

אוניברסיטת בר אילן, הפקולטה לרפואה בגליל

הנושא בעברית: הסיבות למתן עודף של מנות דם

הנושא באנגלית: The reasons for blood transfusion overuse

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הכרת תודה והקדשות

ברצוני להודות בראש ובראשונה למנחה שלי, ד"ר בראשטר על הסבלנות, הנכונות, הנגישות והעזרה שהעניק לי כמנחה.

כמו כן, ברצוני להודות לסטטיסטיקאית של המרכז הרפואי לגליל, נהריה, הגב' אורלי יקיר, על הסבלנות והעבודה שתרמה לניתוח ולעיבוד הסטטיסטי של העבודה.

אבקש להודות למשפחתי, על התמיכה והאוזן הקשבת.

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תקציר

רקע ומטרת העבודה: מתן עירוי דם נחשב כהתערבות טיפולית נפוצה. על אף הסיכונים הטמונים במתן עירוי דם והעלויות הגבוהות הכרוכות בכך, אחוז לא מבוטל של מנות דם נצרך בצורה שאינה מושכלת. גישה רסטריקטיבית המגבילה מתן עירוי דם (לפיה סף המוגלובין $7-8 \text{ g/dL}$), הינה יעילה יותר בתוצא הקליני ובצריכת מנות דם, לעומת גישה ליברלית (לפיה סף המוגלובין 10 g/dL). למרות שמספר המחקרים בנושא רפואת עירוים הולך וגדל עדיין אין ראייה מדעית מספקת לביסוס קווים מנחים, על כן ההנחיות האמריקאיות הקיימות (AABB) לוקות בחסר. משרד הבריאות הישראלי טרם הוציא הנחיות למתן דם. במחקר זה, חקרתי את הסיבות האפשריות לצריכה מיותרת של מנות דם באמצעות בחינת הידע של רופאים ממחלקות שונות במרכז הרפואי לגליל שבנהריה ברפואת עירוים.

חומרים ושיטות: המחקר הינו מחקר רחב תיאורי. המידע נאסף באמצעות שאלון אנונימי. השאלון חולק ל 79 רופאים ממחלקות כירורגיות ופנימיות, שהועסקו במרכז הרפואי לגליל במהלך שנת 2014. השאלון נכתב ע"י צוות החוקרים והורכב משני חלקים - חלק אשר כלל נתוני רקע אישיים ומנה תשע שאלות, וחלק מקצועי שמנה 25 שאלות. החלק המקצועי נבדק לידע כללי, להיכרות עם הגישה הרסטריקטיבית למתן עירוי דם ולידע על התוויות שונות למתן עירוי דם.

תוצאות: ציונים חושבו בסולם 0-100. הידע הכללי של אוכלוסיית המחקר היה נמוך (ציון ממוצע 47.3). ציון ההיכרות עם הגישה הרסטריקטיבית למתן עירוי דם (ציון ממוצע 49) והידע בנוגע להתוויות השונות למתן עירוי דם (ציון ממוצע 42) היו נמוכים. נמצא שרופאים מהאגף הפנימי היו בעלי ידע כללי גדול יותר לעומת רופאים מהאגף הכירורגי (ציון ממוצע 55 לעומת 41, $P=0.001$) והכירו יותר את נושא הגישה הרסטריקטיבית (ציון ממוצע 60 לעומת 40, $P=0.002$). כמו כן נמצא שרופאים מומחים היו בעלי ידע כללי גדול יותר לעומת רופאים מתמחים (ציון ממוצע 54 לעומת 43, $P=0.005$) והכירו יותר את נושא הגישה הרסטריקטיבית (ציון ממוצע 60 לעומת 40, $P=0.003$). בהשוואת ציוני הידע בנושא ההתוויות השונות למתן עירוי דם, נמצאה מגמה סטטיסטית לטובת רופאים מהאגף הפנימי לעומת הכירורגי (ציון 48 לעומת 37, $P=0.068$) ולטובת רופאים מומחים לעומת רופאים מתמחים (ציון 46 לעומת 39, $P=0.078$). בניית רב משתני נמצא כי לתחום ההתמחות ולותק ישנה השפעה של קרוב ל 30% על ציון הידע הכללי של רופאים בנושא רפואת עירוים. לעומת זאת, נמצא כי מקום לימוד (בוגרי ארץ לעומת בוגרי חו"ל) אינו משפיע על ציון הידע הכללי.

מסקנות סופיות: קיים חוסר ידע כללי ובסיסי בתחום רפואת עירוים בקרב הצוות הרפואי שעשוי לתרום לצריכת מנות דם מיותרות. סוג ההתמחות הרפואית וותק הרופא הם בעלי השפעה על הידע הכללי בנושא רפואת עירוים. למקום לימוד אין כל השפעה. יתכן כי שילוב של היעדר קווים מנחים במדינתנו והנחיות אמריקאיות הלוקות בחסר תורם לחוסר הידע בתחום זה.

מילות מפתח: עירוי דם, צריכת-יתר, הנחיות

Abstract

BACKGROUND: Red blood cell (RBC) transfusion is a common therapeutic intervention. Despite its risks and high costs, a significant percentage of RBC transfusions have been identified to be inappropriately overused. A restrictive blood management (RBM) approach (using hemoglobin threshold 7-8 g/dL) is superior to a liberal approach (using hemoglobin threshold 10 g/dL) in improving clinical outcome, and reducing RBC utilization. Despite a growing number of studies in the field of transfusion medicine, there is still an insufficient evidence for generation of comprehensive guidelines, thus the existing American recommendations are limited. The Israeli Ministry of Health did not establish any guidelines regarding RBC transfusion. In this study, I assessed the potential reasons for the overuse of RBC transfusion by investigating the knowledge of physicians from different wards in the GMC, regarding the field of transfusion medicine.

STUDY DESIGN AND METHODS: This is a descriptive, cross-sectional study. Information was collected via an anonymous questionnaire. The questionnaire was given to 79 physicians from surgical and internal medicine wards, who were employed in the GMC during 2014. The questionnaire was written by the investigating team and was composed of two parts- a personal background part, consisting of nine questions; and a professional part, consisting of 25 questions. The professional part was examined for general knowledge, familiarity with the RBM discipline and knowledge regarding different indications for transfusion.

RESULTS: Scores were calculated on a 0-100 scale. The general knowledge of the population study was low (mean score 47.3). Familiarity with the RBM discipline (mean score 49) and the knowledge regarding indications for transfusion (mean score 42) were low. Internal medicine physicians had greater general knowledge than surgeons (mean scores 55 vs. 41, $P=0.001$) and were more familiar with the RBM discipline (mean scores 60 vs. 40, $P=0.002$). Specialists were found to have greater general knowledge than residents (mean scores 54 vs. 43, $P=0.005$) and were more familiar with the RBM discipline (mean scores 60 vs. 40, $P=0.003$). When comparing the scores of knowledge regarding indications for transfusion, a statistical trend was found in favor of internal medicine physicians over surgeons (mean scores 48 vs. 37, $P=0.068$) and specialists over residents (mean scores 46 vs. 39, $P=0.078$). According to multivariate analysis, field of specialty and seniority account for approximately 30% of the influence on physician's general knowledge score. No influence was found assessing place of graduation aspect (Israel vs. non-Israel graduates).

CONCLUSIONS: There is a lack of general and fundamental knowledge among physicians in the field of transfusion medicine, which may cause for RBC overuse. Field of specialty and seniority, influence the general knowledge regarding transfusion medicine. Place of graduation does not. Absence of Israeli guidelines and limited American recommendations may contribute to the lack of knowledge in transfusion medicine among Israeli physicians

Key Words: blood transfusion, overuse, guidelines

Background

Blood transfusion is often life- saving, however, is associated with significant risk. Historically, infections such as HIV, HBV, HCV were of major concern. Nowadays bacterial sepsis is the most common infectious hazard that may cause significant morbidity & mortality in developed countries [1]. Non-infectious hazards include transfusion hypersensitivity reactions, febrile reactions, transfusion-associated cardiac overload and transfusion-related acute lung injury (TRALI), transfusion-related iron overload and hyperkalemia, and events relating to clinical and administrative procedures such as "wrong blood in tube" and "incorrect blood component transfused" events [1,2].

Transfusion-associated immunomodulation may increase the risk of infections and the risk of cancer recurrence through unknown mechanisms [3].

Despite the risks and high costs associated with red blood cell (RBC) transfusion (annual expenditure of \$1.62 to \$6.03 million per hospital in the United States and Europe) [4], the practice of blood transfusion has been increasing steadily [1, 5].

The American Medical Association has identified blood transfusions in a list of the five most overused therapeutic procedures in the United States [6] where 15 million blood units are given per annum (1 unit every 2 seconds). About 85 million blood units are given worldwide [7]. In Israel, according to Magen David Adom (Israeli equivalent of the Red Cross first aid organization) spokesman, 522,000 blood units were sold to the Israeli hospitals in 2013.

For many decades, the decision to transfuse RBC used a liberal approach- which was defined by the "10/30 rule": transfusion was used to maintain a blood hemoglobin (Hb) concentration above 10 g/dL (100 g/L) and a hematocrit above 30 percent [8].

Re-evaluation of this threshold trigger raised fundamental issues regarding the arbitrariness of this trigger, as well as the lack of evidence base in many aspects of transfusion practice, when compared with other fields of medicine. Hence, a growing number of worldwide studies comparing a restrictive blood management (RBM) approach (using a lower Hb transfusion threshold of 7-8

g/dL) to the previous prevailing, sparsely evidence based, liberal approach (using the 10 g/dL threshold) are being generated.

A major Cochrane systematic review and meta-analysis of clinical trials of RBC transfusion, established by the American Association of Blood Banks (AABB) identified 19 randomized clinical trials comparing higher versus lower transfusion thresholds in a total of 6264 hemodynamically stable medical and surgical patients. This review suggests that compared with a target Hb of 10 g/dL, Hb target values of 7 to 8 g/dL are associated with equivalent or better outcomes [8]. This Cochrane systematic review also served as the base for the most recent guidelines for RBC transfusion established by the AABB Clinical Transfusion Medicine Committee in 2012.

Another study published by the Stanford University Medical Center [9], assessed patient outcomes before and after implementation of a real-time clinical decision support (CDS) triggered for transfusions when the hemoglobin level was 7-8 g/dL. The study compared patient outcomes (mortality and length of stay) hospital-wide from January 2008 to July 2010 (before implementation of the CDS) and from July 2010 to December 2013 (after implementation of the CDS). This study concluded that improved blood utilization using the RBM approach was associated with a stable or an improved outcomes and total savings in acquisition costs of approximately \$6.4 million.

A multicenter, controlled clinical trial of transfusion requirements in critical care, established by the Canadian critical care trials group, showed that a restrictive strategy of RBC transfusion is at least as effective as and possibly superior to a liberal transfusion strategy in critically ill patients (with a possible exclusion of patients with acute coronary syndrome) [10].

Though it is accepted that Hb level should not be used as the sole index for the decision to transfuse, Hb level is an invariably important index for transfusion practiced daily by physicians. Previous RBC transfusion guidelines were published by different societies including the American Society of Anesthesiologists task force, the British Committee for Standards in Hematology, and the Australian and New Zealand Society of Blood

Transfusion [7]. These guidelines generally agree that transfusion is not indicated for Hb >10 g/dL, while the lower threshold varies between 6 g/dL to 8 g/dL. Nevertheless, none of these guidelines dictates specific recommendations for transfusion thresholds.

Therefore, in 2012, the AABB established an evidence based guideline [7] with specific transfusion thresholds regarding hemodynamically stable medical and surgical patients (adult and pediatric) in order to standardize transfusion practice:

Recommendation 1

The AABB recommends adhering to a restrictive transfusion strategy in hospitalized, hemodynamically stable patients.

In adult and pediatric intensive care unit patients, transfusion should be considered at hemoglobin concentrations of 7 g/dL or less.

In postoperative surgical patients, transfusion should be considered at a hemoglobin concentration of 8 g/dL or less or for symptoms (chest pain, orthostatic hypotension or tachycardia unresponsive to fluid resuscitation, or congestive heart failure).

Quality of evidence: high; strength of recommendation: strong.

Recommendation 2

The AABB suggests adhering to a restrictive transfusion strategy in hospitalized, hemodynamically stable patients with preexisting cardiovascular disease.

Transfusion should be considered at a hemoglobin concentration of 8 g/dL or less or for symptoms (chest pain, orthostatic hypotension or tachycardia unresponsive to fluid resuscitation, or congestive heart failure).

Quality of evidence: moderate; strength of recommendation: weak.

Recommendation 3

The AABB cannot recommend for or against a liberal or restrictive RBC transfusion threshold in hospitalized, hemodynamically stable patients with the acute coronary syndrome. Further research is needed to determine the optimal threshold.

Quality of evidence: very low; strength of recommendation: uncertain.

Recommendation 4

The AABB suggests that transfusion decisions be influenced by symptoms as well as hemoglobin concentration, in hospitalized hemodynamically stable patients.

Quality of evidence: low; strength of recommendation: weak.

The practice of transfusion medicine differs between clinicians, hospitals, regions and countries. A wide variety of barriers to guideline adherence exist, which include lack of awareness, lack of familiarity, lack of agreement, lack of outcome expectancy, the habit of previous practice, and external barriers [11].

Although numerous potential reasons may account for transfusion practice differences, a major cause may be the lack of sufficient evidence in the field of transfusion medicine. Unfortunately, there is still limited amount of randomized clinical trials and the majority of evidence is based on retrospective studies [12]. For this reason the clinical guideline established by the AABB does not include patients from many other populations who frequently receive transfusions such as patients with acute coronary syndrome, elderly medical patients recovering from illnesses that result in hospitalization, patients with gastrointestinal bleeding, transfusion dependent patients, patients with coagulopathy or hemorrhagic shock, and patients with traumatic brain injury [7].

Clearly, there is a need to promote safe and evidence-based clinical transfusion practice; more extensive, definitive guidelines should be established and unnecessary transfusions should be avoided.

There is an overwhelming global waste in blood products which can be reduced up to 40%, and by that, minimizing transfusion related morbidity and mortality [7].

According to the International Hemovigilance Network (IHN), hemovigilance is the practice of surveillance procedures covering the whole transfusion chain (from the collection of blood and its components to the follow-up of recipients), intended to collect and assess information on unexpected or

undesirable effects resulting from the therapeutic use of labile blood products, and to prevent their occurrence or recurrence. In the frame of improving safety and transfusion processes, the Israeli Ministry of Health initiated an educational computer program designated for the medical staff in order to increase knowledge and keep physician's awareness regarding technical blood transfusions regulations.

The Israeli Ministry of Health also appointed an Israeli advising committee for transfusion medicine following malfunctions in the Israeli health system that were derived from lack of exposure and imposition of the regulations. Nevertheless, these regulations were most recently updated in 2002 [13] and they do not replace Israeli RBC transfusion guidelines, which currently do not exist.

In this study, we investigated the knowledge of physicians in surgical and internal medicine wards in the Galilee Medical Center (GMC), by answering a questionnaire inquiring the familiarity with the discipline of RBM as well as indications for blood transfusion and their application.

The primary aim of our study was to assess the major aspects and reasons for RBC transfusion over use.

In addition, we segregated the population of study into different groups according to personal background including field of specialty, seniority and place of graduation. We compared between the groups in order to study their influence on physician's knowledge regarding transfusion medicine.

Clarification of the major issues of blood transfusion over utilization can offer further improvement towards reducing unnecessary transfusions.

Materials and methods

1. Hypotheses:

Due to limited American recommendations and lack of Israeli guidelines, we assumed that the general knowledge of the population study would be low (less than 50% correct answers). Other potential reasons may be lack of guidelines adherence and awareness- regardless of the fact whether these guidelines exist or not, habitual use over years as well as lack of knowledge regarding major transfusion related hazards.

By segregating the population study into groups according to field of specialty- surgical and internal medicine, we expected to find better knowledge in questions regarding surgical indications for transfusion among surgical wards, and the same as for internal medicine, regarding medical indications for transfusion.

2. Study design:

This is a descriptive, cross-sectional study. The information was collected via a survey dealing with issues regarding blood transfusion and its indications, using a written questionnaire (appendix 1) that was given to physicians from surgical and internal medicine wards.

3. Subjects:

The population study included physicians employed in the GMC during 2014. The population study composed of 79 physicians out of 105 physicians in internal medicine and surgical wards. 34 physicians from 6 internal medicine departments and one geriatric department representing internal medicine wards; and 44 physicians from two general surgical departments, two orthopedic departments, one obstetrics & gynecology department and one urologic department representing surgical wards (field of specialty was not mentioned by one physician).

In order to assess the level of knowledge, a population sample of 50-60 physicians was sufficient.

Sample size calculation was based on a calculated confidence interval of an estimated mean general knowledge score (calculated as the mean of all

correct answers) of $40\% \pm 20\%$ on a 0-100 scale. For 50 physicians, 5% statistical significance, calculated confidence interval= CI 95% (34, 46).

The responders were physicians during or after residency, who were willing to participate in answering the questionnaire. Rotating interns were not included due to time differences within their rotating period.

The questionnaires were anonymous and were generally given and collected directly by the pollster, during morning meetings.

4. Variables:

Dependent variable: the knowledge

The main dependent variable is the general knowledge. In addition, knowledge was examined in two specific aspects:

1. Familiarity with the RBM discipline
2. Knowledge regarding indications for RBC transfusion

Independent variables: field of specialty, seniority and place of graduation of the participating physicians

5. Questionnaire structure and scoring methods

The questionnaire was written by the investigating team and was validated by colleagues' revision. Questionnaire reliability calculated 0.69.

The questionnaire was composed of two parts- general background and professional.

The general background part consisted of nine partially open ended questions.

The professional part was divided into two main issues:

- 1-questions regarding familiarity with the subject of RBM.
- 2-questions regarding indications for RBC transfusion.

The professional part consisted of 25 multiple choice questions with some options for extended written answers. We omitted four questions (7-9, 20) due to a high level of difficulty. Each correct answer credited for one point and incorrect answer credited for zero points.

A higher weight (three points for correct answer) was given to some of the questions (1, 10) as a matter of a relative importance after revision of the questionnaire.

The mean general knowledge score was calculated as the mean of all correct answers. Scores were multiplied by 100 and ranged from 0 to 100.

6. Statistic methods:

Quantity data was described by Means and STD, Medians and Ranges. Qualitative data was described by Frequencies and Percentages.

Correct answers for questions were marked by the responders and were defined as new variables on a 0-1 scale (0= incorrect answer, 1=correct answer). Reliability was measured for those new variables, for the overall questionnaire and for each group of questions (regarding familiarity with the RBM discipline and regarding different indications for transfusion). Cronbach's alpha coefficient was used for reliability measurement (despite its greater suitability for ordinal variables, and less for dichotomy variables). Some new variables (Indexes) were created according to the responders' knowledge by an average or summation of correct answers.

Univariate analysis:

Quantitative data was compared among groups by Anova test. For Comparison between groups Independent sample t-test or Wilcoxon rank sum test were used, as appropriate.

Ordinal data was compared using Wilcoxon rank sum test.

A qualitative was computed by Chi-square test or Fisher's exact test, as appropriate.

Correlation between Quantitative variables was calculated by Spearman's correlation coefficient test, according to the required test assumptions.

Multivariate analysis:

Anova model was used to examine differences in the knowledge between the demographic subgroups.

6. Ethical aspects:

An exemption of approval was given by the Helsinki committee.

Results

79 physicians agreed to participate in the study. Questionnaires were given to the physicians in the internal medicine and surgical wards in the GMC since February 2014, and were collected during March 2014.

Sample description:

The mean age of the participating physicians was 39.9 years (**table 1**).

The majority of the responding physicians are males (M: F; 77:23%).

Approximately 50% of participating physicians are of non-Jewish religion.

Among participating physicians, 50% have an Israeli ethnic origin and 33.3% from former Soviet Union origin.

71.2% of the physicians graduated outside Israel; with highest rate (30.3%) in the former Soviet Union and second in rate (25.8%) in Eastern Europe. Approximately 29% graduated in Israel. Data regarding place of graduation was not available for 16.5% of the population study.

40.5% of the physicians were specialists while 59.5% were residents. Mean seniority in years was 12.8.

43.6% of physicians belonged to internal medicine wards, while 56.4% belonged to surgical wards.

Table 1: Personal background of population study

		Number of responders	%
Sex	Male	60	76.9%
	Female	18	23.1%
	Not mentioned	1	---
Age (years)	Mean	39.9	
	Standard deviation	10.4	
	Median	37.0	
	Range	26-66	

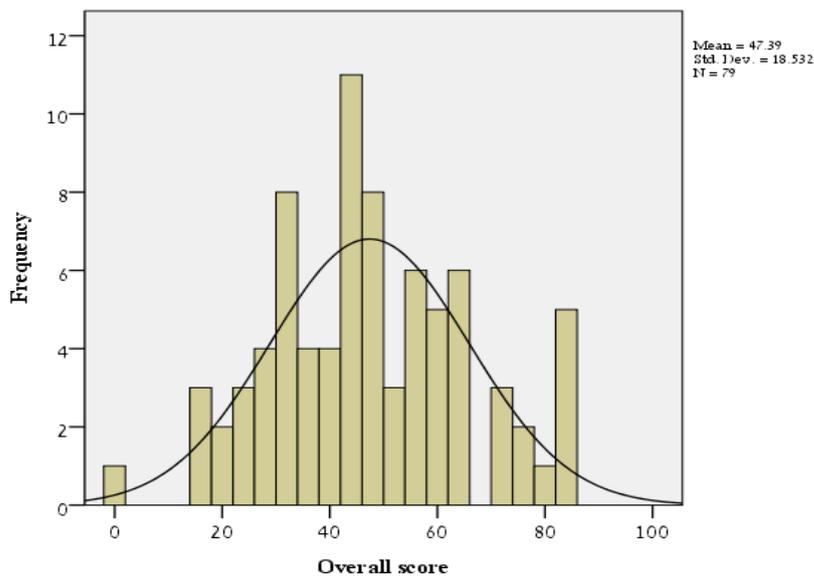
Religion	Jewish or Christian from western Europe or former Soviet Union	43	54.4%
	Muslim	18	22.8%
	Christian Arab	11	13.9%
	Druse	7	8.9%
	Other	5	---
Family ethnic origin	Israel	39	50%
	Former Soviet Union	26	33.3%
	Eastern Europe	7	9.0%
	Western Europe	3	3.8%
	North America	2	2.6%
	South America	0	0%
	Asia- middle east	0	0%
	North Africa	0	0%
	Not mentioned	2	---
Place of graduation	Israel graduates	19	28.8%
	Non-Israel graduates	47	71.2%
	Not mentioned	13 /79	16.5%
Detailed place of graduation	Israel	19	28.8%
	Former Soviet Union	20	30.3%
	Eastern Europe	17	25.8%
	Western Europe	5	7.6%
	North America	0	0%
	South America	0	0%
	Asia- middle east	5	7.6%

	North Africa	0	0%
Seniority (years)	Mean	12.8	
	Standard deviation	10.93	
	Median	9.0	
	Range	0.25-40.0	
Professional status	Specialist	32	40.5%
	Intern	47	59.5%
Field of specialty	Internal medicine	34	43.6%
	Surgical	44	56.4%
	Not mentioned	1	---

Description of the general knowledge score:

The general knowledge scores of the population study are depicted in **Figure 1** and show a normal distribution plot:

Figure 1: general knowledge score



The mean general knowledge score of the population study shown in **table 2** is 47.4. This is the calculated mean of all correct answers in all professional

questions (except the previously mentioned dropped questions) on a 0-100 scale:

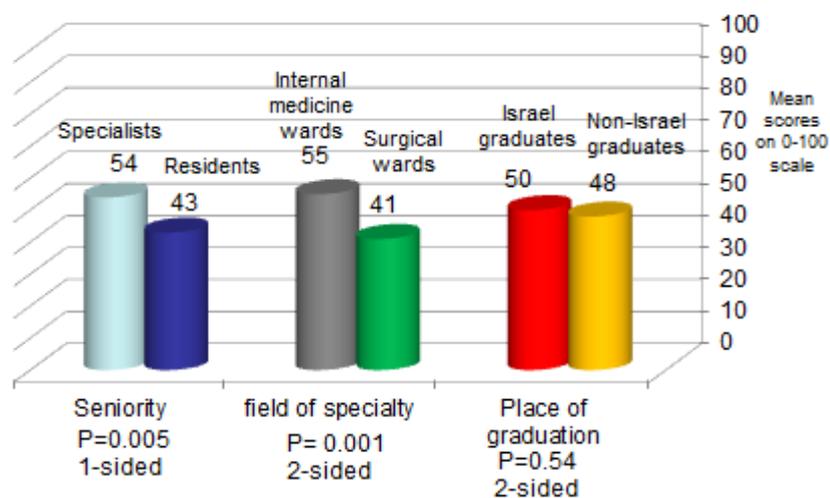
Table 2: mean general knowledge score

N	Valid	79
	Missing	0
Mean		47.39
Median		44.00
Std. Deviation		18.53
Minimum		00
Maximum		100

The mean general knowledge scores were calculated for different subgroups according to personal background, and compared on a 0-100 scale.

Figure 2 represents the differences in mean general knowledge scores between field of specialty, seniority and place of graduation subgroups:

Figure 2: mean general knowledge scores according to personal background



Comparing between fields of specialty, the mean general knowledge of internal medicine wards was higher than surgical wards (P=0.001).

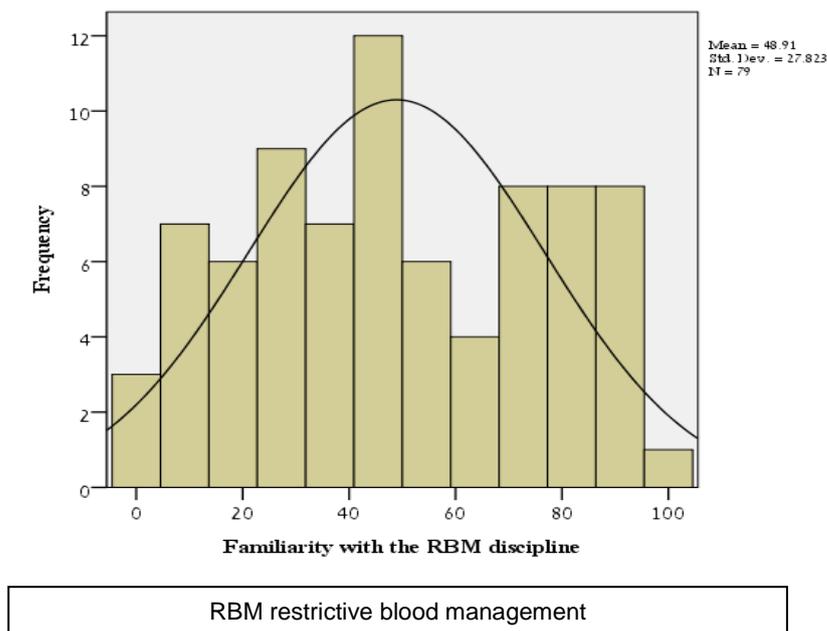
When comparing seniority aspect, the mean general knowledge of specialists was higher than residents (P=0.005).

Comparing the place of Graduation aspect- no clinical or statistical differences were found.

Description of the familiarity with the restrictive blood management (RBM) discipline:

The familiarity with the discipline of RBM was evaluated by nine questions (1, 3-6, 13-14, and 24-25) that normally distribute as shown in **figure 3**:

Figure 3: normal distribution of the scores regarding familiarity with the discipline of RBM

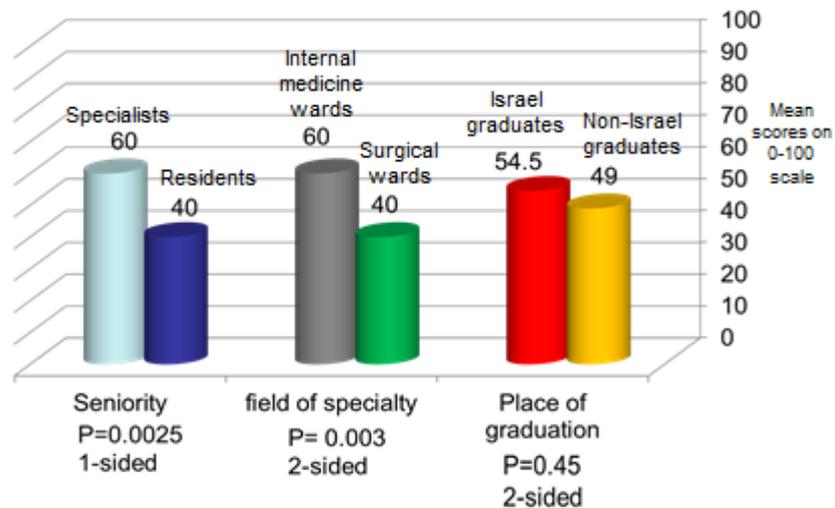


Homogeneity was found among the answers, given a Cronbach's alpha coefficient >0.7.

The mean score of knowledge regarding familiarity with RBM discipline of the population study is 48.9%. This is the calculated mean score of all correct answers to the questions regarding familiarity with the RBM discipline.

The mean scores of questions regarding familiarity with the RBM discipline were calculated and compared on a 0-100 scale according to field of specialty, seniority and place of graduation subgroups, as shown in **figure 4**:

Figure 4: mean scores of questions regarding familiarity with the RBM discipline according to personal background



Comparing between fields of specialty, internal medicine wards had a higher mean score of knowledge regarding familiarity with the RBM discipline than surgical wards (P=0.003).

Similarly, comparing seniority aspect, the mean score of knowledge regarding familiarity with the RBM discipline of specialists was higher than that of residents. (P=0.0025).

Comparing the place of graduation (Israel vs. non Israel graduates) - there was no major difference between the groups and a statistical significance was not found.

Description of the knowledge regarding different indications for transfusion:

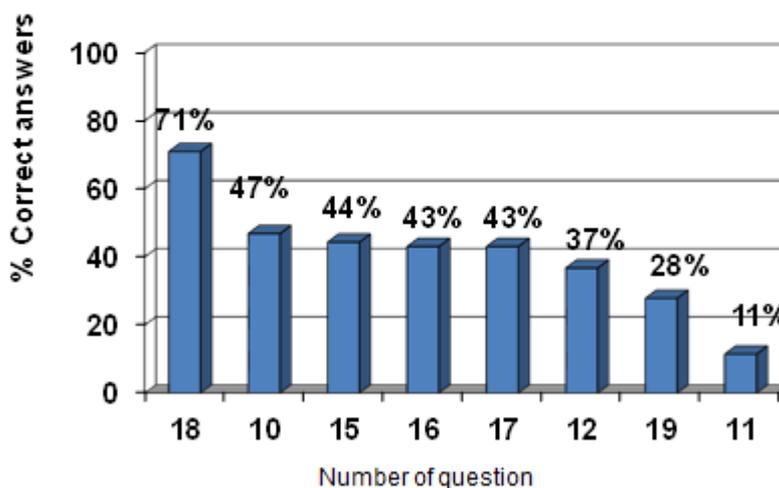
The knowledge regarding indications for transfusion was evaluated by eight questions (10-12, and 15-19) that were further divided into "surgical field

indications" (questions 15, 18) and "internal medicine field indications" (questions 16, 17).

Large heterogeneity was found among the answers (Cronbach's alpha= 0.448). Omission of question 18 did not improve the Cronbach's alpha.

The general distribution of correct answers regarding indications for transfusion is presented in **Figure 5**, in a descending order:

Figure 5: Correctly answered questions regarding indications for transfusion



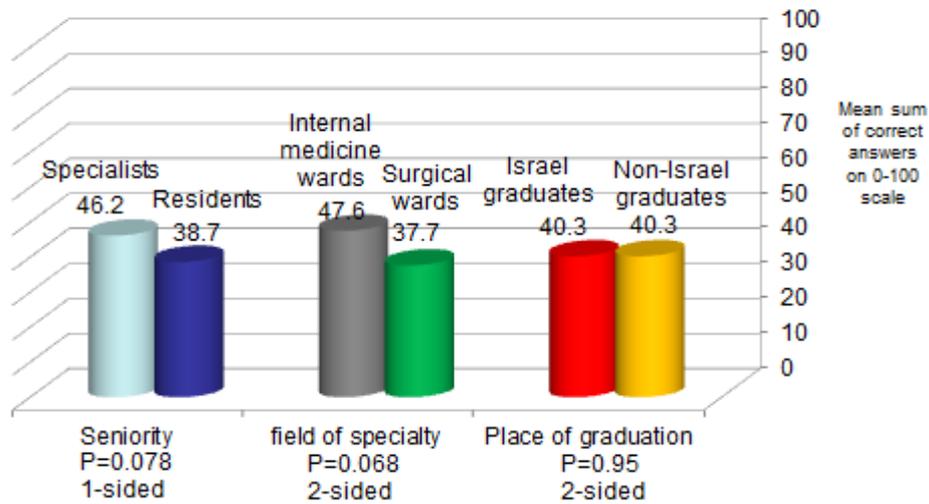
Alpha cronbach = 0.448

General topic asked according to question number:
10, 11- Physiologic reasons for transfusion
12, 19- acute blood loss
15, 18- surgical indications for transfusion
16, 17- internal medicine indications for transfusion

The calculated mean score of the population study regarding indications for transfusion is 42 on a 0-100 scale. This mean represents the sum of all correct answers to each question regarding indications for transfusion.

The mean sum of correct answers to questions regarding indications for transfusion was calculated and compared on a 0-100 scale according to field of specialty, seniority and place of graduation subgroups, as shown in **figure 6**:

Figure 6: The mean sum of correct answers to questions regarding indications for transfusion according to personal background

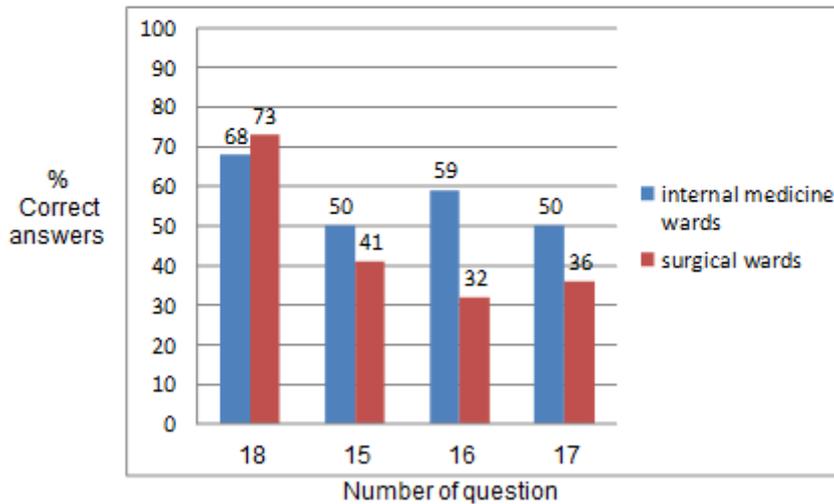


In respect of field of specialty and seniority; a statistical trend was found, demonstrating a better knowledge of indications for transfusion among internal medicine physicians over surgeons ($P=0.068$) and among specialists over residents ($P=0.078$).

Comparing the place of Graduation aspect, no clinical or statistical differences were found.

The mean sum of correct answers for specific surgical and internal medicine indications shown in **figure 7** was calculated and compared on a 0-100 scale according to fields of specialty. Questions 15 and 18 represent surgical indications, while questions 16 and 17 represent internal medicine indications. Though higher scores were found among internal medicine wards (in comparison to surgical wards) in questions 15, 16 and 17, a statistical significance ($P=0.015$) was only found in question 16.

Figure 7: mean sum of correct answers regarding specific indications compared between fields of specialty



Specific indications for transfusion according to question number:
 15, 18- surgical field indications
 16, 17- internal medicine field indications

Results of selected questions:

Knowledge regarding physiologic indications for transfusion:

Two questions (10 and 11) dealt with physiologic reasons for transfusion. 9% of responders answered correctly to both questions. In question 10, physicians were asked to state "TRUE OR FALSE" regarding whether the only reason to transfuse RBC is to improve tissue oxygenation. Physicians who stated "FALSE" were also asked to mention other reasons, if any, for RBC transfusion rather than to improve oxygenation. 53% of physicians stated "FALSE" and at least 30% of them mentioned volume related reasons.

Knowledge regarding guidelines existence:

Question 23 dealt with the existence of guidelines. Physicians were asked to state "TRUE OR FALSE" regarding whether an absence of clear guidelines leads to confusion among physicians regarding RBC transfusion. 63% of responders agreed.

Knowledge regarding transfusion related hazards:

The knowledge about transfusion related hazards was examined in question 21. Question 21 was a multiple choice question and physicians were asked to differentiate between immediate and non-immediate complications of transfusion. 52% of responders answered correctly.

Multivariate analysis:

Variables included in the multivariate analysis: dependent variable- the general knowledge score.

Independent variables- field of specialty, seniority and place of graduation.

A minor clinical and statistical significance was found ($P=0.007$) comparing specialists and residents, in the favor of specialists. Similarly, a minor clinical and statistical significance was found ($P<0.001$) comparing internal medicine and surgical wards, in the favor of internal medicine. No clinical or statistical difference was found in the general knowledge score ($P=0.271$) comparing Israel vs. non-Israel graduates.

Variance percentage explained by the multivariate analysis is 27.7%

R Squared = 0.277 (Adjusted R Squared = 0.241).

In addition, there was no difference in the distribution of physicians in field of specialty ($P=0.821$), nor in the place of graduation ($P=0.584$).

A higher percentage (34% vs. 20%) of Israel graduates were occupied in surgical wards, though a statistical significance was not shown ($P=0.269$).

Discussion

RBC transfusion is a common therapeutic intervention with a considerable variation in clinical practice, which has been cited as one of the five most over-utilized therapeutic procedures in the United States [6]. Our study was primarily aimed to assess the potential reasons for the over use of RBC transfusion by investigating the knowledge of physicians regarding the field of transfusion medicine.

The general knowledge of the population study was low (mean score 47.3). This was also true for both the knowledge regarding familiarity with RBM discipline (mean score 49) and the knowledge regarding indications for transfusion (mean score 42).

Two questions (10 and 11) dealt with physiologic reasons for transfusion had particularly low scores with only 9% of responders answering correctly to both questions. Question 10 was an optional open ended question. When physicians were asked to mention other reasons, if any, for RBC transfusion rather than to improve oxygenation, at least 30% of responders mentioned volume related reasons. This suggests a more fundamental lack of knowledge regarding the field of transfusion medicine.

Studying the influence of seniority aspect on physician's knowledge, a difference was found in the general knowledge and familiarity with the RBM discipline, in the favor of specialists over residents. A trend towards specialists ($P=0.078$) was found in the knowledge regarding indications for transfusion, which may be explained by sample size. These results were in contrast to expected, under the assumption that residents are expected to study more in the frame of their residency and are less affected by habitual practice related to seniority.

Similar results were found comparing internal medicine to surgical physicians, in the favor of internal medicine physicians. These results were also against our expectation according to which we didn't expect to find difference in the knowledge with regards to field of specialty. An exception is the knowledge regarding specific indications for transfusion in which we expected to find

higher scores in questions regarding surgical indications among surgical wards, and the same as for internal medicine. Though higher scores were found among internal medicine wards in three out of four questions, statistical significance ($P=0.015$) was only found in one question (question 16).

Studying the influence of place of graduation (Israel vs. non-Israel graduates), no difference was found in the knowledge regarding transfusion medicine, as expected.

According to the multivariate analysis, field of specialty and seniority account for approximately 30% of the influence on physician's general knowledge score, while place of graduation plays no role. This means that other influencing variables exist as well, which were not included in our model.

Unfortunately, during my research I did not encounter literature to support or contradict our results regarding personal background influences on physician's knowledge in transfusion medicine.

When asked about the existence of guidelines (question 23), 63% of responders agreed that a lack of clear guidelines is a source of confusion among physicians regarding RBC transfusion. Indeed, one of the major issues of transfusion medicine nowadays is the paucity of high quality evidence based on randomized controlled clinical trials [12] which limits the establishment of an extensive definitive system of guidelines. Although the recently established clinical practice guideline by the American Association of Blood Banks (AABB) is based on a Cochrane systematic review and meta-analysis of clinical trials of RBC transfusion, and allows for specific recommendations about transfusion thresholds, no recommendations exist for many patient populations who frequently receive transfusions, and "more definitive recommendations await further clinical trials"... [7]

Israeli RBC transfusion guidelines currently do not exist. Furthermore, the established guidelines published in 2012 by the AABB are not validated by the Israeli Ministry of Health, which do tend to cite the AABB in other aspects of transfusion medicine such as additives to existing technical regulations and routine blood bank workup, and list of medications for assessing blood

donation eligibility [14]. 53% of responders, however, answered that they do use guidelines when ordering RBC transfusion (question 2).

It is possible to assume that those physicians who are familiar with the RBM discipline would probably be familiar with the recent AABB guidelines; however it is impossible to determine such an assumption with certainty, as these guidelines are not valid by the Israeli Ministry of Health. From the same reason it was difficult to assess the magnitude of effect of an inherent lack of guidelines adherence and awareness as potential reasons for RBC transfusion malpractice.

The knowledge about transfusion related hazards was examined in one question (21), due to scope issues. 52% of responders answered correctly. A statistical estimation cannot be made over one question in order to assess the general knowledge about transfusion related hazards. Nevertheless, if knowledge regarding hazards was examined in a larger scale, I would expect to find relatively higher scores than in other aspects of transfusion medicine, because this specific issue is routinely practiced by every physician in the educational computer program of the Israeli Ministry of Health. However, the limited high quality of evidence of the benefits and harms of transfusion is substantiated in the literature and indicated by the AABB as one reason for different RBC transfusion practices [7].

Different blood management programs have been established to improve RBC utilization. The adult and pediatric hospitals at Stanford University medical center [9] have been able to significantly reduce RBC transfusions through implementation of a real time clinical decision support (CDS) using an interruptive alert programmed according to American consensus guidelines which interrupts at time of order entry. The alert contained the guidelines, a link to relevant literature and an "acknowledgment" reason for transfusion. This CDS was implemented following one year of education about transfusion guidelines via electronic communication and in-person meetings. Using an electronic real time CDS such as implemented by the Stanford University hospitals serves as an educational tool for the end user and can potentially

decrease the burden of RBC transfusion utilization carried by the blood bank manager in each Israeli hospital.

One limitation of our study is the composition of population study (exclusively composed of physicians from the GMC) and whether they indeed represent the Israeli physician population as a whole. For this reason, further study demonstrating similar results in other Israeli hospitals would be beneficial. Also, open ended questions instead of multiple choice questions could overcome dishonest answers of participating physicians and possibly be more informative in certain questions.

Final conclusions and recommendations:

1. There is a lack of general and fundamental knowledge in the field of transfusion medicine, which may cause for RBC over use. Conducting similar investigations in other Israeli hospitals would be beneficial. Recurrent education including repetition of the basic physiology of RBC transfusion should be considered accordingly.
2. Personal background such as field of specialty and seniority, but not place of graduation has an influence on physician's general knowledge regarding transfusion medicine.
3. Absence of Israeli RBC transfusion guidelines and limited American recommendations may contribute to the lack of knowledge in transfusion medicine among Israeli physicians.

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