The prospective evaluation of the net effect of red blood cell transfusions in routine provision of palliative care

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Background

Red Blood Cell (RBC) transfusions are commonly used in palliative care. RBCs are a finite resource, transfusions carry risks, and the net effect (benefits and harms) is poorly defined for people with life-limiting illnesses.

Aim

The aim of this study was to examine the indications and the effects of RBC transfusion in palliative care patients.

Design

This international, multisite, prospective consecutive cohort study assessed target symptoms (fatigue, breathlessness, generalised weakness, or dizziness) prior to transfusion and at day 7 by treating clinicians, using National Cancer Institute Common Terminology Criteria for Adverse Events. Assessment of harms was made at day 2.

Setting/participants

One-hundred and one transfusions with day 7 followup were collected. Median age was 72·0 (IQR 61·5-83·0) years, 58% male, and mean Australian-modified Karnofsky Performance Status of 48 (SD 17).

Results

A mean 2·1 (SD 0·6) units was transfused. The target symptom was fatigue (61%), breathlessness (16%), generalized weakness (12%), dizziness (6%) or other (5%). Forty-nine percent of transfusions improved the primary target symptom, and 78% of transfusions improved at least one of the target symptoms. Harms were infrequent and mild. An AKPS of 40-50% was associated with higher chances of symptomatic benefit in the target symptom, however no other predictors of response were identified.

Conclusions

In the largest prospective consecutive case series to date, clinicians generally reported benefit, with minimal harms. Ongoing work is required to define the optimal patient- and clinician-reported haematological and functional outcome measures to optimise the use of donor blood and minimise transfusion-associated risk.

What is already known about the topic?

- Anaemia is common in palliative care, and may contribute to common symptoms in palliative care such as breathlessness and fatigue.
- Red blood cell transfusions are used to treat anaemia in palliative care patients, though the evidence base for the benefit and harms is limited.

What this paper adds

- Fatigue is the most common target symptom for which transfusions are used in palliative care patients.
- Clinicians assessed target symptom improved in approximately 50% of transfusions, however there were no clear predictors of benefit.
- Harms of transfusion were minimal.

Implications for practice, theory or policy

- Blood transfusions for palliative care patients do provide subjective benefit from both clinician- and patient-perspective. Whilst there are no clear predictors of those who benefit, transfusions should be assessed on an individual patient and transfusion basis to determine benefit and indication for future transfusions.
- Ongoing work is required to determine the optimal outcome measures for the benefit of blood transfusions in palliative care patients.

Introduction

Anaemia is common in palliative care patients, with reported inpatient prevalence varying from 50% for any admission to 90% in the last admission before death.[1-5] Causes include chronic inflammation, erythropoietin deficiency, bone marrow infiltration, bleeding, haematinic depletion and treatment effects.

Anaemia may contribute to symptoms including chronic breathlessness and fatigue, limiting quality of life and function.[6] Reversing anaemia through red blood cell (RBC) transfusion may help optimise function and reduce key symptoms. Transfusions are administered in 5-18% of palliative care patients, with higher rates in haematological patients, inpatients and those managed by oncological services.[7-11]

Evidence addressing the net effects (benefits and harms) of RBC transfusions in palliative care is limited, highlighted in two recent systematic reviews.[1,2] These reviews found most patients reported symptomatic benefit for a few weeks, low rates of adverse events, but no baseline predictors of the people most likely to benefit.

Concerns that need to be addressed in prospective studies include transfusion risks (minor circulatory overload, through to life-threatening complications such as lung injury, significant circulatory overload, sepsis, or blood group incompatibility). Transfusions used late in life may be associated with reduced survival[12] and mortality rates 13-33% have been reported for these patients in the fortnight following RBC transfusion,[8,13] likely reflecting the advanced stage of illness rather than a cause-and-effect relationship.

RBC transfusions are also relatively expensive; estimates of the cost of preparation and storage of one RBC unit is US$284 in Australia and US$210-343 in the United States,[14,15] with the total cost (including administration) of a single unit RBC transfusion in US hospitals between US$522-1183.[16] RBC are also a limited resource, raising ethical challenges for palliative care clinicians in balancing individual patient needs and the wider societal requirements.[17]

The aim of this study was to quantify prospectively in a multi-site, consecutive cohort of hospice / palliative care patients the net clinical effects on anaemia-related symptoms of RBC transfusions to help clinicians optimise future care. This study utilised the methodology of an international pharmacovigilance series,[18] but is the first to examine a non-pharmacological intervention, and complements the work of the International Haemovigilance Network.[19]

Methods

This study collected data on RBC transfusions administered as part of routine clinical using an established methodology[18]. Patient demographics, disease, comorbidities (unweighted Charlson Comorbidity Index (CCI)), clinical phase and functional state using the Australia-modified Karnofsky Performance Scale (AKPS) were collected.[20-22]

Benefits and harms were assessed by treating clinicians using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) Likert scales with a change of ≥1 considered as clinically significant.

An expert committee defined target symptoms (fatigue, breathlessness, generalised weakness or dizziness) and harms (fever, infusion related reaction, infusion site extravasation, haemolysis, heart failure, oedema limbs, allergic reaction and anaphylaxis). Clinicians were asked to nominate a primary symptom that RBC transfusion was targeting. Symptoms were assessed at baseline and day 7 for benefits on the basis that transfusions in the palliative setting should give benefits within a few days and be maintained beyond a few days. Harms were assessed at baseline, day 2 and on an *ad*

hoc basis throughout the 7 days on the basis that the majority of harms would be transfusion-related and would present early.

Non-identifying data were then entered *pro forma* using an 128-bit encrypted Web portal (www.caresearch.com.au). Descriptive statistics were used for patient characteristics. Logistic regression was performed for target symptom benefit and benefit in any symptom using age, sex, AKPS, phase, CCI and baseline haemoglobin. *Post-hoc* analysis included comparison of different strata of AKPS on transfusion response using chi-squared test. A p value less than 0.05 was considered statistically significant. Analyses were performed in SPSS version 24 (IBM Corp, Armonk, NY).

Ethical approval was obtained for each participating site, either as ethical waivers (as quality assurance work) or approval as low-risk research.

Results

Seventeen sites (inpatient hospice/palliative care units, consultative services and ambulatory clinics) in five countries entered data (January 2014 - September 2015). At baseline, 141 patients were included, 131 had day 2 toxicity data, and 101 had day 7 benefit data (Table1; Figure 1a).

Patients had a mean 2.1 (SD 0.6) units of RBC transfused, and the predominant primary target symptom was fatigue (62/101 (61%)).

Benefit in the primary target symptom was found in 46/101 (49%; range 42%-67%; Table 2) and in any target symptom in 79/101 (78%). Changes in primary target symptom ratings are shown in Table 3. One target symptom improved in 30/101 (30%), two symptoms in 21/101 (21%), three in 18/101 (18%) and four to five symptoms in 10/101 (10%).

Harms at day 2 were few (16/131 (12%; Table 4)), and severity was mild. A further four patients had *ad hoc* reports of harm. Harms included a delayed allergic reaction, an infusion related reaction, delirium, constipation, seizure and vomiting.

The maximal benefit in the primary target symptom was found at an AKPS of 50 (Figures 1a-c), with benefits increasing with higher levels of function. Patients receiving transfusions with a baseline AKPS of 20-30, 40-50 and 60-70 had benefits in the primary target symptom of 36%, 66% and 41% respectively (p 0.03). Conversely, there was a small reduction in benefit rates with increasing baseline haemoglobin.

Logistic regression found no impact of any baseline factors on benefit target symptoms.

Discussion

In the largest prospective series of RBC transfusions in palliative care patients to date, 49% of patients reduced their primary target symptom, with 78% benefiting for any target symptom. Fatigue was the most common symptom targeted. There were no clear predictors of response by primary target symptom, baseline haemoglobin and phase, though increasing function may have some impact. Harms to patients were infrequent, and minimal.

Subjective improvement has been reported following RBC transfusion in palliative care (51-94%), but when self-reported assessment tools are used for fatigue, breathlessness and well-being, a less

consistent picture emerges.[3,7,10,11,13,23] Clinicians commonly report improvement following RBC transfusion in 65-89% of patients.[3,8,9,11]

Many harms were unlikely related to RBC transfusion. Previously reported harm rates are 6-8%, though these rates do not always reflect systematic collection, nor incorporate severity. [3,13]

The lack of predictors of response to palliative RBC transfusion has been reported previously.[1] Whilst this finding may be true, it may also be due to small study sizes or widely varying patient populations studied.

The finding that patients with an AKPS of 40-50% responded to RBC transfusions more often than those with lower or higher AKPS warrants further study. Three studies have shown no improvement in functional levels following RBC transfusions, using the Barthel Index and Australia-modified Karnofsky Performance Scale.[7,11,13] Without a control arm, it cannot be established whether these people had current levels of function better maintained.

To date, the choice of an optimal outcome measures for RBC transfusions in palliative care patients remains elusive but would ideally incorporate self-report global, symptom-specific and quality of life measures, and functional changes.

In addition to Phase IV studies such as this, to ultimately address the net effect of RBC transfusion patients in palliative care would require a comparison arm. A possible study design to address this question, as used for other clinical questions, is to compare a generous versus conservative threshold for transfusion.

Clinically, RBC transfusions in palliative care patients require a careful, mechanistic based approach, accounting for the context of the patient, their comorbidities, prognosis and their goals of care. Basic investigations of treatable causes for anaemia in palliative care are not routinely undertaken – 9% of patients having transfusions in one study had haematinics checked (B12, folate, ferritin or combination).[8] By contrast, another study of anaemic palliative care patients found occult folate and B12 deficiency in nearly 30% and 7% respectively.[4] Could the use of erythropoietin for those with renal dysfunction, or iron supplementation for those with absolute or functional iron deficiency, ameliorate the need for transfusions in some sub-groups?

Limitations

Data beyond seven days were not gathered. A Cochrane review of RBC transfusions in advanced cancer found that the benefit lasted around 14 days.[2] Other concurrent treatments or changes in clinical condition which may have affected the symptom scores were not collected. The NCI CTCAE only uses a three-point rating scale (five point for breathlessness) without psychometric validation however evidence demonstrates favourable validity, reliability, and responsiveness in a large cohort study.[24]

The incomplete data of benefit for 39 patients limits the generalisability. Reporting of harms beyond day 2 was *ad hoc* and is unlikely to reflect all harms.

Conclusion

In palliative care patients, clinicians believed RBC transfusion gave subjective improvement to three-quarters of patients, with minimal harm. The optimal methodology to measure the net effect of transfusions remains challenging. Future studies should examine treatable causes of anaemia and consider objective measures of response to transfusions, such as activity monitors.

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