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Paper:

Brown, E, Hurlow, A, Rahman, A, Closs, SJ and Bennett, MI (2010) *Assessment of Fatigue after Blood Transfusion in Palliative Care Patients: A Feasibility Study*. *Journal of Palliative Medicine*, 13 (11). 1327 – 1330.

<http://dx.doi.org/10.1089/jpm.2010.0143>

Assessment of Fatigue after Blood Transfusion in Palliative Care Patients: A Feasibility Study

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Abstract

Background: Blood transfusions are often used as a potential treatment for cancer-related fatigue in anaemic palliative care patients. However, evidence of benefit using validated outcomes measures is lacking.

Aim: The aim of this study was to test the feasibility of using two such tools; the Brief Fatigue Inventory and FACT F-fatigue subscale, to measure change in fatigue following a blood transfusion.

Method: Anemic cancer patients receiving specialist palliative care and undergoing transfusion for fatigue, completed the tools pre- and 3 days post-transfusion.

Results: Thirty patients with cancer-related fatigue who received a blood transfusion completed the study. Both measures were capable of detecting statistical and clinically significant change in fatigue following transfusion. Furthermore, the measures showed significant differences between patients that did, or did not, report an overall improvement in fatigue. Patients found the measures easy to complete with no preference for one over another. Future clinical trials of blood transfusion for the management of fatigue should incorporate these validated outcome measures.

Introduction

CANCER-RELATED FATIGUE has been defined as a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.¹ It has been reported as one of the most common cancer-related symptoms, with a prevalence of 32%–90%.^{2,3} Fatigue has a significant impact on quality of life (QOL); 61% of patients with cancer reported that it affected their lives more than cancer-related pain and 19% were so debilitated by fatigue that they felt an urge to die.⁴ Despite the scale and depth of this symptom it remains under recognised and under treated in patients with cancer.¹ This may reflect a failure to acknowledge its profound impact on QOL, a general acceptance of the inevitability of fatigue and a perceived paucity of treatment options.

The cause of cancer-related fatigue is multifactorial and not clearly understood. Various studies have shown an association between fatigue and biochemical, physical and psychological factors.^{5–7} The management of cancer-related fatigue involves

correction of reversible causes, including anaemia, the use of pharmacologic agents, principally steroids and central nervous system stimulants, lifestyle modification, and exercise.

In practice, since anemia can be identified in approximately 70% of hospice inpatients, the question of whether it is significantly contributing to the symptom of fatigue and therefore should be treated is one commonly encountered by physicians.⁸ Blood transfusion remains the mainstay of treatment for anemia-associated fatigue, and 6%–13% of hospice inpatients are transfused.^{9,10} Although there is no absolute level of hemoglobin to trigger transfusion, mean pretransfusion hemoglobin is usually approximately 8 g/dL with most patients receiving a single transfusion of 2–3 units of blood.^{9,11,12} The mean number of days between transfusion and death ranges from 47 to 117 days.^{9,10,12,13}

In a study of 91 palliative care patients, shortness of breath, well-being, and strength improved significantly 2 days post-transfusion with improvements in well-being and strength sustained over 2 weeks. In this study 76% of patients felt better for the transfusion after 2 days and 72% at 2 weeks.¹¹ In a separate study of 31 patients receiving a blood transfusion

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Accepted June 23, 2010.

after admission to a specialist palliative care unit, 51% reported an improvement in well-being the day after transfusion.¹⁰ A more recent study of 61 transfused palliative care patients reported a significant improvement in shortness of breath, well-being, and fatigue the day after transfusion. However, only in well-being was this improvement sustained at 2 weeks.¹³ In these studies fatigue was either not specifically measured or not measured using a validated fatigue assessment tool.

A number of tools have been developed and validated for the assessment of fatigue in cancer patients. These include the Functional Assessment of Cancer Therapy–Fatigue subscale (FACT F–Fatigue Subscale) and the Brief Fatigue Inventory (BFI).^{14,15} Both tools are short yet retain strong psychometric properties.¹⁶

This multicenter, prospective study was designed to evaluate the feasibility of using these two tools to assess the efficacy of blood transfusion in cancer-related fatigue treatment in a future large open label study exploring predictors of response to transfusion.

Methods

The study received ethical approval from Leeds East Research Ethics Committee (REC reference no. 07/H1306/96) and all patients provided written informed consent.

Patients were recruited from four specialist palliative care units over a 17-month period, between 2007 and 2009. Patients were invited to participate if they were receiving specialist palliative care from one of the units, either as an inpatient or via day therapy, and a blood transfusion was planned to manage their fatigue in keeping with local unit practice. Inclusion criteria were: more than 18 years of age, a cancer diagnosis, able to provide written informed consent, and judged by their clinician to have the mental capacity to participate in the study. Recruitment was continued until 30 patients had analyzable data, in keeping with guidance on pilot study design.¹⁷

Fatigue was measured using the FACT F–Fatigue Subscale and BFI questionnaires. The FACT–Anemia was designed to measure QOL and anemia-related symptoms in patients with cancer using a 55-item questionnaire.¹⁵ The 13-item fatigue subscale of this questionnaire has been shown to have good internal reliability ($\alpha = 0.93, 0.95$), has been used to predict hemoglobin levels and to assess response to fatigue treatment.^{15,18} Each item is measured on a 5-point Likert scale with a total possible score of 0–52, where higher scores denote lower levels of fatigue. An improvement or deterioration in score of 3 or more points indicates a minimal clinically important difference.¹⁹

The BFI was developed and validated internationally for the assessment of fatigue in patients with cancer.¹⁴ It has good internal reliability ($\alpha = 0.96$) and has been used to assess response to fatigue treatment.^{14,20} The 9-item questionnaire rates fatigue severity (now, usual and worst) and its impact on function using 0–10 numerical rating scales where higher scores denote higher levels of fatigue. The mean of the total score is calculated as the global fatigue score (0–10). Severe fatigue, with the greatest impact on function, is indicated by a worst fatigue level of 7 or more.¹⁴

We measured fatigue using the two scales in the 24 hours prior to transfusion and 3 days after the last unit trans-

fused. This time frame was chosen to allow levels of 2,3-diphosphoglycerate in the transfused erythrocytes to return to normal. This affects the affinity of hemoglobin for oxygen and therefore may affect transfusion effectiveness.²¹ Participants were asked to state their preference of questionnaire with regards to ease of completion and relevance to their situation after completion of the baseline questionnaires. During the final assessment they were asked to indicate “yes” or “no” to a simple question enquiring whether they felt the blood transfusion had helped their fatigue.

Data on baseline demographics, cancer type, presence of metastases, pretransfusion hemoglobin, place of transfusion, and number of red cell units transfused were collected.

Primary outcome measures were change in FACT F–Fatigue Subscale and BFI between baseline and 3 days posttransfusion. Secondary outcome measures were patients’ assessment of the impact of transfusion on fatigue, preference for fatigue tool, and recruitment rate. We did not check posttransfusion hemoglobin because this is not normal clinical practice.

Change in paired fatigue scores between baseline and 3 days posttransfusion were compared using Wilcoxon signed-rank test. Median changes in fatigue scores for patients that reported an improvement (responders) and those who did not (nonresponders) were compared using the Mann-Whitney *U* test. All *p* values were two-sided and a value of <0.05 was considered significant. Data were analyzed using SPSS 16.0 software (SPSS Inc., Chicago, IL).

Results

Of the 58 patients approached, 48 commenced the study with 32 completing. Data for analysis were obtained from 30 patients (1 patient did not meet the inclusion criteria and 1 had data missing). Of those who commenced the study but did not complete it, 13 of 48 dropped out between the first and second set of questionnaires, which was due to deteriorating health or death in 8 of 48 and 1 of 48 due to finding the questionnaires too arduous.

The mean age was 68 (range, 53–91) and 19 of 30 patients were male. The site of the underlying primary cancer was as follows: gastrointestinal tract, 14; prostate, 7; respiratory system, 2; breast, 2; hematological, 2; gynecological, 2; renal–urinary tract, 2; other, 1; and 24 of 30 had metastatic disease. Baseline median fatigue scores were 12.5 (1.00–47.67) on the FACT F–Fatigue Subscale (0–52), 7.72 (1.89–10.0) on the BFI global fatigue score (0–10) and 9.0 (3.0–10.0) on worst fatigue on BFI (0–10).

The majority of transfusions (28/30) occurred on an inpatient basis. The mean pre transfusion hemoglobin level was 7.96 g/dL (5.3–10.7 g/dL). The mean number of units transfused was 2.53 (range, 1–5) with 18 of 30 of patients receiving 2 units. Transfusion episodes occurred over a mean of 1.6 days (range 1–4).

There was a statistically significant improvement in fatigue as measured by both fatigue tools between baseline and 3 days posttransfusion (Table 1). Compared to baseline the median change in score improved by 5 points ($p < 0.001$) on the FACT F–fatigue subscale, and by 1.01 points ($p < 0.05$) on the BFI. In terms of the proportion of patients experiencing a minimal clinically important difference, 21 of 30 patients reported an improvement in FACT F–Fatigue Subscale of 3 or

TABLE 1. MEDIAN FATIGUE SCORES

<i>Fatigue tool</i>	<i>Pretransfusion (range)</i>	<i>Posttransfusion (range)</i>	<i>Median change (range)</i>
FACT F-Fatigue Subscale	12.5 (1.0–47.67)	23.50 (0.0–52.0)	5.00 ^a (–9–37)
BFI GFS	7.72 (1.89–10.0)	5.44 (0.56–8.88)	–1.01 ^b (–9.44–4.22)
BFI worst	9.0 (3.0–10.0)	6.50 (0–10)	–1.50 ^a (–10–4)

^a*p* ≤ 0.001.

^b*p* ≤ 0.05.

FACT F-Fatigue Subscale, Functional Assessment for Cancer Therapy Fatigue Subscale; BFI GFS, Brief Fatigue Inventory Global Fatigue Score; BFI worst, Brief Fatigue Inventory worst fatigue score.

more points. The number of patients reporting severe fatigue on the worst fatigue domain of the BFI (score of 7 or more) fell from 27 of 30 patients at baseline to 15 patients following transfusion.

Following transfusion 22 patients reported that it had helped their fatigue, 3 were unsure, and 5 reported no noticeable improvement. Nonresponders were classed as those who were unsure and those who noted no improvement following transfusion. No significant difference was found between these two groups at baseline in either fatigue score or other characteristics. After transfusion there was a statistically significant difference in fatigue scores between these groups, with responders showing an improvement in fatigue (Table 2). Of the 21 patients who achieved at least a minimal clinically important difference using the FACT F-Fatigue Subscale, 18 classified themselves as responders, and 3 did not.

Regarding ease of use, 12 patients preferred the FACT F-Fatigue Subscale, 9 the BFI and 9 expressed no preference. Regarding relevance of the questionnaire, 12 patients had no preference, 10 preferred the FACT F-Fatigue Subscale and 7 the BFI, none of which reached statistical significance.

Discussion

Both the FACT F-Fatigue Subscale and BFI were able to detect statistically significant changes in fatigue after a blood transfusion. They also appear to reflect the patient experience of improvement in fatigue. After transfusion, changes in the scores of 21 patients suggested that this statistically significant change was clinically meaningful also.

This study adds to the findings of previous studies showing an improvement in well-being and strength after blood transfusion by specifically measuring fatigue using validated fatigue tools. Patient response has previously been elicited by asking patients whether they felt better 1–2 days after trans-

fusion or whether their well being was improved the day after transfusion. We specifically asked whether the blood transfusion had helped fatigue as it is likely that semantics are important here. Weakness, strength, and well-being may not be equivalent to fatigue and this justifies the need to use validated assessment tools.

Despite the development of other treatment options such as psychostimulants,²² the clinical issue remains that the majority of specialist palliative care patients are both anemic and suffering from fatigue and that blood transfusion is understandably considered an option for management. However, this treatment option is one that is a valuable resource, invasive to the patient, and not without risk. To complicate decision making further, it is difficult to determine the chance of benefit from transfusion in this setting using clinical data. For example, two studies in palliative care patients found no significant correlation between haemoglobin level and fatigue.^{23,24} Similar studies in this context have also found that pretransfusion hemoglobin level does not correlate with response to transfusion.^{10,11} We were also unable to detect in our study any pretransfusion differences in patients that subsequently did, or did not, respond based on self-ratings. These findings contrast with studies in patients with cancer without advanced disease where hemoglobin level is more closely correlated to fatigue and clinical response to hemopoetic growth factors.²⁵ This highlights the multifactorial nature of fatigue in advanced disease.

We did not set out to test the effectiveness of blood transfusion for fatigue and so our findings of benefit should be regarded with caution. Our study was not blinded or placebo controlled and there may be a strong placebo response to receiving a blood transfusion. Most transfusions occurred on an inpatient basis and the act of admission to a specialist palliative care unit may in itself aid fatigue as might improvements in control of other symptoms. We did not control for changes in baseline medications, including potential

TABLE 2. MEDIAN FATIGUE SCORES OF RESPONDERS COMPARED TO NONRESPONDERS

<i>Fatigue tool</i>	<i>Response group</i>	<i>Pretransfusion</i>		<i>Posttransfusion</i>		<i>Median change</i>	
		<i>Score</i>	<i>p</i>	<i>Score</i>	<i>p</i>	<i>Score</i>	<i>p</i>
FACT F-Fatigue Subscale	Nonresponders	9.00	0.111	8.00	0.001	–1.00	0.012
	Responders	18.00		27.00		9.50	
BFI Global Fatigue Score	Nonresponders	8.28	0.313	8.06	0.005	–0.50	0.041
	Responders	7.06		4.83		–1.71	
Worst fatigue on BFI	Nonresponders	8.00	0.071	9.00	0.008	0.00	0.08
	Responders	8.00		6.00		–2.50	

p values calculated between responders and nonresponders.

FACT F-Fatigue Subscale, Functional Assessment for Cancer Therapy Fatigue Subscale; BFI, Brief Fatigue Inventory.

treatments for fatigue although in our local centers it is good clinical practice not to start a second treatment while awaiting the outcome of a first.

In summary, this is the first study to investigate validated measures of fatigue to assess response to transfusion in patients within palliative care services. We have demonstrated that these measures are capable of detecting statistical and clinically significant change in fatigue following transfusion. Furthermore, the measures showed significant differences between patients that did, or did not, report an overall improvement in fatigue. Patients found the measures easy to complete with no preference for one over another. Future clinical trials of blood transfusion for the management of fatigue should incorporate a validated outcome measures such as FACT F–Fatigue Subscale or BFI. Although these data support a potential effect of blood transfusion on quality of life for some patients, there remains a need to determine predictors of response to blood transfusion before we can state this with certainty.

Acknowledgments

We would like to thank all the participants and staff at the following Specialist Palliative Care units: St. Gemma's Hospice, Leeds; Wheatfields Hospice, Leeds; Wakefield Hospice and Kirkwood Hospice, Huddersfield. In particular thanks to Dr. Charlotte Clare and Dr. Anne Marie Seymour who acted as coinvestigators at their respective sites.

Author Disclosure Statement

No competing financial interests exist.

References

- Mock V, Atkinson A, Barsevick AM, Berger AM, Cimprich B, Eisenberger MA, Hinds P, Kaldor P, Otis-Green SA, Piper BF: Cancer-related fatigue: Clinical practice guidelines in oncology. *J Natl Comp Canc Netw* 2007;5:1054–1078.
- Ashbury FD, Findlay H, Reynolds B, McKerracher K: A Canadian survey of cancer patients' experiences: Are their needs being met? *J Pain Symptom Manage* 1998;16:298–306.
- Solano JP, Gomes B, Higginson IJ: A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. *J Pain Symptom Manage* 2006;31:58–69.
- Curt GA: The impact of fatigue on patients with cancer: Overview of fatigue 1 and 2. *Oncologist* 2000;5:9–12.
- Sood A, Moynihan TJ: Cancer-related fatigue: An update. *Curr Oncol Rep* 2005;7:277–282.
- Shafqat A, Einhorn LH, Hanna N, Sledge GW, Hanna A, Juliar BE, Monahan P, Bhatia S: Screening studies for fatigue and laboratory correlates in cancer patient undergoing treatment. *Ann Oncol* 2005;16:1545–1550.
- Hwang SS, Chang VT, Rue M, Kasimis B: Multidimensional independent predictors of cancer-related fatigue. *J Pain Symptom Manage* 2003;26:604–614.
- Dunn A, Carter J, Carter H: Anaemia at the end of life: Prevalence, significance, and causes in patients receiving palliative care. *J Pain Symptom Manage* 2003;26:1132–1139.
- Brown E, Bennett M: Survey of blood transfusion practice for palliative care patients in Yorkshire: implications for clinical care. *J Palliat Med* 2007;10:919–922.
- Monti M, Castellani L, Berlusconi A, Cunietti E: Use of red blood cell transfusions in terminally ill cancer patients admitted to a palliative care unit. *J Pain Symptom Manage* 1996;12:18–22.
- Gleeson C, Spencer D: Blood transfusion and its benefits in palliative care. *Palliat Med* 1995;9:307–313.
- Laird BJA, Whyte G, Laird JH, Soutar RL, Welsh J, Fallon MT: An observational study of red cell transfusion in specialist palliative care. *Palliat Med* 2008;22:874–875.
- Mercadante S, Ferrera P, Villari P, David F, Giarratano A, Riina S: Effects of red blood cell transfusion on anaemia-related symptoms in patients with cancer. *J Palliat Med* 2009;12:60–63.
- Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, Huber SL: The rapid assessment of fatigue severity in cancer patients: Use of the brief fatigue inventory. *Cancer* 1999;85:1186–1196.
- Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E: Measuring fatigue and other anemia-related symptoms of cancer with the functional assessment of cancer therapy (FACT) measurement system. *J Pain Symptom Manage* 1997;13:63–74.
- Schwartz AH: Validity of cancer-related fatigue instruments. *Pharmacotherapy* 2002;22:1433–1441.
- Browne RH: On the use of a pilot sample for sample size determination. *Stat Med* 1995;14:1933–1940.
- Spathis A, Dhilian R, Booden D, Forbes K, Vrotsou K, Fife K: Modafinil for the treatment of fatigue in lung cancer: A pilot study. *Palliat Med* 2009;23:325–331.
- Cella D, Eton DT, Lai J, Peterman AH, Merkel DE: Combining anchor and distribution-based methods to derive minimal clinically important differences on the functional assessment of cancer therapy (FACT) Anemia and fatigue scales. *J Pain Symptom Manage* 2002;24:547–561.
- Hanna A, Sledge G, Mayer ML, Hanna N, Einhorn L, Monahan P, Daggy J, Bhatia S: A phase 2 study of methylphenidate for the treatment of fatigue. *Support Care Cancer* 2006;14:210–215.
- Davies A, Wang S: Blood transfusions in patients with advanced cancer. *Palliat Med* 1997;13:318.
- Minton O, Sone P, Richardson A, Sharpe M, Hotopf M: Drug therapy for the management of cancer related fatigue. *Cochrane Database Syst Rev* 2008;1:CD006704.
- Stone P, Hardy J, Broadley K, Tookman AJ, Kurowska A, Hern RA: Fatigue in advanced cancer: A prospective controlled cross-sectional study. *Br J Cancer* 1999;79:1479–1486.
- Noergaard Munch T, Zhang Z, Willey J, Lynn Palmer J, Bruera E: The association between anaemia and fatigue in patients with advanced cancer receiving palliative care. *J Palliat Med* 2005;8:1144–1149.
- Cella D, Kallich J, McDermott A, Xu X: The longitudinal relationship of haemoglobin, fatigue and quality of life in anemic cancer patients: Results from five randomized clinical trial. *Ann Oncol* 2004;15:979–986.

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