National variation in transfusion strategies in patients with upper gastrointestinal bleeding

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ABSTRACT

INTRODUCTION: An optimal transfusion strategy for patients with upper gastrointestinal bleeding (UGIB) has yet to be established. The national guidelines contain recommendations for patients with life-threating bleeding in general, but no specific recommendations for patients with UGIB. We hypothesised that there are variations in transfusion strategies for patients with UGIB across the Danish regions.
METHODS: We performed a retrospective, register-based, analysis on transfusions given to all patients with non-variceal UGIB in Denmark in 2011-2013. We compared the results from the five regions in Denmark in order to discover regional differences.
RESULTS: A total of 5,292 admissions with treatment for non-variceal UGIB were identified, and analysis was made for the total group and a massive transfusions group (330 admissions). In the Capital Region, transfusion of platelets was more likely than in any other region for all patients (p < 0.01) including the massive transfusion group (p = 0.03). In the North Region, transfusion of fresh frozen plasma was more likely for the massive transfusion group (p = 0.01).
CONCLUSION: The observed differences warrant further prospective cohort studies in order to provide a foundation for transfusion recommendations for patients with UGIB.
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TRIAL REGISTRATION: not relevant.

Non-variceal upper gastrointestinal bleeding (UGIB) is a common cause of emergency admissions. The 30-day mortality is around 11%, and it has remained the same since the 1940s despite recent treatment advances [1-3].

A standardised and multidisciplinary approach is essential in order to resuscitate and effectively achieve haemostasis. National guidelines exist for treatment of bleeding ulcers [4] and for transfusion strategies for bleeding patients in general [5, 6]. These guidelines, which were updated in 2014, recommend a restrictive transfusion strategy as evidence regarding liberal transfusion of packed red blood cells (PRBC) indicates a harmful effect on mortality levels [7, 8]. The European Society of Gastrointestinal Endoscopy guideline on diagnosis and management of non-variceal UGIB also recommends restrictive transfusion of PRBC, aiming for target haemoglobin levels between 7 g/dl and 9 g/dl (4.3

mmol/l and 5.6 mmol/l) [9]. Evidence regarding transfusion of fresh frozen plasma (FFP) and platelets (PLT) was sparse in regards to UGIB until a recent study showed an association between transfusion of PLT and a reduction in the need for re-endoscopy [3]. In other groups of patients with substantial bleeding, especially trauma patients, studies indicate that transfusing whole blood or higher ratios of platelets and FPP to PRBC seems beneficial [10, 11]. This has led to recommendations on a balanced transfusion strategy in massively bleeding patients [5], but an optimal transfusion strategy for patients with UGIB remains controversial [12].

With this study we set out to investigate whether transfusion strategies used across Denmark are comparable. Given the sparse evidence and no specific recommendations, we hypothesised that regional differences would be identified.

METHODS

This is a retrospective, nationwide register-based study. The study represents secondary use of retrospective data obtained to establish the effect of transfusion strategy on outcomes following UGIB [3]. Information was extracted from the national Danish Patient Registry (DPR) and the Danish Transfusion Database (DTDB) [13, 14]. The DPR holds information on all inpatient and outpatient contacts in the healthcare system, private and public. The dataset includes information on dates of admission, diagnosis and interventions performed during the admission or outpatient visit. The DTDB contains information on recipient, date, time and type of all transfusions given, nationwide.

We obtained data on all admissions where haemostatic therapeutic endoscopic interventions in either the stomach or duodenum had been employed from 1 January 2011 to 31 December 2013. These data were extracted from the DPR. Patients with variceal bleeding were excluded. From the DTDB, we extracted units of PRBC, FFP and PLT transfused to the above-identified patients during their hospitalisation. The datasets were cross-matched utilising the Danish civil registration number, a unique numeric identifier given to every Danish citizen.

Admissions were separated according to region, and we further segregated massively transfused patients, de-

TABLE 1

Admissions and transfused blood products according to region and group: all admissions and massive transfusion group.

Region	Admissions, n	30-day mortality, %[a]	PRBC, n	FFP, n	PLT, n
Total group (N = 5,292)					
Capital	1,581	10.2	10,164	3,210	1,209
Zealand	825	12.7	5,249	1,685	316
South Denmark	1,445	12.5	7,927	2,480	494
Central Denmark	838	10.4	4,439	1,338	243
North Denmark	603	11.4	3,819	1,453	239
Massive transfusion group (N = 330)					
Capital	109	15.6	2,516	1,262	563
Zealand	53	30.0	1,234	581	140
South Denmark	70	34.3	1,766	880	233
Central Denmark	63	20.6	1,615	979	246
North Denmark	35	22.8	946	589	128

FFP = fresh frozen plasma; PLT = platelets; PRBC = packed red blood cells.
a) No difference in 30-day mortality for either the total group (p = 0.45) or the massive transfusion-group (p = 0.28) was found.

TABLE 2

Number of transfused blood products per admission, mean (standard deviation).

Region	PRBC	FFP	PLT
Total group (N = 5,292)			
Capital	6.4 (8.1)	2.0 (4.8)	0.8 (2.8)
Zealand	6.4 (7.0)	2.0 (3.7)	0.4 (3.4)
South Denmark	5.5 (7.6)	1.7 (4.3)	0.3 (1.4)
Central Denmark	5.8 (7.6)	1.8 (5.2)	0.4 (1.4)
North Denmark	6.3 (8.9)	2.4 (6.1)	0.4 (1.4)
p-value[a]	NS	NS	9.2×10^{-9}
Massive transfusion group (N = 330)			
Capital	23.1 (16.6)	11.6 (11.6)	5.2 (4.2)
Zealand	23.3 (12.5)	10.9 (7.6)	2.6 (2.5)
South Denmark	25.2 (16.8)	12.6 (11.5)	3.3 (4.3)
Central Denmark	25.6 (15.6)	15.5 (14.2)	3.9 (3.7)
North Denmark	27.0 (19.6)	16.8 (11.4)	3.7 (3.9)
p-value[a]	NS	0.01	0.03

ANOVA = analysis of variance; FFP = fresh frozen plasma; NS = non-significant; PLT = platelets; PRBC = packed red blood cells.
a) Result of ANOVA analysis of differences between the regions.

TABLE 3

Transfusion ratios of fresh frozen plasma/packed red blood cells and platelets/packed red blood cells in massive transfusion group, mean (standard deviation); N = 330.

Region	FFP/PRBC ratio (p[a] = 0.01)	PLT/PRBC ratio (p[a] = 2.1×10^{-9})
Capital	0.50 (0.25)	0.25 (0.12)
Zealand	0.46 (0.22)	0.11 (0.10)
South Denmark	0.52 (0.22)	0.13 (0.08)
Central Denmark	0.54 (0.32)	0.15 (0.08)
North Denmark	0.73 (0.32)	0.14 (0.12)

ANOVA = analysis of variance; FFP = fresh frozen plasma; PLT = platelets; PRBC = packed red blood cells.
a) Result of ANOVA analysis of differences between the regions.

fined as transfusion of ten or more units of PRBC over 24 hours at any time during hospital admission (massive transfusion group).

Statistical analyses: All statistical analyses were performed using the "R" software package. Data are presented as means with standard deviation. Comparisons between groups were made using the ANOVA test with post-hoc Bonferroni correction for multiple comparisons.

The choice of a parametric statistical approach was based on an underlying assumption of normality owing to the size of the data material. Our results should be interpreted with this in mind.

Trial registration: not relevant.

RESULTS

A total of 5,292 admissions with treatment for non-variceal UGIB in Denmark were identified. The massive transfusion group consisted of 330 admissions. Transfusion requirements for the total and the massive transfusion groups are listed by region in **Table 1**.

No differences in 30-day mortality between regions could be identified for the total group (p = 0.45) or the massive transfusion group (p = 0.28) (Table 1).

Transfusions of blood products per admission for both groups by and between regions are listed in **Table 2**. In the capital region, transfusion of platelets was more likely than in any other region for all patients (p < 0.01), including the massive transfusion group (p = 0.03). In the North Region, transfusion of FFP was more likely for the massive transfusion group (p = 0.01). When comparing transfusion ratios of FFP/PRBC and PLT/PRBC in the massive transfusion group, the same differences were found, with a higher FFP/PRBC ratio in the North Region (p = 0.01) and a higher PLT/PRBC ratio in the Capital Region (p < 0.01) (**Table 3**).

Table 4 shows p-values for the between-region analysis. The table and supports the mentioned findings.

There were no significant differences in transfusion of PRBC between regions in any groups and no differences in transfusion of FFP in the total group.

DISCUSSION

In this study we observed a difference in transfusion strategies across the Danish regions for patients with non-variceal UGIB. While no differences were found in regards to PRBC, transfusion of PLT is more likely in one region (the Capital Region) for all patients, and transfu-

sion of FFP was more likely in another region (North Region) for massively transfused patients.

The national guidelines for transfusion contain no specific recommendations for treatment of UGIB, but for patients with life-threatening bleeding the recommendation is that a balanced transfusion strategy with ratios of 1:1:1 of PRBC: FFP: PLT should be employed [5].

These recommendations are based on a meta-analysis of massively transfused trauma patients [15] and supported by a recent large randomised clinical trial [11]. While some of the same physiological consequences of life-threatening bleeding will apply, the population of patients with UGIB is often elderly and/or with comorbid cardiovascular conditions that differentiate them from an often younger trauma population that does not have the same rate of comorbidities. The UGIB population will more likely receive drugs such as anticoagulants, which will also affect the amounts and ratios of transfusion.

Interestingly, no regions adhered completely to the established guidelines in massive transfusion. As such, although guidelines call for a 1:1 ratio of FFP/PRBC, the highest observed ratio was 0.73 (Table 3). This discrepancy was also observed in PLT/PRBC transfusion ratios.

The definition of life-threatening bleeding in the national guidelines is transfusion of ten or more PRBC within six hours. In this study, the period is longer (24 hours), but both definitions are debatable [16]. Furthermore, it should be acknowledged that the definition of massive transfusion used in this study (ten units of PRBCs within 24 hours) hosts the inherent risk of introducing survivor bias, thus excluding massively haemorrhaging patients not surviving long enough to obtain ten units of PRBCs [17]. This will inevitably impact on the composition of the massive transfusion group in this study, and results from this group should be interpreted with this in mind. All regions in Denmark now employ a standard acute transfusion pack with blood products in the recommended balanced ratio, given to patients with life-threatening bleeding.

Monitoring haemostasis and guiding transfusion with viscoelastic tests is becoming more available, and using either trombelestography (TEG) or thrombelastometry (ROTEM) is recommended in the national guidelines for patients with non-life-threatening bleeding in whom transfusion of FFP or PLT is considered [5]. In the study period, the accessibility of viscoelastic tests varied across the regions. In the Capital and Zealand regions, TEG was available in all hospitals; in the Central and North Regions, ROTEM was available in some, but not all hospitals; in the South Region, no viscoelastic tests were available. Furthermore, a recent focus on some aspects of platelet function that are not readily detectable by standard viscoelastic assays has sparked interest in employing specialised platelet function analytic devices.

Especially in the capital region, this focus has triggered the introduction of platelet aggregometry (Multiplate) in the clinical armamentarium as well as regional guidelines. Although it remains speculative, the observed increased used of platelets in the capital region could be a consequence of the increased availability of platelet function testing.

It is also interesting to note the apparent agreement on PRBC transfusions between regions. The comparable levels may reflect the fact that PRBC transfusion triggers are based on haemoglobin levels, which is considered a standard test in every UGIB admission. In contrast, FFP or PLT transfusion are often triggered by the above-mentioned functional test, which was not available at all hospitals during the study period. This might explain some differences in transfusion strategy.

As stated, the national guidelines on transfusion only provide indicators for resuscitation of shocked patients, but contain no specific recommendations on the treatment of patients with UGIB [4]. In this regard, the variation in transfusion strategy across regions is understandable, but nonetheless unsatisfying.

A recent study on transfusion in the same population

TABLE 4

p-values for post-hoc analysis with Bonferroni correction of use of platelets between regions in the total group and massive transfusion group. In the massive transfusion group, the post-hoc analysis was also made for transfusion ratios of platelets/packed red blood cells and fresh frozen plasma/packed red blood cells.

| | Region | | | | |
Group	Capital	Zealand	South Denmark	Central Denmark	North Denmark
Total (N = 5,292)					
PLT:					
Capital Region	–	1.40×10^{-5}	2.80×10^{-9}	6.60×10^{-9}	0.01
Zealand	1.4×10^{-5}	–	NS	NS	NS
South Denmark	2.8×10^{-9}	NS	–	NS	NS
Central Denmark	6.6×10^{-9}	NS	NS	–	NS
North Denmark	0.01	NS	NS	NS	–
Massive transfusion (N = 330)					
PLT:					
Capital Region	–	0.01	0.02	NS	NS
Zealand	0.01	–	NS	NS	NS
South Denmark	0.02	NS	–	NS	NS
Central Denmark	NS	NS	NS	–	NS
North Denmark	NS	NS	NS	NS	–
PLT/PRBC:					
Capital Region	–	3.3×10^{-12}	1.7×10^{-10}	7.2×10^{-8}	3.2×10^{-5}
Zealand	3.3×10^{-12}	–	NS	NS	NS
South Denmark	1.7×10^{-10}	NS	–	NS	NS
Central Denmark	7.2×10^{-8}	NS	NS	–	NS
North Denmark	3.2×10^{-5}	NS	NS	NS	–
FFP/PRBC:					
Capital Region	–	NS	NS	NS	0.01
Zealand	NS	–	NS	NS	7.7×10^{-5}
South Denmark	NS	NS	–	NS	0.02
Central Denmark	NS	NS	NS	–	0.01
North Denmark	0.01	7.7×10^{-5}	0.01	0.01	–

FFP = fresh frozen plasma; NS = non-significant; PLT = platelets; PRBC = packed red blood cells.

Variations in transfusion strategies for patients with upper gastrointestinal bleeding across the Danish regions.
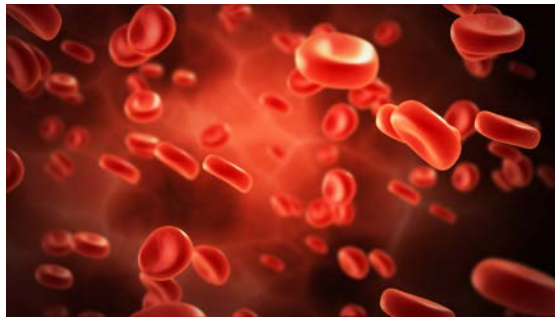
as the one used in this study indicated an association between mortality and all types of blood products as well as transfusion ratios, but also an association between transfusion of platelets and better haemostasis (measured as fewer re-endoscopies) [3]. This supports a restrictive transfusion practice to lower mortality, and raises an interest in further study of the influence of blood components on the outcome in this population [7, 8]

Differences in 30-day mortality between regions were, however, not identified in this study. In contrast to the above-mentioned results, this could suggest that the major determinant of outcome in UGIB were factors unrelated to transfusion strategy (i.e. timing of intervention, comorbidities, etc.) While this brings into question the importance of the observed differences in transfusion strategies identified in this study, it is important to underline that this study was not designed to investigate associations between transfusion strategies and mortality. Furthermore, the potential adverse effects of overzealous transfusion (transfusion reactions etc.) were not investigated. Care should thus be taken when interpreting this lack of differences in mortality between regions.

This study is limited by its retrospective design and narrow data collection. We have obtained information only on the amount, timing and type of transfusions related to admissions, with no demographic characteristics of the patients. Although one might assume a certain degree of heterogeneity across the regions in this relatively large material, we cannot take into account different comorbidities and pharmacologic data. Both in regards to daily medicine, like anticoagulants, and in-hospital administered drugs like anti-fibrinolytics, this is likely to have an impact on the findings. Furthermore, as is the case for any retrospective database study, the results are critically dependent on the quality of the investigated data. Although we have used well-validated national databases, we cannot rule out that some transfusions may not have been registered in the national transfusion database.

With no similar studies or evidence on this subject, no conclusions can be drawn in regards to the effects of

the reported differences in transfusion strategies. Also, there is ongoing progression in this field, and our data might already be outdated. The national guidelines were updated after the study period, in 2014, and the present variation in transfusion strategy is unknown. However, Scandinavian guidelines have been available since 2008, stating the same recommendations regarding balanced transfusions [18], so much of the evidence from the updated guidelines was available at the time. With visco-elastic tests becoming more readily available, individual transfusion strategies are likely to prevail in difficult cases of life-threatening bleeding, but there should still be an overall national guideline. It is important to acknowledge that differences are likely to exist, and that prospective cohort studies are needed to evaluate and guide transfusion strategies for this population in the future.

LITERATURE

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