

REVIEW ARTICLE

**Blood Transfusions and Palliative Care:
Systematic Literature Review**

Authors

Marta Lorenzo Ibáñez^a, Dra. María Nabal Vicuña^b, Luis May Málaga^c, Diana C. Forero Vega^d

Affiliations

^a Degree in Medicine. Lleida University (Universidad De Lleida). Spain.

^b Doctor in Medicine and Surgery. Family and Community Medicine Specialist. Master in Palliative Medicine. Master in Bioethics. Palliative Care Unit Coordinator at the Arnau de Vilanova University Hospital (Lleida, Spain).

^c Degree in Medicine and Surgery. Family and Community Medicine Specialist. Master in Palliative care. Palliative Care Unit at the Arnau de Vilanova University Hospital (Lleida, Spain).

^d Degree in Medicine and Surgery. Family and Community Medicine Specialist. Master in Palliative Integrated Care for Persons with Advanced Diseases. Palliative Care Unit at the Arnau de Vilanova University Hospital (Lleida, Spain).

Correspondence

Diana C. Forero Vega

Email: dforerovega@hotmail.com

Abstract:

Anemia is an important condition related with symptoms in the later stages of disease; according to World Health Organization its prevalence is between 68-77% in patients with advanced cancer. There is no specific clinical guideline and we do not have clear evidence of the effect of blood transfusions in palliative care.

Objective: Understand indicators and complications of the transfusions on advanced cancer patients.

Methodology: In 2019 a systematic review on PubMed and Cochrane took place, using the key words: Palliative care AND Blood transfusion; analyzing: Type of study; sample size; Pathologies; transfusion criterion; Transfusions benefits; side effects; Survival; and amount of transfused concentrates.

Results: 81 articles selected, adding 6 after a full text reading. For the most part, patients with solid tumors are described and some with no oncology pathology. The symptoms indicated by the transfusion are: Fatigue, dyspnea, asthenia, headache and/or brisk bleeding. Transfused unit's average was 2 units. Only two studies present a post-transfusion recovery and less than half display information as to associated mortality.

Conclusions: There is no consensus regarding the transfusion indication. The asthenia recovery, well-being, and quality of life based on subjective criteria, are the main effects described. More studies are required.

Keywords: Palliative care AND Blood transfusion.

INTRODUCTION

The main objective of palliative care is to improve the quality of life of the patients that present life-threatening diseases by the means of preventing and relieving their suffering ^[1]. The main symptoms that interfere with these patients' quality of life are fatigue, pain, and dyspnea. Anemia is an important condition related with dyspnea, as well as fatigue, in the later stages of the disease and is present in 68-77% of the patients with advanced cancer ^[2]. Blood transfusions are used as a treatment of the related anemia symptoms.

There is no specific clinical protocol/guideline and we do not have clear evidence of the effect of blood transfusions in palliative care. This procedure is not exempt neither from risks nor from side effects such as fluid overload or infections. In addition, these patients present an impairment in the general condition as well as cachexia and functional impairment, all due to the diseases progression, which are important to be taken into account when considering any kind of procedure, such as blood transfusions.

Furthermore, there is an ethical debate in regards of the implementation of blood transfusions to this group of patients. Beneficence, non-maleficence, autonomy and justice, as well as the use of resources, should be considered in the decision-making process for this treatment.

There are still many unanswered questions such as: Which factors should be contemplated in the decision of transfusion? Which are the effects of the transfusions on the symptoms, quality of life and survival? Is there a risk of adverse effects on the palliative patients?

Because of this, we consider relevant and necessary to conduct a systematic review of the available literature about this matter and so we can be able to answer the questions above.

OBJECTIVE

Better understanding of the indicators and complications, described in the referenced articles, of blood transfusions on advanced cancer patients.

METHODOLOGY

On January 2019 articles published in English and Spanish between 01/01/2013 and 01/31/2019 were searched on the PubMed and Cochrane databases.

The selection criteria were as follows:

- Abstract availability
- Adults (>18 years)
- Language: Spanish and English

The exclusion criteria were as follows:

- <18 years.
- Onco-hematological diseases
- Studies on animals

Articles that did not appear in the initial search but were related with the found articles, were also added to the literature.

Key words used for searching articles were "**Blood transfusion AND palliative care**".

All studies that analyzed the use of blood transfusion on palliative care patients were included. Clinical cases and case series, as well as press releases and other opinion pieces/articles were excluded.

The article selection was first done based on the title of the article. Then, based on the article's abstract, articles that were not related to this study were excluded. Lastly, a last exclusion was made after reading the full article.

The analyzed parameters in the articles were as follows:

- Type of study
- Study sample
- Pathologies
- Transfusion's criterion
- Results: Transfusion's benefits
- Side effects
- Survival
- Amount transfused
-

RESULTS

In PubMed database a total of 64 articles were found. From the 64 articles, 11 achieved the inclusion and exclusion criteria based on the title, 2 of those were excluded based on the abstract. After reading the remaining articles only 6 articles were

included (Figure 1).

In the Cochrane database a total of 17 articles were found (1 review and 16 essays). Only 1 of the 17 was included based on the title and after reading the article's abstract it was discarded (Figure 2).

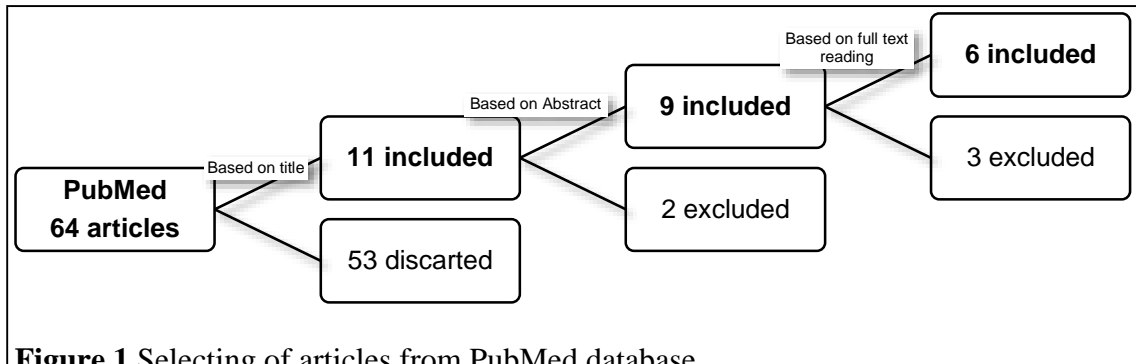


Figure 1 Selecting of articles from PubMed database

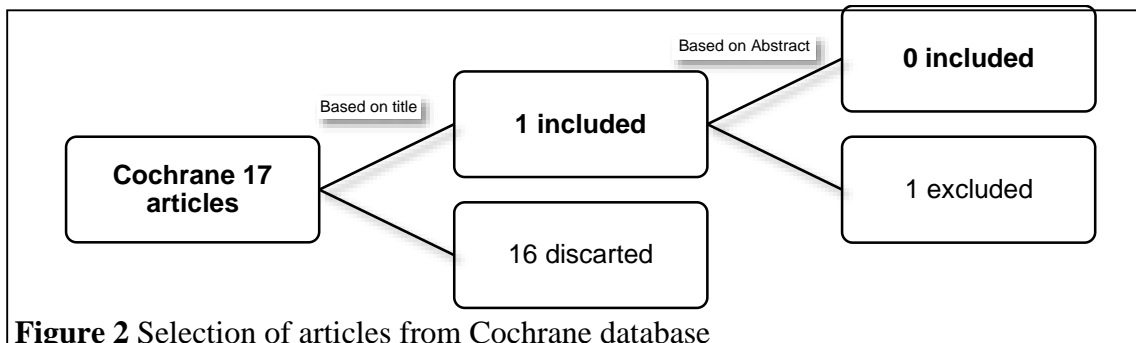


Figure 2 Selection of articles from Cochrane database

Thus, 6 articles were included from which:

- 2 are systematic reviews ^[4,8]
- 2 are prospective cohort studies ^[3,7]
- 1 is a prospective observational study ^[5]
- 1 is a descriptive retrospective study ^[6]

The main characteristics of each study are summarized in Table 1.

Table 1: Included studies in the systematic literature review, which link blood transfusion and palliative care

Author	Year	Type of study	N	Pathology	Transfusion's criteria	Results	Side effects	Survival	Quantity
Timothy H.M, et al. ³	2017	Prospective cohort	141 patients	<ul style="list-style-type: none"> Advanced malignancy (96%) Heart failure (2%) Others (1%) 	<ul style="list-style-type: none"> Fatigue (59%) Dyspnea (21%) Generalized weakness (9%) Dizziness (5%) 	<u>Benefit: 101/141</u> <ul style="list-style-type: none"> 49% in primary guiding symptom 78% any guiding symptom 51-94% subjective improvement No significant improvement on Fisher's test Low severity side effects (12%) Maximum benefit in the primary guiding symptom achieved with AKPS of 50 	<u>Toxicity 2nd day: 16/131</u> <ul style="list-style-type: none"> Fever Reactions related with the infusion Local extravasation Homolysis Heart failure Oedemas Allergic reactions Others 	•	2.1
Timothy H.M, et al. ⁷	2016	Prospective cohort	31 patients (44 blood transfusions)	<ul style="list-style-type: none"> Advanced malignancy (97%) 	<ul style="list-style-type: none"> Fatigue/Lethargy (93%) Dyspnea (16%) Headache (7%) Active bleeding (14%) 	<u>Benefit:</u> <ul style="list-style-type: none"> 89% Clinician subjective evaluation. 94% subjective symptoms from the patient Minor according to following scales: RUG-ADL, AKPS, SAS of dyspnea and fatigue (benefit on at least one scale in 50%) Minor improvement of dyspnea and fatigue 	-	64% (28/44)	2.3
K. Neoh, et al. ⁵	2019	Prospective observational	465 transfusions	<u>84% of solid tumors:</u> <ul style="list-style-type: none"> Prostate (17%) Low G-I (16%) High G-I (13%) Lung (8%) Gynecologic (8%) Breast (6%) Renal, hepatic (4%) Bladder (4%) <u>12% hematological neoplasm</u>	<ul style="list-style-type: none"> Low Hb (51%) or low Hb + dyspnea (40%) Fatigue (16%) 	<u>Benefit:</u> <ul style="list-style-type: none"> 18% improvement after 30 days 31% transitory improvement (<14 Days) 11% no improvement 32% death after 30 days Improvement observed generally through subjective input from the clinical. In 53 patients (14%) evaluated with AKPS scale, 83% did not present improvement after 30 days.	-	68% (315/465)	20
S. Goksu, et al. ⁶	2014	Observational retrospective	398 patients	<u>Solid tumors:</u> <ul style="list-style-type: none"> Not small lung cells (27%) Pancreas and biliary tract (10%) Colon (8.8%) Gynecologic (7.3%) Breast (6.5%) 	<ul style="list-style-type: none"> Low Hb(73.9%) Active bleeding (26.1%) 	<ul style="list-style-type: none"> Blood transfused on 38.4% of the patients (42.3% anemic patients) 90% of the patients presented anemia at the time of admission Higher survival in anemic patients who were transfused (153/398) than in those not transfused: 15 days vs 8 days (p<0.001) 	-	Only deceased patients are included in this study	4.37

Table 1: Included studies in the systematic literature review, which link blood transfusion and palliative care

Author	Year	Type of study	N	Pathology	Transfusion's criteria	Results	Side effects	Survival	Quantity
N. Chin-Yee, et al. ⁸	2017	Systematic review	13 articles	<u>Advanced malignancy</u> • Hematologic • Prostate • G-I • Ovarian <u>Other</u>	• Low Hb • Symptomatic anemia (Fatigue, weakness, dyspnea, and/or dizziness) • Active bleeding • Benefit in previous transfusions	• 9/13 articles: Symptoms improvement as primary result. Three subjective scales. Six objective scales (AKPS, FACT-F, ESAS, etc.) • 8/9 improvement of fatigue or GGS • 4/13 improvement of survival • 4/13 increased of Hb • 1/13 sustaining Hb one month after transfusion • 1/13 comparing group: No association between transfusion and fatigue caused by cancer • 2/13 information about improvement's duration: One with an average improvement of 18.5 days. The other one with improvement after 2 days but not after 15 days	77 complications in 3/13 of the studies: • Immune reaction • Local reaction • Reaction to the transfusion • unspecific reactions	-	-
M.E. Uceda, et al. ⁴	2014	Systematic review	43 articles (21 from clinics)	• Hematologic malignancies • Bleeding solid tumors • Hospitalization • Oncological	• Low Hb (<8g/dl) • Clinical parameters	• 6/21 articles: 60% of the patients experienced quality of life or wellbeing improvement • Superior improvement in home discharged patients (78.6%) • Benefits are observed early (Days) but are not maintained after 3 weeks	-	-	<30

Hb = Hemoglobin; RUG-ADL = Resource Utilization Group-Activities of Daily Living; AKPS = Australia-modified Karnofsky Performance Status; SAS = Symptom Assessment Scores; G-I = Gastro-intestinal; FACT-F = Functional Assessment of Cancer Therapy; ESAS = Edmonton Symptom Assessment System; GGS = Good General State of Health

Patients included in the studies present mainly an oncologic pathology (solid tumors). In the *T.H.M To, et al.* study, patients with cardiac failure are included, as well as other patients, although these pathologies represent less than 4%^[3].

The criteria for the blood transfusion were Hemoglobin levels and/or symptomatic anemia. The symptoms that justify the red cells transfusion were: Fatigue, dyspnea, asthenia, headache or brisk bleeding. There was consensus between different works on fatigue associated with low hemoglobin as a reason for blood transfusion.

In almost all studies, the transfused unit's average was 2 units. The only exception was the study *S.Goksu, et al.*, which used a transfused unit's average of 4.37 units with a range from 1 to 24 units^[6].

DISCUSSION

In the 4 observational studies^[3,5,6,7], “the subjective improvement of the symptom evaluated by the clinician” is used as a response measurement for the blood transfusion. This improvement does not represent a significant statistical improvement in the scales. Scales such as *Australia-modified Karnofsky Performance Status or AKPS*^[3,7,5] (Numeric scale from 0 to 100, which evaluates functionality), *Resource Utilization Group-Activities of Daily Living or RUG-ADL*^[7] (Functionality scale from 4 to 18, which evaluates every day activities such as mobility and eating habits) or *Symptom Assessment Scores or SAS*^[7] (Numeric scale, which evaluates symptoms such as fatigue and dyspnea)

In the systematic review the *N. Chin-Yee, et al*^[8], objective scales are used in 6 of the 9 articles. Scales such as *Visual Analog Scale (VAS)*, *Functional Assessment of Cancer Therapy: Fatigue or FACT-F* (Questionnaire about fatigue and symptoms related with anemia in patients with cancer), *Edmonton Symptom Assessment System or ESAS* (Scale that evaluates the subjective

severity of the symptoms in patients with cancer) or *AKPS*. The systemic review of *M.E. Uceda, et al*^[4] does not mention the use of scales. Here the evaluation of the benefits is done based on subjective measures such as wellbeing and quality of life. All the above seems to reflect the lack of agreement regarding the best assessment tool for the symptoms involved in anemia and its response to treatment.

This lack of answers measured by scales can have several justifications: On the one side, one should consider their sensitivity and their limited capacity to detect changes when they are small. On the other hand, it is a multifunctional etiology in which the blood transfusion can play a marginal role. Furthermore, patients and clinical reports improvement can also be influenced by a placebo effect of the blood transfusion. The evaluation of the effect of blood transfusions remains a challenge.

Only two of the reviewed studies address the duration of the improvement. In the review of *M.E. Uceda, et al.* an early improvement of the symptoms is registered (after 2 days), however, it is not maintained after 3 weeks^[4]. *K. Neoh, et al.* shows an improvement on 18% of the patients after 30 days, a transitory improvement (<14 days) on 31% and no improvement on 11%^[5].

S. Goksu, et al. register significantly higher duration in the last period of hospitalization on anemic patients that were transfused (15 days vs 8 days) ($p < 0.001$)^[6]. It is important to point out this is a retrospective study with a sample of deceased oncology patients in a third level hospital, which lacks a Palliative Care Unit. Of the 398 patients, 358 presented anemia (Average hemoglobin of 9.9 g/dl). 153 patients received transfusion (38.4% of all the patients and 43% of the anemic patients). The authors do not indicate which criteria motivated or excluded blood transfusions, nor indicate the group characteristics, thus are the survivable analysis clearly biased; Patients

with the worst prognosis probably received no transfusion and lived for shorter time, but their in-patient care was shorter.

Regarding side effects, two articles [3,8] register side effects of low intensity in a low percentage of the patients. These side effects are: Fever and local and allergic reactions. The rest of the studies do not have this information. There is no congestive heart failure reported as side effect in any of the articles.

K. Neoh, et al. [5] pointed out that patients lacked a proper diagnostic and treatment of the anemia before transfusion. At the same time, a lack of monitoring of *Transfusion-Associated Circulatory Overload* risk, as it is recommended by the *National Institute for Health and Care Excellence*, which recommend a monitoring of the effects through measuring post-transfusional hemoglobin, as well as a transfusion of 1U/24 at most and the need of relating the transfused amount with the patient's weight. Two articles refer to mortality. The article of *T.H.M. To, et al.* [7] registers that 36% of the blood transfusions were done to inpatients that died (50% after 15 days and 38% after a week). *K. Neoh, et al.* [5] register a 32% mortality after 30 days of study's begin. In both studies circumstances and causes of death are not specified. It is also not specified which groups had the highest mortality.

There is a lack of consensus between the articles regarding the hemoglobin values that could justify a blood transfusion. Furthermore, these articles do not monitor or measure earlier levels of hemoglobin in patient where a blood transfusion was conducted, basing the patient's improvement on subjective criteria. *K. Neoh, et al.* [5] only register a measurement of hemoglobine post-transfusion on 28% of the patients. Therefore it would be important to correlate levels of earlier hemoglobin and symptomatology presented with earlier levels and symptomatology improvement.

In *T.H.M. To, et al.* [7] article, a hemoglobin is registered before the blood transfusion (Average hemoglobin of 7.8 g/dL) as well as an average hemoglobin after the blood transfusion (Average hemoglobin of 10.1 g/dL). The study reports lack of significant improvement in objective scales of the patients with the highest levels of hemoglobin (>8 g/dL) or patients with increased hemoglobin ≥ 2 g/dL post-transfusion.

We also observed the lack consensual criteria to justify the therapeutic abstention in the case of the blood transfusions in the patients treated by Palliative Care Teams.

Only two articles present information regarding the place where the transfusions took place. *N. Chin-Yee, et al.* [8] registers the location of the blood transfusion mainly in the Intensive Care Unit (5/13), a smaller percentage in the patient's home (2/13) and in oncology units (1/13). Nevertheless, it is not specified which is the best location for the patient, nor are the associated costs related to the blood transfusions.

M.E. Uceda, et al. [4] argument that for the majority of the authors, it is advisable to do the blood transfusions in the patient's home to ensure the patient's and family's comfort. This allows for a reduction of the hospital costs, for both patient and clinical institution. That only drawback is that blood transfusions require an infrastructure and security measurements, which nowadays is no easy task for many organizations. The costs studies usually generalize the costs at a global hospital level, thus the lack of cost-effectiveness studies of blood transfusions in palliative care, as well as the lack of contrast of executing the process in a hospital or in the patient's home. Does it make sense to make blood transfusions in the patient's home on patients with limited functionality? A question out of scope, but worth asking.

CONCLUSIONS

The amount and quality of the included articles in this systematic review do not allow achieving the initial objectives of this work.

The main indication of the blood transfusion in patients with advanced hematological diseases is the symptomatic anemia (Fatigue, dyspnea, asthenia, and headache).

There is a lack of consensus in palliative care regarding the indication criteria of a blood transfusion. Moreover, there is also a lack of consensus regarding the hemoglobin figures and symptom's intensity of the patients.

The main effect of blood transfusions in the patients is the improvement of the asthenia, wellbeing and quality of life based on subjective criteria. This improvement is significant when scales are used for its evaluation.

Blood transfusions in palliative care present few side effects: Fever, local reactions and allergic reactions. Congestive heart failure is not reported as a side effect.

There is the need of more studies which better define the role of blood transfusions in terms of symptomatic alleviation and survival in advanced cancer patients.

References

1. WHO, <https://www.who.int/cancer/palliative/definition/en/>, [Online].
2. Preston NJ, Hurlow A, Brine J, Bennet MI Transfusiones de sangre para la anemia en pacientes con cáncer avanzado. *Cochrane*, 2012.
3. To T.H.M, LeBlanc T.W, Eastman P, Neoh K, Agar MR, To L.B, et al. The Prospective Evaluation of the Net Effect of Red Blood Cell Transfusions in Routine Provision of Palliative Care. *Journal of Palliative Medicine*, 2017. Vol. 20 (pp. 1152-1157)
4. Uceda Torres M.E, Rodríguez Rodríguez J.N, Sánchez Ramos J.L, Alvarado Gómez F, et al., Transfusion in Palliative Care Patients: A Review of the Literature. *Journal of Palliative Medicine*, 2014. Vol 17 (pp. 88-104)
5. Neoh K, Gray R, Grant-Casey J, Escourt L, Malia C, Boland JW, et al. National comparative audit of red blood cell transfusion practice in hospices: Recommendations for palliative care practice. *Palliative Medicine*, 2019. Vol. 33 (pp. 102-108)
6. Goksu S, Gunduz S, Unal D, Uysal M, Arslan D, Tatli A.M, et al. Use of blood transfusions at the end of life: does it have any effect on survival of cancer patients? *Asian Pacific Journal of Cancer Prevention*, 2014. Vol. 15 (pp. 4251-4254)
7. To T.H.M, To L.B, Currow D.C Can We Detect Transfusion Benefits in Palliative Care Patients? *Journal of Palliative Medicine*, 2016. Vol. 19 (pp. 1110-1113)
8. Chin-Yee N, Taylor J, Rourke K, Faig D, Davis A, Fergusson D, et al. Red blood cell transfusion in adult palliative care: a systematic review. *Transfusion*, 2017. Vol. 58 (pp. 233-241)