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Red blood cell transfusion in patients with subarachnoid hemorrhage: a multidisciplinary North American survey

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Abstract

Introduction: Anemia is associated with poor outcomes in patients with aneurysmal subarachnoid hemorrhage (SAH). It remains unclear whether this association can be modified with more aggressive use of red blood cell (RBC) transfusions. The degree to which restrictive thresholds have been adopted in neurocritical care patients remains unknown.

Methods: We performed a survey of North American academic neurointensivists, vascular neurosurgeons and multi-disciplinary intensivists who regularly care for SAH patients, in order to determine hemoglobin (Hb) concentrations which commonly trigger a decision to transfuse. We also assessed minimum and maximum acceptable Hb goals in the context of a clinical trial and how decision-making is influenced by advanced neurological monitoring, clinician characteristics and patient-specific factors.

Results: The survey was sent to 531 clinicians, of whom 282 (53%) responded. In a hypothetical patient with high grade (WFNS 4) SAH, the mean Hb concentration at which clinicians administer RBCs was 8.19 g/dl (8.07 to 8.30). Transfusion practices were comparatively more restrictive in patients with low grade SAH [mean Hb 7.85 g/dl (7.73 to 7.97)] (P<0.0001) and more liberal with delayed cerebral ischemia (DCI) [mean Hb 8.58 g/dl (8.45 to 8.72)] (P<0.0001). In each setting, there was a broad range of opinions. The majority of

respondents expressed willingness to study a restrictive threshold $\leq$ 8 g/dl (92%) and a liberal goal $\geq$ 10 g/dl (75%); in both cases, preferred transfusion thresholds were significantly higher among patients with DCI (P<0.0001). Neurosurgeons had higher minimum Hb goals than intensivists, especially for high grade patients (β=0.46, P=0.003), and were more likely to administer two, rather than one unit of RBCs (56% vs. 19%, P<0.0001). Institutional use of transfusion protocols was associated with more restrictive practices. More senior clinicians preferred higher Hb goals in the context of a clinical trial. Respondents were more likely to transfuse with $P_{bt}O_2$ values <15 mmHg and lactate:pyruvate ratios > 40.

Conclusions: There is widespread variation in the use of RBC transfusions in SAH patients. Practices are heavily influenced by the specific, dynamic clinical characteristics of patients and may be further modified by clinician specialty and seniority, the use of protocols, and advanced neurological monitoring.

Introduction

The prevention of "secondary" brain injury is a key paradigm of neurocritical care [1]. Inadequate cerebral oxygen delivery is an important mechanism that may contribute to secondary injury. This is particularly true for patients with aneurysmal subarachnoid hemorrhage (SAH), where delayed cerebral ischemia (DCI) and infarction frequently contribute to poor outcomes. When carefully sought, angiographic vasospasm can be observed in about two-thirds of patients during the two weeks after aneurysm rupture [2]. Among patients who survive, evidence of acute infarction can be detected in more than 50% using magnetic resonance imaging (MRI) [3]. In contrast to other neurocritical care conditions, the high risk of delayed ischemia *after* admission to hospital provides a unique opportunity to provide neuroprotection prior to additional insults.

Because the concentration of hemoglobin (Hb) is a major determinant of arterial oxygen content, there is a strong therapeutic rationale for the avoidance of anemia in brain injury [4]. Physiological studies have demonstrated improvements in cerebral oxygenation when RBC transfusions are used to raise Hb levels in anemic SAH patients, particularly when oxygen delivery and cerebral perfusion are reduced [4-7]. Several observational studies have found an association between lower Hb concentrations and poor outcomes [8-10]. Although the correction

of anemia is straightforward, the use of allogeneic red blood cell (RBC) transfusions to do so has potentially deleterious implications. For example, associations with acute lung injury and nosocomial infections have been described, which could neutralize any physiological advantage [11-13].

Large multi-center randomized controlled trials involving heterogeneous critically ill patients have not found any benefit to the liberal use of RBC transfusions to maintain "higher" Hb concentrations (> 9-10 g/dl); however, neurocritical care patients comprised only a small subset of the total patient population [14-15]. It is currently unknown to what extent restrictive transfusion thresholds (e.g. < 7 g/dl) have been adopted in brain-injured patients. A previous international survey suggested that most intensivists still consider a hematocrit of about 30% to be "optimal" in SAH patients. However, it does not necessarily follow that clinicians would transfuse liberally in order to achieve this goal [16]. Furthermore, there are no data indicating how transfusion decisions are guided by multi-modal neurological monitoring, what demographic and clinical factors may influence practices and how low (or high) clinicians might allow transfusion thresholds to be in the context of a clinical trial.

In view of this uncertainty, we conducted a cross-sectional survey of North American clinicians involved in the decision to transfuse critically ill SAH patients.

Materials and methods

The survey was endorsed by the clinical trials committee of the Neurocritical Care Society. Our sampling frame consisted of neurointensivists, multi-disciplinary intensivists who regularly care for SAH patients, and vascular neurosurgeons. We specifically targeted individuals who work at academic institutions with neurocritical care fellowship and/or neurosurgery residency training programs, since these are the most likely to participate in future clinical trials.

As of March, 2010, there were 42 United States (U.S.) centers with neurocritical care fellowship programs accredited by the United Council for Neurologic Subspecialties. Through the Society of Neurological Surgeons, we obtained a list of an additional 56 U.S. centers with neurosurgical residency training, but no accredited neurocritical care fellowship program. Through the Canadian Residency Matching Service website, we identified 12 primarily English-speaking universities with neurosurgery residency programs.

Program directors were contacted to obtain a list of local intensivists and vascular neurosurgeons that care for SAH patients. For centers from which we received no response, we obtained the names and e-mail addresses of relevant individuals from the respective programs' websites.

The survey was self-administered, voluntary and submitted on-line, using SurveyMonkey®. Individuals were contacted by e-mail, with three subsequent reminders at approximately one week intervals. No monetary or other incentive was offered for questionnaire completion. Respondents had the option of filling the survey out anonymously.

Survey development was initiated by two investigators (AK, PL), based on a PUBMED and MEDLINE review of relevant literature [4], with feedback from other experts (MD, AN, RLM). Themes that were considered important to explore included the following: (1) Transfusion thresholds in both "low grade" [minimal neurological deficits; defined in this study as World Federation of Neurological Surgeons (WFNS) grade 1-3] and "high grade" (presence of stupor or coma; WFNS grade 4-5) SAH patients; (2) Transfusion thresholds among patients with moderate-severe angiographic or transcranial Doppler (TCD)-defined vasospasm, but no clear symptoms of DCI; (3) Transfusion thresholds among patients with angiographic vasospasm and neurological deterioration (DCI); (4) Willingness of clinicians to accept transfusion thresholds above or below their usual practices in the setting of a clinical trial; (5) Modification of transfusion thresholds based on information provided by multi-modal neurological monitoring.

Most relevant information was collected by presenting an interactive case of a typical patient with aneurysmal SAH who becomes anemic (Appendices in Additional files 1 and 2). Item reduction was accomplished by piloting the survey among three vascular neurosurgeons and four neurointensivists, to ensure that it could be completed in approximately five minutes and that the most important themes had been considered. These preliminary responses were not included as part of the final survey results.

Several subgroup analyses were planned *a priori,* to determine how transfusion practices might be modified based on the following factors: (1) Geography (U.S. vs. Canada); (2) Base specialty (neurosurgery vs. intensivists); (3) Seniority (years in practice); (4) Presence of an institutional transfusion protocol; (5) Use of multi-modal neurological monitoring [defined as the use of at least one of the following: $P_{bt}O_2$ probes, microdialysis catheters, jugular venous oximetry or continuous cerebral blood flow (CBF) monitors].

Statistical analysis was performed using SAS, version 9.1 (Cary, NC) and MedCalc, version 11.3 (Mariakerke, Belgium). The normality of data was assessed using the Shapiro-Wilk test. Between-group comparisons of continuous data were performed using the Student's t-test or Wilcoxon rank sum test, depending on the distribution of data. Two-sample paired tests were used where applicable. Clinicians' transfusion thresholds in multiple different settings were compared using the Friedman test (non-parametric approach analogous to repeated-measures ANOVA); adjustment for multiple comparisons was made using the Bonferroni method. Categorical data were assessed with Chi-square analysis or Fisher's exact test, as appropriate based on the number of responses per cell. Associations between transfusion thresholds and clinician characteristics were explored using generalized linear regression models (Proc GLM in SAS). Multivariable analysis, including all of the variables from our subgroup analysis, was performed using a backwards elimination process, where the least significant variables were discarded one by one if $p>0.05$. Models were assessed for heteroscedasticity using White's Test; if present, a heteroscedasticity-consistent standard error was used. We also assessed interactions (effect measure modification) between variables, and included the relevant interaction terms in the initial multivariable models if they were statistically significant ($p<0.05$) in univariate analysis.

Results:

Demographics

The survey was sent to 531 individuals, of which 282 (53%) responded. The response rate was higher in Canada compared with the U.S. (69% vs. 43%; $p<0.0001$). There were notable cross-border differences in the base specialties of respondents; the majority were neurologists (55%) and neurosurgeons (23%) in the U.S. compared with internists (37%) and anesthesiologists (27%) in Canada (Table 1).

Transfusion Thresholds In Clinical Practice (Figure 1)

Transfusion thresholds differed significantly depending on the specific clinical characteristics of patients (Figure 1; $p<0.001$). In a hypothetical patient with WFNS grade 4 SAH [Glasgow Coma Scale (GCS) 9, without a focal neurological deficit] and the development of anemia on the third day in hospital, the mean Hb concentration at which clinicians would choose

to administer RBCs was 8.19 g/dl (95% CI 8.07-8.30; medians and IQR presented in Figure 1). However, opinions varied widely from as low as 7 g/dl (26%) to as high as 10 g/dl (13%).

Transfusion practices were more restrictive in a patient with WFNS grade 1 SAH (GCS 15) [mean Hb = 7.85 g/dl (95% CI 7.73-7.97)] ($p<0.0001$ compared with grade 4 SAH). In contrast, in a patient with evidence of moderate-severe TCD vasospasm (middle cerebral artery flow velocities 180-205 cm/second, Lindegaard Ratios 5-6) on the sixth day in hospital, without any coinciding neurological deterioration, the mean transfusion threshold rose to 8.35 g/dl (95% CI 8.22-8.48) ($p=0.001$ compared with the same patient on day 3, without TCD vasospasm). When there was both angiographic vasospasm and concomitant observable neurological deterioration (DCI), the mean threshold was even higher at 8.58 g/dl (95% CI 8.45-8.72) ($p<0.0001$ compared with the same patient on day 6 with only TCD vasospasm]. For each clinical scenario, there was a wide range of responses (Figure 1).

For patients with Hb concentrations slightly below (< 1 g/dl) clinicians' usual transfusion threshold, most respondents (74%) initially administer one unit of RBCs, while a minority (26%) routinely gives two units. The proportion that administer two units was larger in the U.S. compared with Canada (34% vs. 17%, $p=0.002$) and among neurosurgeons compared with intensivists (56% vs. 19%, $p<0.0001$).

Transfusion Thresholds In A Randomized Controlled Trial (Figure 2)

In the patient with grade 4 SAH, 63% of respondents expressed willingness to accept an Hb threshold lower than their own in a clinical trial. When clinicians who have the most restrictive threshold (7 g/dl) were excluded, the proportion rose to 84%. More than 70% of respondents thought it was ethically acceptable to randomize patients to a transfusion trigger as low as 7 or 7.5 g/dl (Figure 2A). Similarly, 94% of respondents were willing to accept an Hb threshold higher than their own in a study, in most cases $\geq$ 10 g/dl (Figure 2B).

Acceptable lower transfusion thresholds were influenced by the presence or absence of DCI [mean acceptable threshold with DCI = 7.69 g/dl (median 7.5; IQR 7.0-8.0); mean acceptable threshold without DCI = 7.41 g/dl (median 7.0; IQR 7.0-8.0) ($p<0.0001$). However, even with DCI, 63% of respondents expressed their willingness to study an Hb threshold lower than their own (84% when those with a threshold of 7 g/dl were excluded). More than half supported allocating patients to a transfusion trigger of 7 or 7.5 g/dl (Figure 2A). Ninety percent of respondents were willing to study an Hb target higher than their own. The majority favoured an upper target of 10

g/dl, but a sizable proportion was willing to transfuse to levels exceeding 11 g/dl (Figure 2B). The mean upper acceptable Hb target was greater in patients who develop DCI [mean 10.31 g/dl (median 10.0; IQR 10.0-11.0) vs. mean 10.11 g/dl (median 10.0; IQR 10.0-10.5); p<0.0001].

Clinician Characteristics Influencing Transfusion Practices – Subgroup Analysis (Figures 3 & 4)

U.S. clinicians consistently reported transfusing at higher Hb concentrations than Canadian clinicians (Figure 3A). However, this difference only reached statistical significance for patients with DCI [mean Hb in U.S. = 8.74 g/dl (95% CI 8.55-8.92); mean Hb in Canada = 8.44 g/dl (95% CI 8.25-8.63); p=0.03]. There were no major differences in the maximum and minimum Hb concentrations clinicians from either country would consider acceptable in a randomized controlled trial (Figure 4A)

Neurosurgeons reported more liberal transfusion thresholds than intensivists (Figure 3B). Differences were statistically significant for patients with grade 4 SAH, grade 1 SAH, and TCD vasospasm. Neurosurgeons were also less willing than intensivists to accept very low Hb concentrations (e.g. 7-7.5 g/dl) in the setting of a randomized controlled trial and were more willing to transfuse to relatively high Hb targets (e.g. 10-11.5 g/dl) (Figure 4B).

Clinicians who routinely use multi-modal neurological monitoring in SAH patients report targeting higher Hb concentrations, especially in patients with DCI [mean Hb with multimodal monitoring = 8.82 g/dl (95% CI 8.55-0.10); mean Hb without monitoring = 8.50 g/dl (95% CI 8.35-8.66); p=0.04] (Figure 3C). Appendix 2 in Additional file 2 shows specifically how use of $P_{bt}O_2$ and microdialysis monitoring may modify practices. The use of institutional transfusion protocols was associated with more restrictive thresholds, especially in grade 1 SAH patients [mean Hb with transfusion protocol = 7.70 g/dl (95% CI 7.54-7.87); mean Hb without protocol = 7.98 g/dl (95% CI 7.80-8.16); p=0.01] (Figure 3D).

There were no significant associations between clinician experience (years in practice) and conventional transfusion practices in any of the clinical settings. However, more experienced respondents were less willing to accept lower Hb thresholds in the restrictive arm of a randomized controlled trial (grade 4 SAH: β=0.01, p=0.009; DCI β=0.02, p=0.01). In the liberal transfusion group, more experienced respondents would be willing to transfuse to higher Hb targets (grade 4 SAH: β=0.02, p=0.04; DCI: β=0.02, p=0.01)

Clinician Characteristics Influencing Transfusion Practices – Multivariable Analysis (Table 2)

Using multivariable analysis, several independent predictors of transfusion practices were identified (Table 2A). Hemoglobin thresholds were more liberal among neurosurgeons than intensivists (grade 4 SAH: β=0.46, p=0.003; TCD vasospasm: β=0.31, p=0.04) and more restrictive among clinicians who use transfusion protocols (grade 1 SAH: β=-0.42, p=0.0008). In grade 1 SAH patients, we also found significant effect measure modification between use of a protocol and neurosurgical specialty (β=0.88, p<0.0001). For example, although the use of a protocol generally predicted more restrictive practices, the opposite was true among neurosurgeons [mean transfusion threshold with protocol = 8.43 g/dl (95% CI 8.00-8.86); mean threshold without protocol = 8.18 g/dl (95% CI 7.81-8.55)]. In patients with DCI, use of multi-modal neurological monitoring remained independently associated with a more liberal transfusion threshold (β=0.32, p=0.04).

In the context of a randomized controlled trial, neurosurgical specialty and increased clinician seniority were associated with less willingness to accept very restrictive transfusion thresholds (Table 2). In the liberal transfusion arm, we found significant effect measure modification between neurosurgical specialty and years in practice. The highest Hb targets were generally found among neurosurgeons with a greater degree of experience. For example, among neurosurgeons who have been in practice for more than 10 years, the mean highest acceptable Hb goal was 10.60 g/dl (95% CI 10.13-11.07), compared with 10.04 g/dl (95% CI 9.62-10.45) among neurosurgeons in practice for fewer years and 10.22 g/dl (95% CI 10.03-10.41) among intensivists in practice for more than 10 years.

Clinicians using transfusion protocols were less willing to target higher Hb goals in patients with DCI (β=-0.35, p=0.003). However, this effect was modified by clinician specialty; for example, the mean highest acceptable Hb target was 10.70 g/dl (95% CI 10.26-11.15) among neurosurgeons using a protocol, but only 10.57 g/dl (95% CI 10.14-11.00) when no protocol was used.

Discussion:

Our findings describe current RBC transfusion practices among patients with SAH cared for at North American academic centers. We observed variations in the Hb concentrations which trigger a decision to transfuse, distributed over a numerically modest, but clinically significant range of 7 to 11 g/dl (Figure 1). Although a threshold of 7 g/dl is widely advocated for general critical care patients, tolerance for such a low Hb level is less common in SAH patients. The

variability in clinicians' practices provides a strong impetus for a definitive randomized controlled trial.

Many clinicians do not practice with a fixed Hb threshold. Instead, the decision to transfuse varies based on the clinical status of the patient. Survey respondents were more likely to transfuse patients with high-grade, rather than low-grade, SAH. This practice suggests that clinicians believe anemia to be potentially more harmful among patients with a greater degree of brain injury. Clinicians are even more likely to transfuse if patients develop cerebral vasospasm, especially if there is concomitant neurological deterioration (DCI). This observation indicates that most clinicians do not consider marked hemodilution to be an appropriate method to treat vasospasm and DCI. Indeed, although hemodilution increases CBF, this practice may compromise oxygen delivery [17-18]. In some SAH patients, there may be additional systemic factors (e.g. neurogenic cardiac dysfunction or known coronary artery disease) which may influence the decision to transfuse; these were not incorporated into this survey.

The stated willingness of most clinicians to modify their transfusion practices in the context of a randomized controlled trial further demonstrates equipoise. Almost three-quarters of respondents considered it reasonable to randomize a patient with grade 4 SAH to a transfusion threshold of 7 or 7.5 g/dl. However, clinicians were less willing to accept such a low Hb when patients develop DCI. The vast majority also thought it was acceptable to target an Hb concentration of greater than 10 g/dl as part of a liberal transfusion strategy. Among patients with DCI, a notable proportion of clinicians were willing to target even higher Hb levels. These findings suggest that a comparison of two fixed Hb thresholds may not represent the most relevant approach to study in a randomized controlled trial. Indeed, it has been pointed out that there may be unintended, harmful consequences in studies that use fixed treatment protocols for therapies that are more often "titrated" in day-to-day practice [19]. An alternative approach is to use adaptive trial designs, where therapy titration is permitted based on prospective rules. For example, the upper and lower transfusion triggers could be adjusted based on the presence or absence of DCI and radiographic evidence of vasospasm.

Our findings suggest that vascular neurosurgeons are less tolerant of Hb reductions than intensivists. Neurosurgeons were also more likely to administer two, rather than one unit of RBCs when Hb levels dropped below their usual transfusion thresholds. These findings are consistent with a previous survey, which reported that U.S. neurosurgeons are more likely than

trauma surgeons or intensivists to target Hb concentrations of at least 10 g/dl in patients with severe traumatic brain injury [20].

We identified additional factors which may influence the transfusion decision. Although differences were small, clinicians who report using a transfusion protocol generally appear to be slightly more restrictive in their use of RBCs. This was not true for vascular neurosurgeons; however, our data does not allow us to determine whether this apparent discrepancy is due to variations in protocols, lack of compliance or chance. The preferred transfusion thresholds in a randomized trial would be higher for clinicians with a greater degree of seniority. The reasons for this observation are also unclear: possibilities could include less familiarity with published literature advocating restrictive transfusion strategies, increased scepticism regarding the applicability of such studies to SAH patients or greater reluctance to adapt practices. These observations, together with interdisciplinary and international differences in transfusion preferences, should be taken into consideration in the planning of future studies. This will help maximize clinician "buy in" and ensure that study results are widely generalizable.

This is the first survey to assess how transfusion practices are influenced by advanced neurological monitoring. We found that clinicians who use invasive multi-modal neurological monitoring may be more liberal in their use of transfusions, especially among patients with DCI. In order to keep the survey brief, we restricted further questioning to the use of $P_{bt}O_2$ probes and microdialysis catheters (Appendix 2 in Additional file 2). The majority of clinicians are more likely to transfuse when $P_{bt}O_2$ values fall below 15 mmHg. A considerably smaller proportion would be more likely to transfuse when the level is 15-20 mmHg. It is important to point out that transfusion is usually only considered as a method to raise $P_{bt}O_2$ if other strategies (optimizing cerebral perfusion pressure and PO_2) have failed. A definitive, "critical" $P_{bt}O_2$ threshold value has never been identified with certainty. Based on associations with poor outcomes, levels of 10-20 mmHg have been advocated both in patients with severe traumatic brain injury and SAH [21-23]. Evidence of ischemia on positron emission tomography has been demonstrated at a $P_{bt}O_2$ threshold of approximately 14 mmHg [24]. An ongoing, NIH-sponsored phase II clinical trial in traumatic brain injury patients uses a $P_{bt}O_2$ threshold of 20 mmHg to initiate therapy [25]. The clinical significance of an elevated LPR is less clear to clinicians; only one third of respondents indicated that a value greater than 40 would influence them to transfuse. However, experience with microdialysis in SAH is limited in North America (Table 1). Among clinicians who report regular use of microdialysis, a LPR threshold of about 35-40 appears to be considered critical. A

high LPR has been shown to be predictive of poor outcomes after SAH [26]. However, pronounced LPR elevations may occur in the absence of ischemia [27], and may not be modified by the administration of RBCs [28].

Survey validity is enhanced by a high response rate. To maximize responses, we corresponded with program directors prior to initiation of the survey, sent three reminder e-mails to potential respondents and deliberately kept the questionnaire short. The survey was case-based, with interactive scenarios designed to reflect typical clinical practice. Our response rate (53%) is relatively consistent with other published surveys of physicians [29-30]. However, as with most surveys, it is impossible for us to determine whether there were systematic differences in transfusion practices between responders and non-responders. In addition, there may be differences between what clinicians *perceive* that they do and how they *actually* practice. Because of a higher response rate, we can be more confident of the validity of our findings among Canadian, rather than U.S. clinicians.

Although our sampling frame was selected specifically to target clinicians most influential in the care of patients with SAH, we may not have surveyed *all* potential "decision-makers"; in particular, we did not include responses from residents or nurse practitioners. Since the survey was performed without any funding, we did not provide a monetary (or other) incentive and chose to perform only an internet-based, rather than postal questionnaire. There is some data to suggest that response rates are higher with postal surveys [31]. On the other hand, our response rate, especially from Canadian intensivists and neurosurgeons, compares favourably with what has been reported elsewhere [29-31]. Because most respondents completed the survey anonymously, we could not record which particular center they work at. Thus, it is possible that our results could have been influenced by variations in the number of responders per center; it is conceivable that this could have led us to underestimate the degree of variability in transfusion practices. Finally, it remains unclear to what degree our findings reflect current practices in other regions of the world.

Conclusions

There is widespread practice variation in the use of RBC transfusions in the management of SAH patients at North American academic medical centers. Equipoise is further demonstrated by the willingness of clinicians to compare relatively divergent Hb transfusion thresholds in the context of a randomized clinical trial. Transfusion practices are heavily influenced by the specific,

dynamic clinical characteristics of patients and may be further modified by clinician specialty, the use of protocols and years in practice.

Key messages

- There is widespread practice variation in the use of RBC transfusions among North American clinicians caring for critically ill patients with aneurysmal subarachnoid hemorrhage (SAH). Most clinicians do not use an Hb transfusion trigger of 7 g/dl and are willing to modify their usual practices in the context of a randomized controlled trial.
- Clinicians target higher Hb goals among patients with higher grade SAH and in the presence of cerebral vasospasm or delayed cerebral ischemia (DCI). Thus, comparison of "fixed" Hb thresholds, applied regardless of specific clinical circumstances, may not represent the optimal approach in future clinical trials assessing "liberal" versus "restrictive" transfusion practices.
- There are significant inter-disciplinary differences in clinicians' transfusion practices. Vascular neurosurgeons appear to be more aggressive in their use of RBC transfusions than intensivists. International differences between American and Canadian practices were also observed.
- Most clinicians are more likely to transfuse patients if the brain tissue oxygen tension ($P_{bt}O_2$) is less than 15 mmHg. There is more uncertainty when $P_{bt}O_2$ is 15-20 mmHg and with information derived from cerebral microdialysis (lactate to pyruvate ratio).

Abbreviations

CBF: cerebral blood flow; DCI: delayed cerebral ischemia; GCS: Glasgow Coma Scale; Hb: hemoglobin; IQR: interquartile range; LPR: lactate:pyruvate ratio; MRI: magnetic resonance imaging; $P_{bt}O_2$: brain tissue oxygen tension; RBC: red blood cell; SAH: subarachnoid hemorrhage; TCD: transcranial Doppler; WFNS: World Federation of Neurological Surgeons score.

Authors' contributions

AHK & PL conceived, designed and carried out the survey. They were also responsible for the analysis and interpretation of the data, and the drafting and revision of the manuscript. JIS, AMN and RLM assisted in designing the survey, interpreting the data and revising the manuscript. All authors approved the final manuscript.

Competing interests

This study was performed without any funding. The authors declare that they have no competing interests.

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Figure legends

Figure 1. Hemoglobin concentrations at which North American clinicians transfuse patients with aneurysmal SAH†. Abbreviations: DCI = delayed cerebral ischemia; Hb = hemoglobin; "Grade" = World Federation of Neurological Surgeons classification. † Box plots demonstrate median and interquartile range. Circles represent "outside values" (± 1.5 times the interquartile range). Means and 95% confidence intervals are presented in the text. * $p < 0.0001$ in relation to Grade 4 SAH (assessed using paired Wilcoxon rank sum test; Bonferroni correction for multiple comparisons). ** $p = 0.001$ in relation to Grade 4 SAH (assessed using paired Wilcoxon rank sum test; Bonferroni correction for multiple comparisons).

Figure 2. Distribution of minimum and maximum Hb concentrations which clinicians consider acceptable transfusion thresholds for a randomized controlled trial. A. Minimum Acceptable Transfusion Threshold. B. Maximum Acceptable Transfusion Threshold. Abbreviations: DCI = delayed cerebral ischemia; "Grade" refers to World Federation of Neurological Surgeons classification; Hb = haemoglobin.

Figure 3. Relationship between respondent characteristics and transfusion thresholds†. A. Country. B. Specialty‡. C. Use of Multimodal Neurological Monitoring. D. Use of Transfusion Protocol. Abbreviations: DCI = delayed cerebral ischemia; "Grade" refers to World Federation of Neurological Surgeons classification; Hb = haemoglobin. † Box plots demonstrate median and interquartile range. Circles represent "outside values" (± 1.5 times the interquartile range). Boxes represent "far out values" (± 3 times the interquartile range). ‡ The term "intensivist" refers both to individuals who practice exclusively as neurointensivists and to multi-disciplinary intensivists who regularly care for patients with subarachnoid hemorrhage. * $p<0.05$ using Wilcoxon rank sum test.

Figure 4. Relationship between respondent characteristics and acceptable transfusion thresholds in the setting of a randomized controlled trial†. A. Country. B. Specialty. C. Use of Multimodal Neurological Monitoring. D. Use of Transfusion Protocol. Abbreviations: DCI = delayed cerebral ischemia; "Grade" refers to World Federation of Neurological Surgeons classification; Hb = haemoglobin. † Box plots demonstrate median and interquartile range. Circles represent "outside values" (± 1.5 times the interquartile range). Boxes represent "far out values" (± 3 times the interquartile range). ‡ The term "intensivist" refers both to individuals who practice exclusively as neurointensivists and to multi-disciplinary intensivists who regularly care for patients with subarachnoid hemorrhage. * $p<0.05$ using Wilcoxon rank sum test.

Tables

Table 1. Characteristics of survey respondents from the United States and Canada

	United States (143)	Canada (139)	Total (282)	P Value
Base Specialty				
Neurology	55%	2%	29%	< 0.0001
Neurosurgery	23%	15%	19%	
Anesthesiology	10%	27%	19%	
Internal Medicine	7%	37%	22%	
Emergency Medicine	4%	6%	5%	
Surgery	1%	12%	6%	
Years Of Experience				
0-3	34%	17%	26%	0.04
4-7	15%	24%	20%	
8-10	10%	14%	11%	
11-15	22%	21%	21%	
16-20	7%	10%	9%	
> 20	13%	14%	13%	
Monitoring Tools				
CT angiography	91%	88%	90%	0.50
CT perfusion	69%	24%	46%	< 0.0001
Transcranial Doppler	89%	63%	76%	< 0.0001
$P_{bt}O_2$ probes	34%	6%	21%	< 0.0001
Microdialysis catheters	8%	1%	4%	0.005†
Continuous CBF probes	14%	0	7%	< 0.0001†
Jugular bulb oximetry	13%	12%	13%	0.79
MR perfusion	33%	17%	25%	0.002
None of above	3%	4%	3%	0.75†
Use of institutional transfusion protocol	55%	50%	52%	0.42

Abbreviations: CBF = cerebral blood flow; CT = computed tomography; MR = magnetic resonance; $P_{bt}O_2$ = brain tissue oxygen tension.

† Fisher's exact test.

Table 2. Multivariable analysis assessing associations between respondent characteristics and transfusion thresholds in clinical practice (A) and in the context of a randomized controlled trial (B)†

A. Clinical Practice

Clinical Setting	Predictors remaining in final model	Estimate (β)	P Value
WFNS Grade 4 (Day 3)	Specialty (neurosurgery)	0.46	0.003
WFNS Grade 1 (Day 3)	Transfusion protocol	- 0.42	0.0008
	Transfusion protocol*Specialty (neurosurgery)[‡]	0.88	< 0.0001
TCD Vasospasm (Day 6)	Specialty (neurosurgery)	0.31	0.04[§]
DCI (Day 7)	Multimodal neurological monitoring	0.32	0.04

B. Randomized Controlled Trial

WFNS Grade 4 (Lowest Acceptable Hb)	Specialty (neurosurgery)	0.37	< 0.0001
	Years in practice	0.01	0.009
WFNS Grade 4 (Highest Acceptable Hb)	Specialty (neurosurgery)*Years in practice[§‡]	0.03	0.01
DCI (Lowest Acceptable Hb)	Years in practice	0.02	0.01
DCI (Highest Acceptable Hb)	Transfusion protocol	-0.35	0.003
	Years in practice	0.02	0.007
	Transfusion protocol*Specialty (neurosurgery)[*]	0.66	0.002

Abbreviations: DCI = delayed cerebral ischemia; Hb = hemoglobin concentration; N/R = not relevant; TCD = transcranial Doppler; WFNS = World Federation of Neurological Surgeons scale.

† Multivariable analysis was performed using generalized linear models with stepwise backwards elimination of the least significant variable, where p>0.05. Initial models included country (U.S. vs. Canada), specialty (neurosurgery vs. critical care), multimodal monitoring (yes vs. no), use of a transfusion protocol (yes vs. no) and years in practice

(continuous variable). All interactions were assessed, and those with $p<0.05$ in univariate analysis were incorporated into initial multivariable models.

‡ Years in practice significantly modified practices among neurosurgeons (see text for details).

§ White's heteroscedasticity-specific standard error.

* Neurosurgical specialty significantly modified practices among clinicians who use a protocol (see text for details).

Additional files

Additional file 1:

Title: Appendix 1.

Description: Copy of on-line survey used to collect data for this study (Canadian version).

Additional file 2:

Title: Appendix 2.

Description: Modification of transfusion practices based on information provided by $P_{bt}O_2$ and microdialysis (lactate:pyruvate) monitoring.

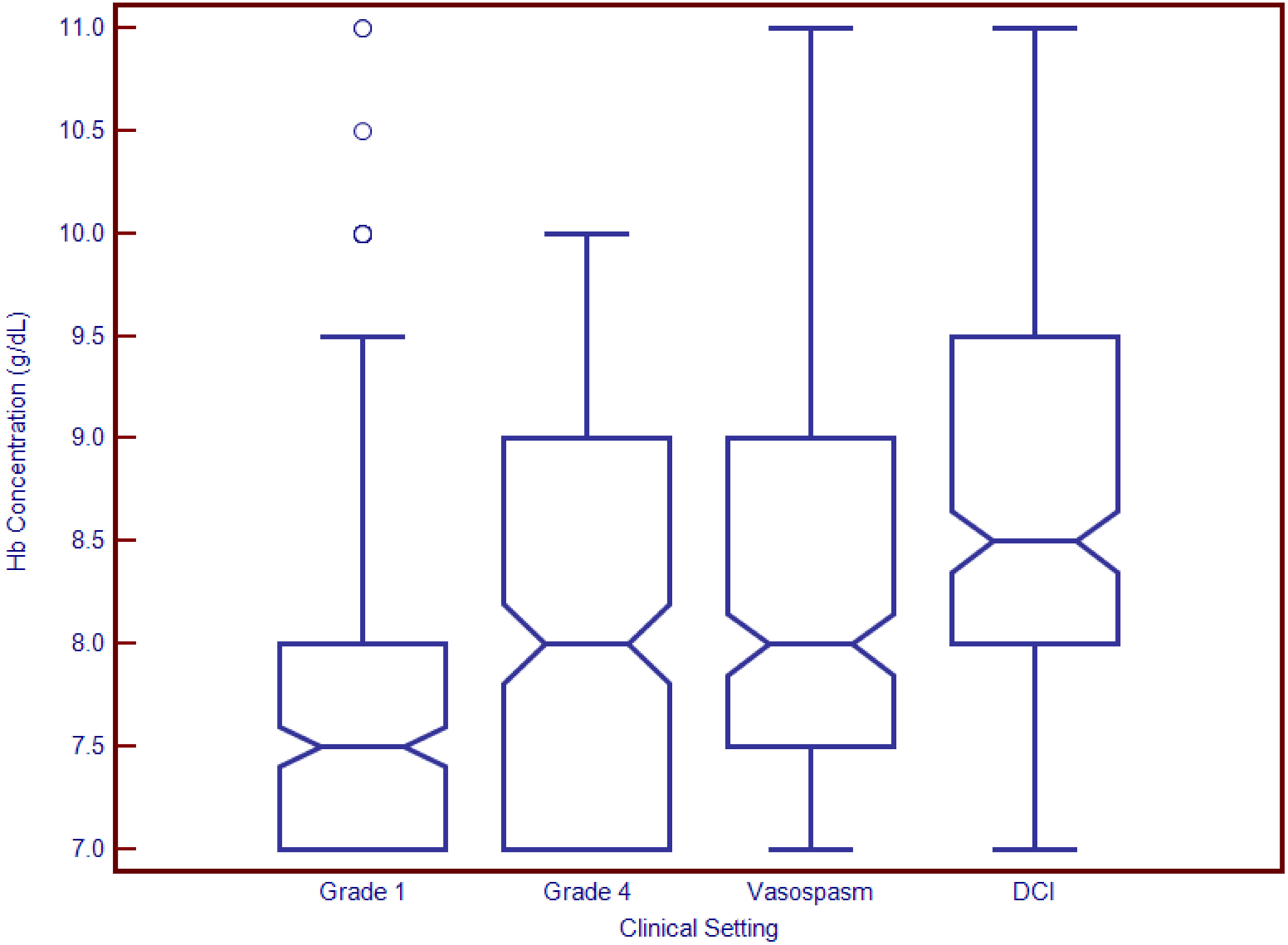
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
Hb Concentration (g/dL)
Grade 1
Grade 4
Vasospasm
DCI
Clinical Setting

Figure 1

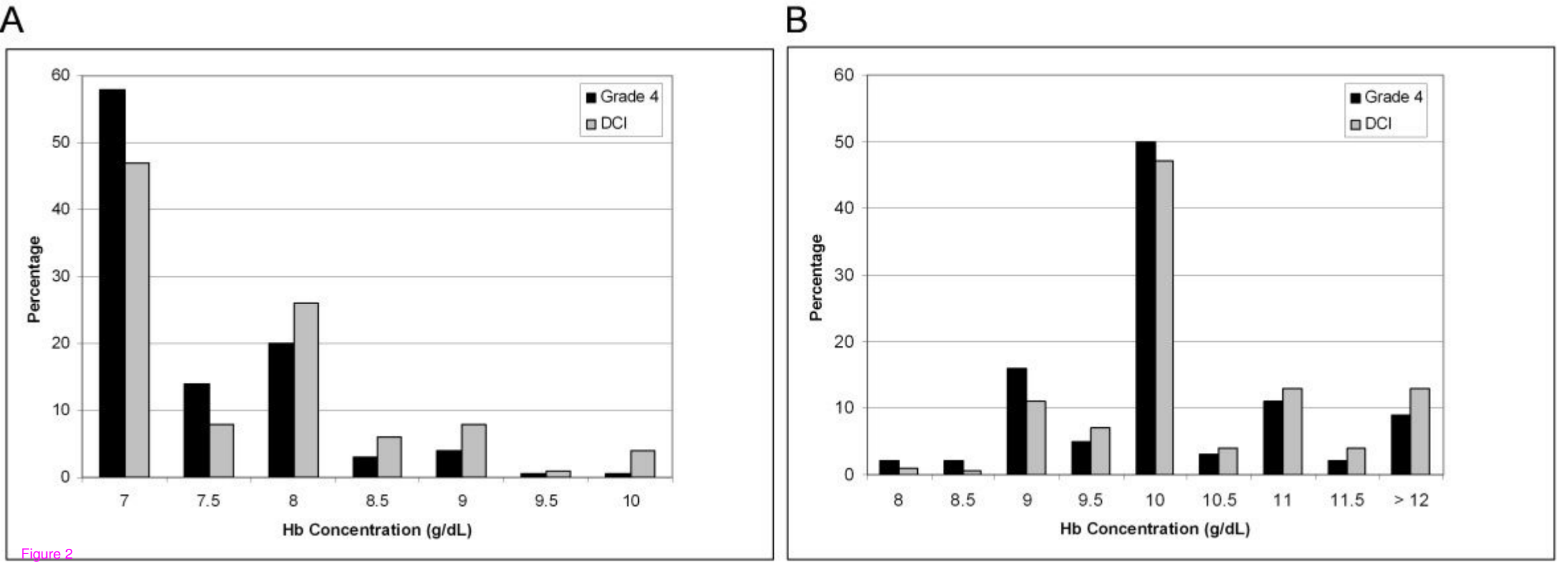
A
60
50
40
30
20
10
0
Percentage
Grade 4
DCI
7
7.5
8
8.5
9
9.5
10
Hb Concentration (g/dL)
B
60
50
40
30
20
10
0
Percentage
Grade 4
DCI
8
8.5
9
9.5
10
10.5
11
11.5
> 12
Hb Concentration (g/dL)

Figure 2

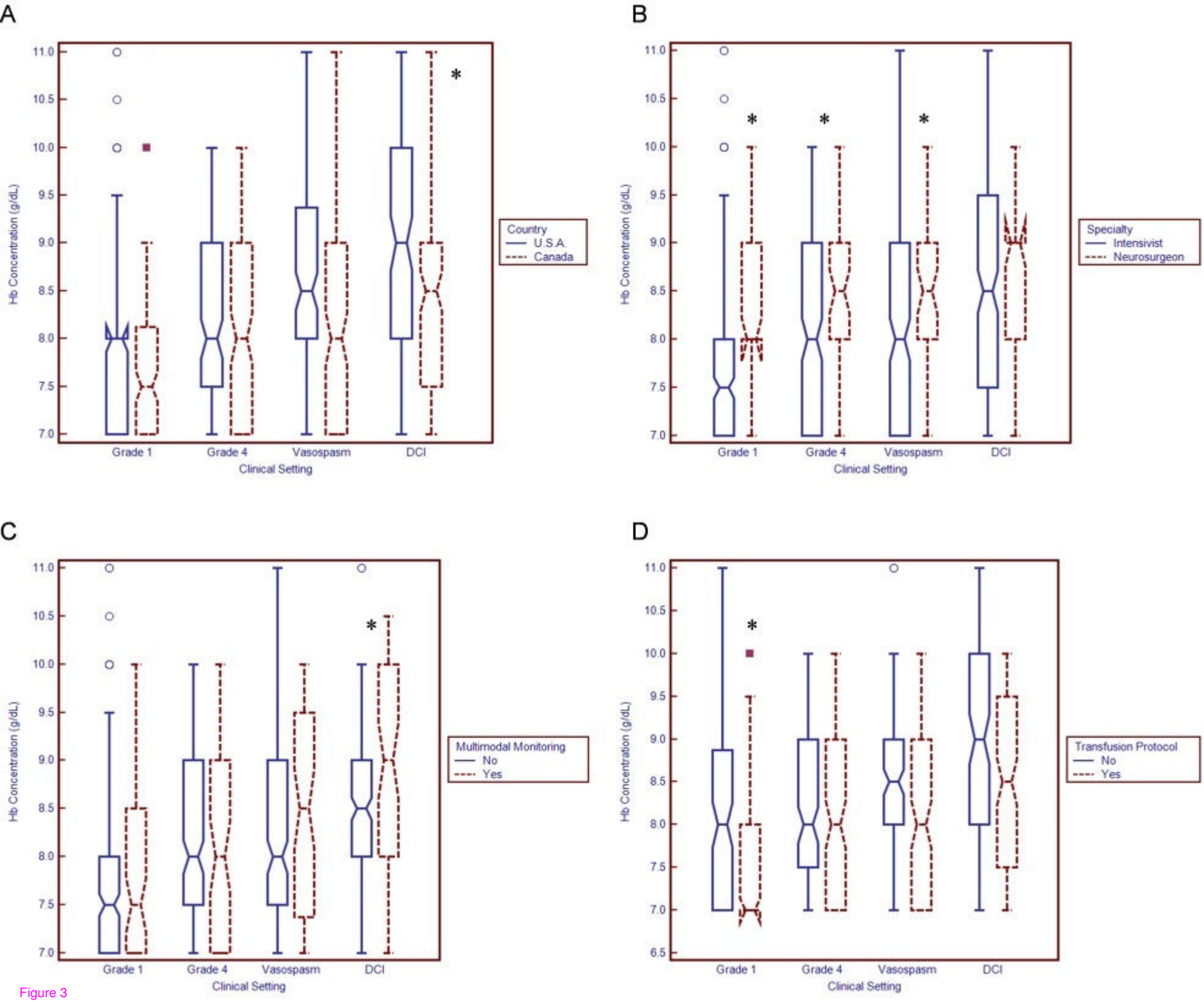
A
Hb Concentration (g/dL)
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
Grade 1
Grade 4
Vasospasm
DCI
Clinical Setting
Country
U.S.A.
Canada
B
Hb Concentration (g/dL)
Grade 1
Grade 4
Vasospasm
DCI
Clinical Setting
Specialty
Intensivist
Neurosurgeon
C
Hb Concentration (g/dL)
Grade 1
Grade 4
Vasospasm
DCI
Clinical Setting
Multimodal Monitoring
No
Yes
D
Hb Concentration (g/dL)
6.5
Grade 1
Grade 4
Vasospasm
DCI
Clinical Setting
Transfusion Protocol
No
Yes

Figure 3

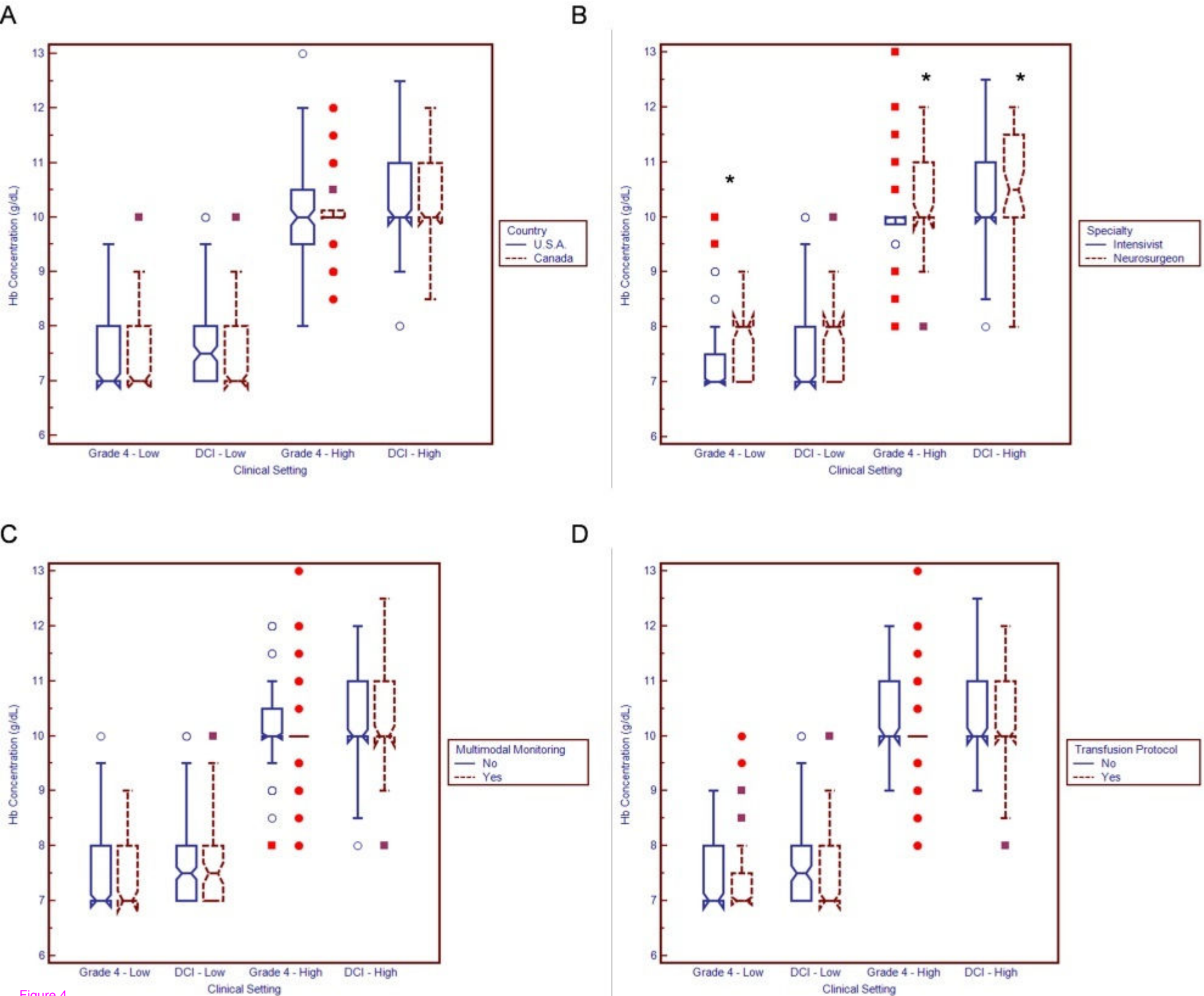
A
B
C
D
Hb Concentration (g/dL)
Clinical Setting
Grade 4 - Low
DCI - Low
Grade 4 - High
DCI - High
Country
U.S.A.
Canada
Specialty
Intensivist
Neurosurgeon
Multimodal Monitoring
No
Yes
Transfusion Protocol
No
Yes

Figure 4

Additional files provided with this submission:

Additional file 1: Critical Care Appendix 1 October 4.pdf, 78K
http://ccforum.com/imedia/4477703275079424/supp1.pdf
Additional file 2: Critical Care Appendix 2 October 4.doc, 26K
http://ccforum.com/imedia/3201463795079424/supp2.doc