated within the literature extensively. This review aims to answer the question whether the emerging new evidence suggests that transfusion is harmful to the vascular surgery patient and whether we should re-consider our previous liberal approach to transfusion.

Methods: A review of the literature using the Pubmed search engine was performed where 476 articles were found, of these 23 were found to be relevant, search terms included "Blood transfusion" AND "Vascular surgery". A review of the literature over the last 5 years was performed; exclusion criteria were any articles not available in English. A standard proforma was used to assess each scientific article.

Results: The literature suggests that blood transfusion increases mortality and morbidity. In 2014 Curley et al. published a systematic review and meta-analysis showing no statistically significant effect between restrictive versus liberal triggers for transfusion, however there was major morbidity associated with a more liberal transfusion approach. Studies have shown BT increases re admission rates, increases surgical site infection and graft thrombosis.

Conclusion: From the literature it can be stated that BT increased morbidity and mortality independently of anaemia and that it should not be undertaken lightly. A restrictive approach at present is advocated in the current literature, however this review highlights the limited evidence available and the need for a large RCT to assess nadir Hb level for transfusion in vascular surgery patients.

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Introduction

The negative effect of blood transfusion in patients undergoing cardiac surgery has been demonstrated within the literature extensively [1]. Within our 'Vascular Unit' anecdotally, it has been noted that patients who have had multiple transfusions had an increased morbidity and mortality. In order to guide clinical practice and local guidelines this literature review was undertaken.

Intraoperative blood loss, perioperative anaemia and perioperative blood transfusions are common practice in Vascular Surgery. By the nature of the atherosclerotic disease process this patient cohort commonly has multiple comorbidities; often including ischaemic heart disease, renal impairment and with chronic anaemia being a frequent finding [2].

Multiple studies have demonstrated that the expected increase in tissue oxygenation following blood transfusion does not seem to occur. Traditionally maintaining more 'physiological' Haemoglobin (Hb) has been thought to maintain tissue oxygenation and reduced myocardial morbidity, but correcting this with transfusion has not seemed to have this effect [3-5].

Another key problem is that the nadir Hb threshold for transfusion in vascular patients has yet to be clearly demonstrated in large studies, thus practice is highly variable. Later this year a large Randomized Control Trial by a study group in Norway should answer the clinical question; at what nadir Hb should vascular patients be transfused. Large studies have indeed demonstrated that in patients at risk of cardiovascular disease, a restrictive approach (<7 g/dL) to transfusion does not lead to an increase in morbidity and mortality as compared with a more liberal approach (>7 g/dL) to transfusion [6].

Traditionally the harmful effects of transfusion were more focused on the transmission of

contaminated blood and haemolytic transfusions reactions. These risks now in the developed world are rare. However, it is becoming increasingly obvious that transfusions cause non-infectious complications such as immunomodulation, lung injury, allo-immunisation, metabolic derangement and major organ dysfunction [4,7]. Respiratory problems are well known in particular Transfusion Related Lung Injury (TRALI) which is one of the most severe complications and causes of transfusion related death [8].

Strong evidence demonstrates that perioperative anaemia increases morbidity and mortality in particular with regards to cardiovascular morbidity [6], this has resulted in the National Institute for Health and Care Excellence (NICE) setting a threshold of 7 g/dL for transfusion in preoperative patients and 8 g/dL for patients with Acute Coronary Syndrome (ACS). In short, there is good evidence to show anaemia is harmful and contributing factors to morbidity and mortality therefore traditionally vascular patients have had high transfusion rates.

This review aims to answer the question whether the emerging new evidence suggests that transfusion is harmful to the vascular surgery patient and whether we should re-consider our previous liberal approach to transfusion.

Methods

A review of the literature using the Pubmed search engine to access MEDLINE database was performed 476 articles were found, of these 23 were found to be relevant, search terms included "Blood transfusion" AND "Vascular surgery". For this review, simultaneously an independent clinical librarian performed a further literature search to ensure relevant scientific papers had not been missed. A subsequent literature search was performed using the search engine Google Scholar 218 results were found, search terms were "perioperative "Blood transfusion" AND "Vascular surgery". Five additional relevant scientific articles were extracted; relevant articles not present on MEDLINEs database were searched and relevant articles extracted. A review of the literature over the last 5 years was performed; exclusion criteria were any articles not available in English. A standard proforma was used to assess each scientific article.

Discussion

Mortality

There is limited information on perioperative outcomes in vascular patients with regards to blood transfusions. Overwhelmingly the literature suggests that blood transfusion increases mortality and morbidity [6,9-11].

In a retrospective US Veterans Administration study of nearly 240,000 patients undergoing non-cardiac surgery Chen et al described the qualifiers for BT. They found that transfusion was beneficial at when patients had haematocrit levels less than 24% and had intraoperative blood loss of a minimum of 4500 mL. When these conditions were not met BT was associated with an increased 30-day mortality and morbidity. In this study in elective vascular patients' length of stay was increased in addition to increased morbidity and mortality if these criteria were not reached [12].

The demonstrable increase in morbidity and mortality appears to be independent of the fact that patients undergoing BT tend to be sicker, more co-morbid patients who have had more complex surgery [5,11].

Morbidity

Myocardal Infarction (MI), Acute Cororary Syndrome (ACS), wound infection rates, thrombotic risk, renal complications and graft patency effects.

In 2014 Curley et al. published a systematic review and meta-analysis assessing 7 Randomised controlled trials within cardiac and vascular surgery evaluating whether a restrictive approach to transfusion or a more liberal approach was beneficial. A total of 1,262 subjects were included in the review. The pooled data showed no statistically significant effect between restrictive versus liberal triggers for transfusion; however there was major morbidity associated with a more liberal transfusion approach including MI, stroke and acute renal failure [9,13,14].

A linear relationship between Acute Coronary Syndrome (ACS) and blood transfusion has been clearly demonstrated in several studies [6,15], however there is some conflicting evidence on whether wound healing is delayed by multiple blood transfusions [10,16]. Reasons for this are poorly understood, and thought to be multi-factorial. They may in part be related to an alteration in nitric oxide biology, subsequent decreased 2,3- diphosphoglyceric acid levels and the release of inflammatory mediators [3].

BT is a mainstay of treatment during resuscitation for the unstable, bleeding patients. Optimal resuscitation for patients with ruptured Abdominal Aortic Aneurysms (rAAA) has not been well defined, clearly these cohort needs BT, but it is clear that when transfusing patients packed red cells (RBCs), outcomes are worse when the components of whole blood are altered [14–16]. Therefore, it has been suggested that in the resuscitation of critical patients with large volume haemorrhages results are improved when the ratios of Fresh Frozen Plasma (FFP) and Platelets (PLTs) to RBCs are high. A mortality benefit has been seen with increased FFP as identified by Montan et al. [14] Transfusing RBCs needs to be considered carefully, clearly in the acute haemorrhage transfusion is imperative but when the clinical picture is more chronic results suggest that by over-transfusing we may be doing more harm than good. The ultimate aim of BT is to improve tissue perfusion and if this is not being achieved then alternative must be investigated.

Packed red Blood cell Transfusion (BT) has been shown to increase re-admission rates, although correlated, direct association has not clearly been found. Whether this is due to increased complications resulting from transfusion or rather a more tumultuous postoperative course; it has not been clearly defined [10,17]. However, BT has been shown to be an independent risk factor for post-operative Myocardial Infarction (MI), pneumonia, thromboembolism and prolonged in hospital length of stay in vascular patients [13,18].

Additionally; some studies have suggested BT increases the risk of surgical site infection and graft thrombosis which has serious implications in vascular surgery whereby blood flow is established regularly through the use of artificial grafts [16]. Evidence for increased surgical site infections has been conflicting and may be related to the immunosuppressive effects of BT, but is likely multifactorial [19].

The immunomodulatory effects of BT have been attributed to a direct immunomodulatory effect by transfer of the donor leukocytes in addition to a resultant alteration in the recipients circulating lymphocytes, T helper and suppressor cells, B-cell function, and change in number of antigen-presenting cells [19]. A dose dependant response has been demonstrated in cardiac and general surgery

patients. The mechanism of how BT might increase morbidity and mortality is likely multifactorial and is not fully understood. It may be related to number of transfusions, thus limiting transfusion number may decrease circulating pro-inflammatory cytokines and decrease risk of infection. This has not been demonstrated in vascular surgery patients; however it is an active area of research at present. In the United Kingdom all BT are leukocyte depleted to help ameliorate the well-established immuno modulatory effects of BT.

Patient groups that are more commonly transfused include; women, non-smokers and Afro Caribbean patients, presumably smokers with their associated polycythaemia have higher Hb levels meaning a threshold level for transfusion is less likely to be reached.

Medical conditions that are associated with higher rates of BT include: preoperative anaemia, hypertension, diabetes mellitus, congestive cardiac failure, significant valvular disease, coronary artery disease, coronary artery bypass grafts, history of cerebrovascular event and renal failure requiring haemodialysis [12,18].

Obi et al. [19] found that of the cohort of vascular patients that are transfused they are more likely to be in-patient hospital transfers rather than being admitted from home; similarly, this group also found that BT patients were less likely to be discharged home ($P<0.001$), but were more likely to be readmitted within 30 days after the procedure. Despite the fact that 'sicker' more co-morbid patients commonly require transfusion more frequently, BT has been shown to be an independently associated with death, MI and pneumonia but not with surgical site infection [11]. Adjustments were made for major covariates; demographics, comorbidities, estimated intra-operative blood loss, preoperative anaemia and use of antiplatelet agents and anti-coagulant medications.

Optimal transfusion thresholds

In this group nadir haemoglobin of 6.7 g/gL to 8.4 g/dL was used. Henke et al showed that this increase in morbidity with BT is independent of pre-operative anaemia and was seen in large cohorts with nadir Hb of both <8 g/dL and >8 g/dL [20]. Other studies have shown that post-operative complications increase in a dose-dependent fashion [11].

In 2014 Curley et al. published a systematic review and meta-analysis assessing 7 Randomised controlled trials within cardiac and vascular surgery evaluating whether a restrictive approach to transfusion or a more liberal approach was beneficial. A total of 1,262 subjects were included in the review. The pooled data showed no statistically significant effect between restrictive versus liberal triggers for transfusion; however there was major morbidity associated with a more liberal transfusion approach including MI, stroke and acute renal failure [12,13,20,21].

In a retrospective US Veterans Administration study of nearly 240,000 patients undergoing non-cardiac surgery Chen et al described the qualifiers for BT. They found that transfusion was beneficial at when patients had haematocrit levels less than 24% and had intraoperative blood loss of a minimum of 4500 mL. When these conditions were not met BT was associated with an increased 30-day mortality and morbidity. In this study in elective vascular patients' length of stay was increased in addition to increased morbidity and mortality if these criteria were not reached [12].

Conclusion

In this review the literature available for Vascular patients is limited but the available data and what we have learned from cardiac, orthopaedic and general surgery patients suggests that whilst transfusion is an important component in resuscitation for bleeding patients. It comes with significant risks and in chronic anaemia and in the perioperative period can be detrimental [22-30]. Other methods to improve tissue perfusion should be utilised as well as techniques to minimise blood loss. The literature has demonstrated a counter-intuitive relationship whereby BT does not increase tissue perfusion as expected. Additionally, the fact that an evidence based nadir Hb threshold has not yet been established in vascular patient's means that a clear risk-benefit analysis for BT cannot yet be made to patients. Once a threshold has been established a clear shift in clinical practice can be made.

From the literature it can be stated that BT increased morbidity and mortality independently of anaemia and that it should not be undertaken lightly. However, few reports have assessed outcomes in Vascular Surgery.

A restrictive approach at present is advocated in the current literature, however this review highlights the limited evidence available and the need for a large RCT to assess nadir Hb level for transfusion in vascular surgery patients. Additionally large studies assessing the specific outcomes in morbidity and mortality specifically in vascular patients would help clarify whether a liberal approach to transfusion is harmful and would allow more complete evidence to support National Guidance or this cohort of vascular surgery patients.

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