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Variation in blood transfusion and coagulation management in Traumatic Brain Injury at the Intensive Care Unit: A survey in 66 neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study.

Running title

Transfusion and coagulation management

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Variation in transfusion and coagulation management in European neurotrauma centers

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Variation in blood transfusion and coagulation management in Traumatic Brain Injury at the Intensive Care Unit: A survey in 66 neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. (DOI: 10.1089/neu.2017.5194)

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Abstract

Our aim was to describe current approaches and to quantify variability between European intensive care units (ICU)s in patients with TBI. Therefore, we conducted a provider profiling survey as part of the ‘Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury’ (CENTER-TBI) study. The ICU Questionnaire was sent to 68 centers from 20 countries across Europe and Israel. For this study, we used ICU questions focused on 1) hemoglobin target level (Hb-TL), 2) coagulation management, and 3) deep venous thromboembolism (DVT) prophylaxis. Seventy-eight participants, mostly intensivists and neurosurgeons of 66 centers completed the ICU questionnaire. For ICU-patients, half of the centers (N=34; 52%) had a defined Hb-TL in their protocol. For patients with TBI, 26 centers (41%) indicated a Hb-TL between 70 and 90 g/l and 38 centers (59%) above 90 g/l. To treat trauma related hemostatic abnormalities the use of fresh frozen plasma (N=48; 73%) or platelets (N=34; 52%) was most often reported, followed by the supplementation of vitamin K (N=26; 39%). Most centers reported using DVT prophylaxis with anticoagulants frequently or always (N=62; 94%). In the absence of hemorrhagic brain lesions, 14 centers (21%) delayed DVT prophylaxis until 72 hours after trauma. If hemorrhagic brain lesions were present, the number of centers delaying DVT prophylaxis for 72 hours increased to 29 (46%). Overall, a lack of consensus exists between European ICUs on blood transfusion and coagulation management. The results provide a baseline for the CENTER-TBI study and the large between-center variation indicates multiple opportunities for comparative effectiveness research.

Keywords: intensive care unit; traumatic brain injury; coagulopathy; transfusion; Europe

Introduction

The management of hemorrhage and disordered coagulation is a common and critically important challenge in trauma patients. This is particularly the case for patients with severe traumatic brain injury (TBI) where physicians have to balance the risks of progressive hemorrhage in the brain against secondary thrombotic complications including deep venous thrombosis (DVT). Many controversies continue to exist regarding the appropriate management for optimizing blood and coagulation status.

Transfusion thresholds for anaemia are a particularly controversial area in TBI. According to the guidelines^{1, 2}, transfusion in general critically ill patients is recommended at a restrictive hemoglobin target level (Hb-TL) of 70 g/l rather than a liberal Hb-TL of 90 g/l or 100g/l. Whether such target levels also apply to patients with TBI is unclear.^{3, 4} Inappropriate use of blood products exposes patients to a number of systemic risks and may even lead to progressive hemorrhagic injury following TBI.³ However, cerebral oxygenation may be improved with higher hemoglobin concentrations^{5, 6} whereas restrictive transfusion thresholds may predispose to brain tissue hypoxia and may increase the risk of early mortality.⁷ On the other hand, a recent large retrospective cohort study indicated that a restrictive blood transfusion policy was not associated with increased mortality and can be cost-effective in patients with TBI.⁸ An additional challenge for the management of both blood - and coagulation status is the presence of coagulopathy.⁹ Both pro- and anticoagulatory abnormalities can be observed after TBI in around one out of three patients.¹⁰⁻¹² Coagulopathy at admission is associated with increased mortality and poor neurological outcome.¹²⁻¹⁴ Coagulopathy may result from defective clot initiation, poor clot formation or hyper fibrinolysis. Acidosis, hypothermia, coagulation factor consumption or dilution, and the more recently described acute coagulopathy of trauma-shock which results from widespread endothelial activation after hypoperfusion may contribute to coagulopathy.¹⁵ Finally, patients with TBI are at increased risk of venous thromboembolism (VTE) (around 20%)¹⁶ compared with general ICU patients (around 6-8%).¹⁷ Here, the balance between the prevention of VTE and the risk of (progressive) hemorrhage of the brain depends largely on the timing of thromboprophylaxis with anticoagulants. However, current Brain Trauma Foundation guidelines do not make clear recommendations on coagulation management.¹⁸

Material and Methods

Participating centers

This study is part of the prospective, longitudinal ‘Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury’ (CENTER-TBI) study in 68 centers from 20 countries across Europe and Israel. The CENTER-TBI investigators and participants are listed in Supplemental Data 1. In 2014, before the start of inclusion of patients, the principle investigators of each center were asked to complete a set of questionnaires on structure and process of care: ‘the Provider Profiling Questionnaires’.¹⁹
²⁰ The questionnaires were about TBI management irrespective of systemic injuries. One of these questionnaires concerned ICU management.

Provider Profiling Questionnaire

The provider profiling questionnaire was developed in a systematic manner. The literature (including guidelines and available surveys) was reviewed and experts of various disciplines (neurosurgeons, (neuro)intensivists, neurologists, emergency department physicians, rehabilitation physicians, medical ethicists, health care economists and epidemiologists) were consulted throughout the different phases in the development process. Preliminary questionnaires were pilot-tested in 16 of the participating centers for unexpected or missing values and ambiguity, and received feedback was incorporated. For more information about the development, administration and content of the total set of provider profiling questionnaires, see Clossen et al., 2016.¹⁹ In this study, we focus on 10 questions (with additional sub questions) on hemoglobin target levels, trauma related coagulation management, and use and timing of thromboprophylaxis (Supplemental Data 2).

Hemoglobin target level and coagulation management

Participants were explicitly asked for their general policy rather than for individual treatment preferences. General policy was defined as ‘the way the large majority of patients (>75%) with a certain indication would be treated’. The ICU questionnaire

consisted mostly of multiple-choice questions and one open question; the Hb-TL in the protocol at the ICU for the general ICU population. For the hemoglobin unit conversion from mmol/L towards g/L we multiplied with the factor 1.6 and then rounded up to tens.

Statistical analysis

Descriptive statistics (frequencies and percentages) were used to describe the treatment policies reported by the participating centers. For some questions in which centers had to indicate how often a certain approach was taken by choosing 'never' (in 0-10% of cases), 'rarely' (in 10-30% of cases), 'sometimes' (in 30-70% of cases), 'frequently' (in 70-90% of cases) and 'always' (90-100% of cases), categories were combined (e.g. combining 'always' and 'frequently') because of low numbers in these categories.

To gain more insight into characteristics that determine treatment policies we divided centers in relatively high- and middle-income countries versus lower-income countries, and in countries from different geographic locations (North and West Europe versus South and East Europe and Israel). The designation into relatively lower-income countries was based on a 2007 report by the European Commission²¹, and the designation into geographic location was based on the classification by the United Nations. Analyses were performed using the Statistical Package for Social Sciences (SPSS) version 21.²²

Results

Participating centers

Sixty-six centers of the 68 centers completed the ICU questionnaire (response rate=97%). The questionnaire was completed by intensivists (N=33; 50%), neurosurgeons (N=23; 35%), administrative staff (N=11; 17%), neurologists (N=5, 8%), anesthesiologists (N=5, 8%) and a trauma surgeon (N=1; 2%). Almost all the centers had an academic affiliation (N=60; 91%) and most centers were designated as a level I trauma center (N=44; 67%). Centers had a median of 33 (interquartile range 22-44) beds for general ICU patients and treated a

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median of 92 (interquartile range 52-160) patients with TBI, of all severities, annually. An extensive overview of all the center characteristics is described in a previous publication.¹⁹

For the management of TBI at the ICU, most centers indicated to follow the 2007 Brain Trauma Foundation (BTF) guidelines (N=28; 42%) or institutional guidelines (N=21; 32%), which were broadly based on BTF and/or national guidelines. Some centers indicated they did not have specific guidelines for management of TBI (N=11; 17%) or that they developed a guideline independently from available guidelines (N=2; 3%).

Hemoglobin target level

Half of the centers (N=34; 52%) reported to have hemoglobin target levels (Hb-TL) described in their protocol for general/non-TBI ICU patients. The reported Hb-TL varied (open question): 110 g/l (N=1; 3%), 100 g/L (N=8; 28%), 90 g/L (N=4; 14%), 80 g/L (N=9; 31%), 70 g/L (N=5; 18%), 80-100 g/L (N=1; 3%) and 70-80 g/L (N=1, 3%). In non-neurological critically ill patients, 35 of the centers (56%) reported a Hb-TL between 70 g/L and 80 g/L. In patient with TBI, 10 of the centers (16%) indicated to use a Hb-TL between 70 and 80 g/L. The remainder of the centers used higher Hb-TL: between 80 g/L and 90 g/L (N= 16; 25%), between 90g/L and 100 g/L (N=20; 31%), and above 100 g/L (N=18; 28%). (Table 1)

[Insert HuijbenTable1]

Coagulation management

Transfusion with fresh frozen plasma was most often reported for correction of trauma related coagulopathy (N= 48; 73%), followed by the use of platelets (N=34; 52%). Coagulopathy was most often managed with vitamin K (N=26; 39%), fibrinogen (N=19; 29%), Prothrombin Complex Concentrate (N= 17; 26%), Tranexamic acid (N=7; 11%) or recombinant factor VIIa (N=3; 5%). One center reported to use Desmopressin, in addition to Tranexamic Acid. (Figure 1)

[Insert HuijbenFig 1]

Most centers indicated that they use deep venous thrombosis (DVT) prophylaxis with anticoagulants frequently (N=18; 27%) or always (N=44; 67%) in patients with TBI. Fourteen centers (21%) indicated they generally wait 72 hours after trauma before commencing DVT prophylaxis in the absence of hemorrhagic brain lesions. However, twice

that number of centers (N=29; 46%) indicated to wait 72 hours after trauma in the presence of hemorrhagic brain lesions. Low molecular weight heparin was most commonly indicated as the prophylactic drug of choice (N=54; 82%), followed by subcutaneous unfractionated heparin (N=7; 11%) and intravenous heparin (N=1; 2%). (Table 2)

[Insert HuijbenTable2]

Most centers indicated that they would always test a coagulation panel prior to the insertion of a parenchymal sensor (N=45; 69%) or a ventricular catheter (N=46; 71%). The reported minimum platelet count for the insertion of a ventricular catheter was variable: $>100 \times 10^9/L$ (N=30; 46%), $>80 \times 10^9/L$ (N=9; 14%) or $>50 \times 10^9/L$ (N=9; 14%). In most of the remaining centers the minimum platelet count depended on the surgeon (N=13; 20%). Also, the reported minimum International Normalized Ratio (INR) considered safe for placement of a ventricular catheter was variable: <1.4 (N=21; 33%), <1.3 (N=17; 26%) or <1.2 (N=8; 12%). Again, in most of the remaining centers the minimum INR was indicated to depend on surgeon's individual preferences (N=15; 23%). There were no centers that answered 'never' on all questions. (Table 3)

[Insert HuijbenTable3]

Twenty-nine centers indicated identical policies for coagulation management (always using DVT prophylaxis, and always obtaining a coagulation panel prior to insertion of a parenchymal or ventricular catheter). The majority of these centers are located in South and East Europe and Israel (N=13, 56%) versus (N=16, 37%) in North and West Europe and the majority are located in high income countries (N=26, 47%), versus (N=3, 27%) in lower income countries.

Discussion

This study shows large between-center variation in blood transfusion and coagulation-directed policies in critically ill patients with TBI. More centers indicated a restrictive Hb-TL (between 70 g/l and 80 g/L) in general ICU patients compared to patients with TBI. Reported coagulation management was variable regarding timing of deep venous

thrombosis (DVT) prophylaxis with anticoagulants, minimum platelet count and INR values prior to ICP probe insertion, and correction of trauma related coagulopathy.

The large between-center differences are likely in part explained by a lack of evidence on optimal management of patients with TBI. A majority of centers in our study reported to adhere to the 2007 Brain Trauma Foundation (BTF) guidelines for the treatment of patients with TBI, but this guideline does not provide specific recommendations on red blood cell transfusion or coagulopathy management. Equally, some trauma guidelines have stated policies on blood transfusion and coagulation in trauma patients of which some pertain to patients with TBI, but recommendations are still scarce.^{1, 2, 23} A recent update of the Cochrane Review of all Red Cell Transfusion trials reported on 12587 patients identified in 31 randomized trials and suggested that a restrictive rather than liberal transfusion practice improves outcomes, but noted the data was very limited for neurocritical care.²⁴ Regarding patients with TBI, several trials have been conducted on blood transfusion management^{25, 26}, and the reversal of coagulopathy^{27, 28}, but these all had a limited power. A recent large retrospective single-center study in TBI patients admitted to the intensive care⁸ found that transfusion guided by a restrictive Hb-TL was associated with significantly less time with fever, higher cost-effectiveness and had the same risk of mortality compared with a liberal Hb-TL. Another explanation for the variation in management would be the between-center variation in the content of available protocols. E.g. we found that even between centers that do have a protocol on red blood cell transfusion policy, the reported Hb-TL still varied substantially. Overall in patients with TBI, there is no conclusive evidence or clear guidance in guidelines and protocols on blood transfusion and coagulopathy treatment. Still, with an aging TBI demographic with an increased prevalence of comorbidity, coagulation management might even become more complex. Concurrent use of anticoagulant and antiplatelet medication is a growing concern, prior warfarin treatment for example is associated with an increased risk of poor outcome.²⁹ In addition, coagulation management in TBI is further complicated by the recent introduction of newer anticoagulants, such as direct thrombin inhibitors (dabigatran, argatroban).³⁰

was completed by 312 physicians of the trauma surgery -, neurosurgery -, and ICU department of level I trauma centers in the United States.³⁸ In the study of Badenes et al. a newly developed multiple-choice survey was used as well, but was completed by 868 respondents, mostly specialists in anesthesiology and intensive care, worldwide.³⁹ In the study of Sena et al. 55% of respondents chose a restrictive policy of 70 g/l or less. Likewise, in the study of Badenes et al. 50% of respondents chose a low Hb-TL of 70 or 80 g/l, while in our study 16% chose a Hb-TL between 70 and 80 g/. The difference could either be explained by a difference in patient population (severely injured patients with TBI in the study of Sena et al.), by a difference in answer options (we did not have an answer option below 70 g/l), or by a difference in policy between Europe and other continents.

Strengths of our study include the comprehensive development process of the questionnaires and the high response rate of 97%. Limitations include the survey-design, resulting in perceived practices rather than actual practices. Although we explicitly asked for general policy and data were anonymously collected, we cannot exclude differences between current findings and actual treatment in the participating centers. In addition, questions were aimed to assess general policy and contained no specific details on patient characteristics. This is not representative for clinical practice (possibly making the questions more difficult to answer). In addition, we could not make a distinction between pharmaceutical versus mechanical DVT prophylaxis. A further limitation comprises the representativeness of our sample. The majority of centers were Academic level I trauma centers with a special interest in neurotrauma. Findings are therefore not generalizable to non-specialized centers. In addition, differences between centers could represent differences in case-mix instead of true practice.

The practice variability we report supports that evidence on optimal treatment approaches is needed. Such evidence can potentially be obtained in a non-randomized design by comparing outcomes between centers with different treatment policies. Such a Comparative Effectiveness Research approach exploits the existing between-center variation. Data on real time patient management and clinically relevant outcomes in the CENTER-TBI study are now being collected.²⁰ Future research on blood transfusion and coagulation management in patients with TBI could lead to prevention of progressive brain hemorrhage and secondary problems like coagulopathy and VTE. For now, the optimal

transfusion strategies to correct coagulopathy in terms of the ratio of packed blood cells, fresh frozen plasma (or similar products) and platelets are still being debated.⁴⁰ This debate pertains both to optimal strategies with regard to reversal of trauma related coagulopathy and management of coagulopathy induced by conventional agents (such as vitamin K antagonists) and newer ones such as direct thrombin inhibitors.^{9, 30, 41} Still, others warn for the use of transfusion considering the possibility of complications of transfusion and unknown effects on (functional) outcome.⁴² Also for coagulation (enhancing) products larger studies are needed to prove a positive balance between the beneficial effects in terms of patient outcome and adverse effects on (thromboembolic) complications.^{27, 28, 42-45} New evidence is clearly needed on these topics, since control of blood and coagulation status could have a large impact on patient outcome, especially in patients with TBI.

Conclusions

In conclusion, we showed substantial variation in blood and coagulation management of patients with TBI at the ICUs in 66 centers in Europe and Israel participating in the CENTER-TBI study. This variation may be largely attributable to the lack of guidelines and high quality evidence on these topics. The large practice variation provides an opportunity to study the effectiveness of different policies in comparative effectiveness research.

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No competing financial interests exist

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Table 1. Red blood cell transfusion policy ^a

Items	Number	N	(%)
questionnaire	completed		
Protocol at the ICU			
Protocol	65		
- Presence of a protocol with a Hb-TL		34	(52%)
- Absence of a protocol with a Hb-TL		31	(48%)
Transfusion at Hb-TL in protocol (open question)			
	29		
- 110 g/L		1	(3%)
- 100g/L		8	(28%)
- 90 g/L		4	(14%)
- 80 g/L		9	(31%)
- 70 g/L		5	(18%)
- 80-100 g/L		1	(3%)
- 70-80 g/L		1	(3%)
In non-neurological critically ill patients			
Transfusion at Hb-TL	63		
- > 100 g/L		1	(2%)
- Between 90 g/l and 100g/L		6	(9%)
- Between 80 g/l and 90 g/L		21	(33%)
- Between 70 g/l and 80 g/L		35	(56%)
In patients with TBI ^b			
Transfusion at Hb-TL	64		
- > 100 g/L		18	(28%)
- Between 90 g/l and 100g/L		20	(31%)
- Between 80 g/l and 90 g/L		16	(25%)
- Between 70 g/l and 80 g/L		10	(16%)

Table 2. Coagulation policies, deep venous thrombosis ^a

Items	Number	N	(%)
questionnaire	completed		
DVT prophylaxis			
Frequency of DVT prophylaxis	66		
- Never (0-10%)		1	(2%)
- Rarely (10-30%)		0	(0%)
- Sometimes (30-70%)		3	(4%)
- Frequently (70-90%)		18	(27%)
- Always (90-100%)		44	(67%)
Start in the absence of hemorrhagic lesions	65	26	(40%)
- < 24 hours		24	(37%)
- 24-72 hours		14	(21%)
- > 72 hours		1	(2%)
- Never	63		
Start in the presence of hemorrhagic lesions		5	(8%)
- < 24 hours		25	(40%)
- 24-72 hours		29	(46%)
- > 72 hours	64	4	(6%)
- Never		10	(16%)
Start after intracranial surgery		31	(48%)
- < 24 hours		21	(33%)
- 24-72 hours		2	(3%)
- > 72 hours			
- Never			
Pharmacological DVT prophylaxis	66		
- Subcutaneous unfractionated heparin		7	(11%)
		1	(2%)

Table 3. Coagulation policies, ICP monitoring ^a

Items	Number	N	(%)
questionnaire	completed		
Checks prior to insertion of parenchymal sensor for ICP monitoring			
Coagulation panel	65		
- Never (0-10%)		4	(6%)
- Rarely (10-30%)		2	(3%)
- Sometimes (30-70%)		5	(8%)
- Frequently (70-90%)		5	(8%)
- Always (90-100%)		45	(69%)
- Not available ^b		4	(6%)
Checks prior to insertion ventricular catheter for ICP monitoring			
Coagulation panel	65		
- Never (0-10%)		3	(4%)
- Rarely (10-30%)		2	(3%)
- Sometimes (30-70%)		5	(8%)
- Frequently (70-90%)		4	(6%)
- Always (90-100%)		46	(71%)
- Not available ^b		5	(8%)
Minimum platelet count	65		
- >150 x10 ⁹ /L		1	(2%)
- >100 x10 ⁹ /L		30	(46%)
- > 80 x10 ⁹ /L		9	(14%)
- > 50 x10 ⁹ /L		9	(14%)
- Depending on the surgeon		13	(20%)
- No minimum		0	(0%)
- Other		3	(4%)
Minimum INR	65		

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Deep venous thrombosis (DVT) prophylaxis

The responses to the following questions should represent, as best as practicable, a general consensus on treatment at your centre, rather than individual management preferences.

	Never (0-10%)	Rarely (10-30%)	Sometimes (30-70%)	Frequently (70-90%)	Always (90-100%)
53. How often is DVT prophylaxis used?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

54. If you use DVT prophylaxis, when is DVT prophylaxis initiated?

	< 24 hrs	24-72 hrs	< 72 hrs	Never
In the absence of hemorrhagic lesions	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
In the presence of hemorrhagic lesion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
After intracranial surgery	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

55. In patients who receive DVT prophylaxis, what medication is given?

- Subcutaneous unfractionated heparin
- Low-molecular weight heparin
- Other, please specify.....

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 Variation in blood transfusion and coagulation management in Traumatic Brain Injury at the Intensive Care Unit: A survey in 66 neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. (DOI: 10.1089/neu.2017.5194)
 This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

56. Coagulopathy related to the trauma is treated with :

	Never (0-10%)	Rarely (10-30%)	Sometimes (30-70%)	Frequently (70-90%)	Always (90-100%)
Fresh Frozen plasma (FFP)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Platelets	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fibrinogen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Novo 7 (recombinant factor VII)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vitamin K	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
PCC (Prothrombin Complex Concentrate)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other, please specify...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

General ICU treatments / protocols

Red blood cell policy

61. Does the Intensive Care Unit (ICU) protocol specify a target goal for hemoglobin concentration?

- No
- Yes, please specify

62. Do you have a transfusion target in patients with Traumatic Brain Injury (TBI) in the acute phase?

- >100 g/l or 6 mmol/l
- Between 90g/l or 5.5 mmol/l and 100 g/l or 6 mmol/l
- between 80 g/l or 5 mmol/l and 90 g/l or 5.5 mmol/l
- Between 70 g/l or 4.0 mmol/l and 80 g/l or 5 mmol/l

63. What is your transfusion target in patients with non-neurological critical illness?

- >100 g/l or 6 mmol/l
- between 90g/l or 5.5 mmol/l and 100 g/l or 6 mmol/l
- between 80 g/l or 5 mmol/l and 90 g/l or 5.5 mmol/l
- Between 70 g/l or 4.0 mmol/l and 80 g/l or 5 mmol/l