VoxSanguinis
The International Journal of Transfusion Medicine

ISBT International Society of Blood Transfusion

Vox Sanguinis (2014) **107**, 158–165

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DOI: 10.1111/vox.12133

ORIGINAL PAPER

Transfusion-associated anaphylaxis during anaesthesia and surgery – a retrospective study

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Vox Sanguinis

Received: 11 September 2013, revised 9 December 2013, accepted 11 January 2014, published online 19 February 2014

Background and Objectives Transfusion-associated anaphylaxis (TAA) is a severe adverse reaction reported to occur in 1:9000–90 000 transfusions. According to the Danish Registration of Transfusion Risks (DART), the frequency is 1:300 000 transfusions, which suggests insufficient reporting of TAA in Denmark. Our aims were to identify possible cases of TAA, to characterize their symptoms and tryptase levels and to investigate the reporting of TAA to the haemovigilance systems.

Material and methods We reviewed 245 patients with suspected allergic reactions during anaesthesia and surgery, investigated at the Danish Anaesthesia Allergy Centre (DAAC). Based on the outcome of this investigation, the patients were classified as DAAC positive (confirmed hypersensitivity to identified agent, $n = 112$), or DAAC negative (no confirmed hypersensitivity, $n = 133$). Data on case history, details of blood transfusion and results of laboratory and clinical investigations were collected. TAA cases were identified according to the recommendations of the International Society of Blood Transfusion (ISBT).

Results Ten possible TAA cases (30% of all transfused patients) were identified, all DAAC negative. The frequency of elevated serum tryptase, hypotension and male sex was significantly higher among these cases compared with the remaining DAAC negative ($P < 0{\cdot}05$), but not different from the DAAC-positive patients. One case had been reported to the Blood Bank haemovigilance system and none to DART.

Conclusion We identified unreported cases of possible TAA, which resembled the DAAC-positive patients with respect to elevated tryptase and symptoms. By applying the ISBT criteria of adverse transfusion reactions, we conclude that TAA during anaesthesia and surgery is likely to be underreported in Denmark.

Key words: adverse transfusion reactions, anaesthesia, anaphylaxis, blood transfusion, haemovigilance, surgery.

Introduction

Transfusion-associated anaphylaxis (TAA) is a severe and potentially life-threatening complication to blood transfusion [1–3]. TAA may occur after administration of all types of blood components, but is most frequently seen after transfusion of platelets. The mechanism behind TAA is often unknown, but recipient anti-IgA is a known cause of TAA in Europe [4]. TAA is identified by relevant symptoms, time linkage to transfusion and elevated serum tryptase (s-tryptase) according to the International Society of Blood Transfusion (ISBT) [5]. In Denmark, severe adverse reactions should be reported to the Danish Health Authorities, based on registrations made by the Blood Bank haemovigilance system. Furthermore, the volunteer

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and anonymous reporting of severe complications to transfusion to the Danish Registration of Transfusion Risks (DART) database is encouraged. The incidence of TAA in Denmark is estimated at 1:300 000 transfusions according to the DART registrations 1999–2010 [6]. TAA may be underreported in Denmark, since TAA reported in studies and haemovigilance databases from other countries varies between 1:9000 and 1:90 000 transfusions [1, 3, 7–9]. During anaesthesia and surgery, a large number of drugs and substances are administered, making it difficult to determine the cause of anaphylaxis in this situation. According to the ISBT criteria, however, TAA should be considered a possibility if anaphylaxis occurs within 4 h of transfusion with blood components. The association between reaction and transfusion is considered probable when the evidence clearly is in favour of attributing the adverse event to the transfusion [5]. Based on the low number of TAA registrations made by DART from 1999–2010, we hypothesized that TAA in Denmark is underreported. Our aims were to identify cases of possible TAA among patients with reported allergic reactions during anaesthesia and surgery, to characterize TAA cases by symptoms and s-tryptase and to compare them to patients with and without confirmed hypersensitivity reactions to drugs or other substances encountered during surgery. Furthermore, we wished to investigate the reporting of possible TAA cases to the Blood Bank haemovigilance system and DART.

Materials and methods

Study population

We retrospectively analysed 245 patients, who had been investigated at the Danish Anaesthesia Allergy Centre (DAAC) during 2004–2011 due to suspected allergic reactions during anaesthesia and surgery. The purpose of investigations in DAAC was to determine the cause and mechanism of the reactions, with the aim to avoid future, potentially lethal, re-exposure to the eliciting allergen. DAAC is the Danish national reference centre for the investigation of patients with suspected allergic reactions during anaesthesia. Anaesthesiologists from all of Denmark are encouraged to refer cases of suspected perioperative allergic reactions on a voluntary basis (failure to do so is not pursued). They are asked to take a blood sample within 1–4 h of the reaction for s-tryptase analysis and fill in a DAAC referral form, including detailed information on all drugs and substances the patient was exposed to prior to the reaction, as well as information on symptoms, treatment, timing of s-tryptase blood sample in relation to the reaction and relevant medical history. Once the patient is referred, the DAAC investigation programme follows a standardized protocol, investigating all drugs and substances patients have been exposed to prior to the allergic reaction including anaesthetic drugs, antibiotics, chlorhexidine, latex etc. Investigations include *in vitro* tests (s-tryptase, specific IgE antibodies and basophil histamine release–test), skin tests (skin prick tests, intradermal tests) and drug provocation (if possible) [10]. Registration or investigation of suspected TAA was not a part of the DAAC protocol prior to this study. In the current study, DAAC patients with a positive outcome, that is, cases in which it had been possible to determine a cause for the reactions, are referred to as *DAAC positive*. Patients who had a negative outcome of the DAAC investigations are referred to as *DAAC negative,* see Fig. 1. Blood components were not excluded as allergic agents in either group. All data regarding clinical symptoms during the allergic reactions were extracted from medical reports and anaesthetic charts by two of the authors (GL and MK), and time linkage to transfusion was determined. Based on this, GL and MK independently assessed each case as possible or probable TAA, and any discrepancies were resolved by conference with a third party (author LHG and RL). The allergic reactions were classified in reaction class 1–4 according to severity: reaction class 1: generalized cutaneous signs, erythema, urticaria with or without angioedema. Reaction class 2: moderate multiorgan involvement with cutaneous signs, hypotension and tachycardia, bronchial hyperreactivity. Reaction class 3: severe life-threatening multiorgan involvement requiring specific treatment, for example collapse, tachycardia, or bradycardia, cardiac arrhythmia, bronchospasm; cutaneous signs may be absent or occur only after the arterial blood pressure recovers. Reaction class 4: circulatory or respiratory arrest [10]. This is consistent with the ISBT classification of allergic transfusion reactions in which reaction class 1 involves only mucocutaneous signs and symptoms occurring during or within 4 h of transfusion (non-severe). Reaction class 2 (severe) and 3 (life threatening) involve respiratory and/or cardiovascular symptoms. According to ISBT, there is anaphylaxis, when in addition to mucocutaneous symptoms there is airway compromise or severe hypotension requiring vasopressor treatment usually occurring during or very shortly after transfusion. Reaction class 4 is death [5].

Serum tryptase was measured in 178 patients (73%) 1–4 h after the reaction ($T_{reaction}$) and compared with baseline s-tryptase levels measured more than 4 weeks later (T_{basal}). S-tryptase was considered elevated at a difference of $T_{reaction}$-T_{basal} >2·2 μg/l, based on the findings in a previous study [11]. Hypotension was defined as a systolic pressure of ≤75 mmHg. Further, a decrease in systolic blood pressure of at least 20 mmHg or 20% (except during anaesthesia induction) was defined as hypotension.

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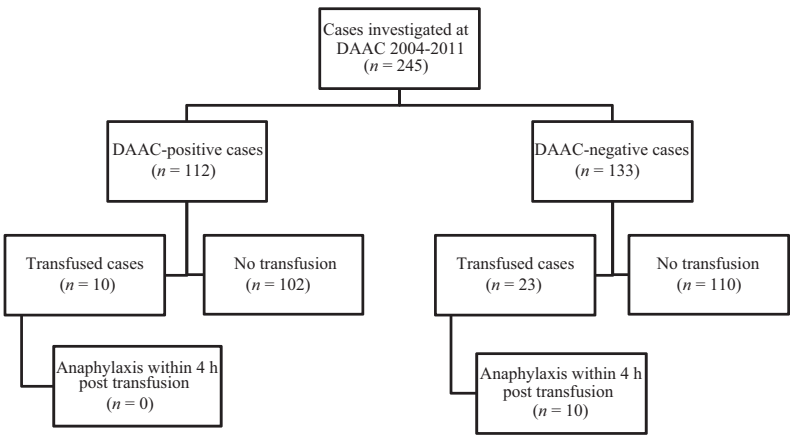

Fig. 1 Distribution of patients. DAAC-positive cases: patients investigated at the Danish Anaesthesia Allergy Clinic (DAAC) with a positive outcome (eliciting allergen had been determined). DAAC-negative cases: patients investigated at DAAC with a negative outcome (eliciting allergen had not been determined).

Tachycardia was defined as heart-rate >100 beats/min + an increase of 10 beats/min or as an isolated increase of 20 beats/min (except during the termination of anaesthesia).

Identification and inclusion of TAA cases

Data on transfusion on the day of anaesthesia and surgery were retrieved from computerized records from all the Danish Blood Banks. These data contained information on the date and time the blood components were issued from the Blood Bank, quantity and type of transfused components as well as information on any registered adverse events. The anaesthetic charts of all patients who received transfusion on the day of anaesthesia and surgery (n = 33) were carefully examined to determine the exact time of transfusion and time linkage to the reaction. If a patient had been transfused with any blood component within 4 h prior to the time of reaction, the patient was included as a TAA case (regardless of being DAAC-positive or –negative) as defined by the ISBT [5]. Cases of TAA were considered *possible* when the evidence was indeterminate for attributing the adverse event to the transfusion or an alternate cause, and *probable* when the evidence clearly was in favour of attributing the adverse event to the transfusion according to the ISBT [5]. In all possible TAA patients, the serum IgA level was determined. Blood Bank haemovigilance records and DART were investigated to see whether any of the possible TAA cases had been reported.

Statistics

Age was described using nonparametric statistics (median), comparisons were tested by the Mann–Whitney *U*-test. Sex and the frequency of elevated s-tryptase, the distribution of reactions per reaction class and the proportion of symptoms were compared between the DAAC-positive, DAAC-negative and possible TAA cases using Pearson's chi-square test. Poisson regression was used to adjust for age and sex [12]. All analyses were performed using STATA 12 (Statacorp LP, College Station, TX, USA). A significance level of $P < 0{\cdot}05$ was used.

Results

Demographic characteristics of the 245 patients, among which 112 were DAAC positive and 133 were DAAC negative, are shown in Table 1. There were 33 (13·5%) transfused patients in the whole cohort and significantly more transfused patients in the DAAC-negative group ($P = 0{\cdot}003$). When compared with the DAAC-negative group, the DAAC-positive group was characterized by: a higher incidence of severe reactions (reaction class 2 or 3; $P < 0{\cdot}001$), a higher occurrence of hypotension ($P < 0{\cdot}001$) and tachycardia ($P = 0{\cdot}002$), and a higher frequency of elevated s-tryptase ($P < 0{\cdot}001$). Median s-tryptase values ($T_{reaction}$) and interquartile ranges were 14·4 μg/l (IQR 4·73–32·5 μg/l) and 4·76 μg/l (IQR 2·63–8·89) for the DAAC-positive and DAAC-negative group, respectively.

Possible TAA cases

Among the 33 patients who received transfusion, we identified 10 possible TAA cases in nine patients (30% of all transfused patients) fulfilling the ISBT criteria, see Table 2. All 10 possible TAA cases were identified among the 23 transfused patients in the DAAC-negative group (43%), none were found among the transfused patients in the DAAC-positive group, as no relevant time linkage between transfusion and reaction could be found in any case (see materials and methods for details on time linkage and classification). All TAA reactions were severe or life threatening as they were classified as reaction class 2 (30%) or 3 (70%) according to the Scandinavian Guidelines of Anaphylaxis during Anaesthesia, which is consistent with the ISBT classification [5, 10]. Nine of ten cases had hypo-

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Table 1 Demographics and reactions in patients investigated at the Danish Anaesthesia Allergy Clinic from 2004–2011

	DAAC positive[a], *n* = 112 (%)	DAAC negative[b], *n* = 133 (%)	Total (%)	*P*-value	*P*-value[c]
Female sex	56 (50)	80 (60)	136 (56)	0·11	
Age/median	53	45	50	0·02	
Reaction class[d]					
1	20 (18)	47 (35)	67 (27)	<0·001	0·004
2	22 (20)	39 (29)	61 (25)		
3	61 (54)	44 (33)	105 (43)		
4	8 (7)	3 (2)	11 (4)		
Elevated s-Trp[e]	56 (63)	19 (21)	75 (42)	<0·001	<0·001
Hypotension	85 (76)	70 (53)	155 (63)	<0·001	0·004
Tachycardia	46 (41)	29 (22)	75 (31)	0·001	0·002
Bronchospasm	25 (22)	21 (16)	46 (19)	0·19	0·28
Angioedema	27 (24)	39 (29)	66 (27)	0·36	0·42
Urticaria	35 (31)	35 (26)	70 (29)	0·39	0·41
Flushing	14 (13)	11 (8)	25 (10)	0·28	0·36
Rash	47 (42)	55 (41)	102 (42)	0·92	0·66
Pruritus	29 (26)	31 (23)	60 (24)	0·64	0·20
Transfused	10 (9)	23 (17)	33 (13)	0·06	0·003

[a]Patients investigated at the Danish Anaesthesia Allergy Clinic (DAAC) with a positive outcome (eliciting allergen had been determined).

[b]Patients investigated at DAAC with a negative outcome (eliciting allergen had not been determined).

[c]Adjusted for sex and age.

[d]1 Unknown.

[e]Elevated serum tryptase (s-Trp): $Trp_{reaction\ time} - T_{basal} > 2{\cdot}2$ μg/l. 67 s-Trp not done.

tension, and symptoms from two or more organ systems were present in all 10 cases. In six of seven cases measured, we found elevated levels of s-tryptase. Seven of ten patients had received transfusion by more than one type of blood component before the reaction, and only three had received platelet concentrate. In 50% of the patients, onset of TAA reaction was within five minutes of start of transfusion. In these patients the product transfused immediately prior to the reaction was RBCs in two patients, FFP in two patients, and one patient received RBCs and FFP at the same time, see Table 2 for details. In 9 of 10 cases, the patient recovered after treatment with sympathomimetics with or without antihistamines and steroid. One patient had a prolonged recovery including an ICU stay (see Table 2 for details). In all possible TAA cases, serum IgA levels were within the normal range (0·70–4·30 g/l). Two patients suffered from pollen allergy. Only one of the 10 cases of possible TAA had been registered by the Blood Bank haemovigilance system, and none could be identified in the annual DART reports during the period 2003–2010.

Comparison of the possible TAA cases to DAAC-positive and DAAC-negative groups

The possible TAA cases were similar to patients in the DAAC-positive group with regard to sex ($P = 0{\cdot}23$), age ($P = 0{\cdot}34$), frequency of severe reactions ($P = 0{\cdot}13$), elevated s-tryptase ($P = 0{\cdot}23$) and hypotension ($P = 0{\cdot}31$). Compared with the DAAC-negative group, the possible TAA cases had a higher frequency of male sex and reaction class 2 or 3 ($P = 0{\cdot}04$ resp. $P = 0{\cdot}01$), elevated s-tryptase ($P < 0{\cdot}001$) and hypotension ($P = 0{\cdot}01$). Thus, the possible TAA cases resembled the DAAC-positive group.

Discussion

We identified 10 cases of possible TAA according to ISBT's proposed standard criteria. The cases were found in a group of patients with well-characterized severe suspected allergic reactions during anaesthesia and surgery, in whom no allergen could be identified on subsequent investigation. According to the ISBT criteria, the cases should be considered adverse reactions based alone on the temporal association, which is <4 h for allergic transfusion reaction [5]. All cases of possible TAA were classified as reaction class 2 or 3, which corresponds to the ISBT categories of severe and life-threatening allergic reactions. The presence of elevated s-tryptase in six of the seven measured cases indicates that the reactions are likely to be mast cell mediated [4, 13, 14]. The TAA cases resembled the DAAC-positive group with respect to the

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Table 2 TAA cases

Sex[a]	Age[a]	Reaction class[a]	Hypotension[a]	s-Trp, reaction[b]	Elevated s-Trp[c]	Type of surgery[d]	Blood products[e]	Onset after initiation of transfusion	TAA registered	Recovery
M	60	2	+	<1·0	–	Ortho	FFP	5 min	–	R[h]
M	58	3	+	7·47	+	Cardio	PC[f], RBC, FFP	5 min	–	R[i]
M	66	3	+	Not done	Not done	Cardio	RBCs[g], FFP	5 min	–	R[i]
M	75	3	+	19·30	+	Cardio	RBCs[g], PC[f], FFP	5 min	–	R[i]
F	46	2	+	5·53	+	Gyn	RBCs, FFP	5 min	–	R[i]
M	56	3	+	16·40	+	Cardio	RBCs	10 min	+	R[i]
F	43	3	+	17·6	+	Gyn	RBCs, FFP	10 min	–	R[j]
M	69	3	+	8·57	+	Cardio	FFP, RBCs[g]	20 min	–	R[k]
M	54	3	+	Not done	Not done	Cardio	RBCs, PC[f], FFP	25 min	–	R[j]
F	38	2	–	Not done	Not done	Neuro.	RBCs	3 h	–	R[l]

TAA = Transfusion-associated anaphylaxis.

[a]Significant differences, see text.

[b]Serum tryptase (s-Trp) /μg/l measured within 4 h after the reaction.

[c]Elevated serum tryptase (s-Trp): s-Trp reaction time – s-Trp basal > 2·2 μg/l.

[d]Ortho:orthopedic; Cardio:cardiovascular; Gyn:gynecological; Neuro:neurological.

[e]Blood products transfused within 4 h before the reaction (listed chronologically). FFP: fresh frozen plasma PC: platelet concentrate (pooled) RBC: red blood cells.

[f]Irradiated.

[g]Filtered.

[h]Recovery (R) after treatment with ephedrine, antihistamines and steroids.

[i]Recovery after treatment with adrenaline, antihistamines and steroids.

[j]Recovery after treatment with only adrenaline and antihistamines.

[k]Recovery after treatment with noradrenaline, antihistamines and steroids.

[l]Prolonged recovery at intensive care unit (ICU) after treatment with antihistamines and steroids.

following: distribution of sex, severity of clinical reaction, frequency of elevated s-tryptase and the presence of hypotension. Transfusion with several components, particularly RBC and/or FFP, was the most frequent, but platelet concentrate was implicated in only 30% of the cases. This is interesting, since others have reported a higher risk of allergic reactions associated with the transfusion of platelets [4, 15]. However, the results in this study may reflect the relatively small sample size. According to the ISBT definitions, all ten cases should have been reported to the Blood Bank haemovigilance systems as possible or probable TAA. The fact that none of the TAA cases identified in this study appeared in the DART registrations, and only one in the Blood Bank haemovigilance system, suggests that TAA in this patient category is underreported in Denmark.

Neither the available information from the DAAC database, the anaesthetic charts nor the data collected from the Blood Bank databases in this retrospective study provide conclusive evidence that the transfused blood components were responsible for the allergic reactions in any of the ten cases. However, several factors are in favour of attributing the allergic reactions to the blood components: the temporal association, the exclusion of alternative allergens through a thorough, standardized investigation and the finding that none of the possible TAA cases were identified in the DAAC-positive group.

Determining the eliciting factor in allergic or anaphylactic reactions associated with the administration of blood components is often a difficult task, as the aetiology and pathophysiology are only partly understood [4]. However, among the recognized causes of TAA, recipient anti-IgA appears to be the most frequently reported [16, 17]. Even though anti-IgA measurements were not available in our TAA cases, the fact that they all had normal IgA concentrations makes anti-IgA a less likely causative agent, although TAA has also been associated with anti-IgA antibodies in a minor part of patients with normal serum concentrations of IgA [16]. Atopic individuals are predisposed to acute transfusion reactions, but only two of the TAA cases in our study had a preexisting pollen allergy, otherwise there were no diagnosed allergies in this group [18]. Since 9 of 10 cases were not reported to the Blood Bank haemovigilance system at the time of reaction, no confirmatory post-transfusion AB0 compatibility investigations had been made, and we therefore

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cannot completely exclude the possibility of an acute haemolytic transfusion reaction among these 9 TAA cases. However, the presenting symptoms and elevated s-tryptase levels are more indicative of an allergic causality. Within the set-up of the Danish Blood Banks as well as in other similar blood banks, AB0 incompatible transfusions are extremely rare and therefore cannot explain all the TAA cases found in this study [19].

Transfusion-associated anaphylaxis in the haemovigilance perspective

In Denmark, healthcare personnel must report the outcome (the details of the complication or no complications) of each transfused unit of blood to the Blood Bank, which in turn reports the severe reactions to the Health Authorities [20]. Furthermore, the Blood Banks voluntarily and anonymously report severe adverse reactions to DART, which is the Danish analogue to the British haemovigilance system, Serious Hazards of Transfusion (SHOT) [6, 9]. TAA is generally thought to be a rare phenomenon according to haemovigilance databases and the literature [1, 3, 21, 22], but the reported incidences from haemovigilance databases across Europe show great variation, from 1:9000 transfused units in the Netherlands to 1:90 000 in the UK [7, 8, 9, 23–26], see Table 3. The incidence in Denmark is remarkably lower than in other countries. Denmark is comparable with Holland and Norway in

Table 3 Reported frequencies of anaphylaxis in European haemovigilance databases

	Denmark Danish Registry of Transfusion Risks (DART)[a,b]		United Kingdom Severe Hazards of Transfusion (SHOT)[a,b]		Germany Paul-Ehrlich-Institut report 2010 [25]	
Year	Case reports[c]/ transfusions[d] (*n*/*n*)	Incidence/ 100 000[e]	Case reports[f]/ transfusions[g] (*n*/*n*)	Incidence/ 100 000[e]	Case reports[h]/ transfusions[d] (*n*/*n*)	Incidence/ 100 000[e]
2010	0/518 469	0	34/2 898 425	11·7	110/6 120 000	18·0
2009	2/538 505	0·4	30/2 903 760	10·3	61/6 080 000	10·2
2008	1/531 694	0·2	32/2 845 459	11·4	36/6 110 000	5·9
2007	0/544 293	0	27/2 914 228	9·3	49/6 000 000	8·2
2006	1/530 440	0·2	22/3 002 797	7·3	45/5 750 000	7·8
2005	2/509 825	0·4	5/3 103 200	1·6	29/5 700 000	5·1
	Holland Transfusion reactions in patients (TRIP)[a,b]		**Ireland National Haemovigilance Office (NHO)[a,b]**		**Norway Transfusion complications (TROLL)[a,k]**	
Year	Case reports[i]/ transfusions[j] (*n*/*n*)	Incidence/ 100 000[e]	Case reports[f]/ transfusions[g] (*n*/*n*)	Incidence/ 100 000[e]	Case reports[c]/ transfusions[d] (*n*/*n*)	Incidence/ 100 000[e]
2010	72/670 490	10·7	51/188 031	27·1	6/264 945	2·3
2009	71/699 720	10·1	28/198 355	14·7	18/260 414	6·9
2008	65/706 868	9·3	41/196 339	21·6	12/267 427	4·6
2007	54/700 980	7·7	40/187 845	22·2	3/250 591	1·2
2006	19/699 904	2·8	29/188 154	16·1	1/257 935	0·4
2005	26/711 458	3·6	22/186 482	12·2	3/244 719	1·3

[a]Annual reports www.haemovigilance.dk (Denmark), www.shotuk.org (United Kingdom), www.tripnet.nl (Holland), www.giveblood.ie/clinical_services/haemovigilance/publications (Ireland), www.hemivigilans.no (Norway).

[b]The haemovigilance database is based on volunteer and anonymous reporting.

[c]Case reports of anaphylaxis during or within 4 h of transfusion.

[d]Total number of transfused blood components (RBCs, FFP, PC).

[e]Incidence of case reports of anaphylaxis per 100 000 transfusions.

[f]Case reports of anaphylaxis during or within 24 h of transfusion.

[g]Total number of blood components issued from the transfusion services incl. SD-FFP, cryoprecipate, granulocytes.

[h]Case reports of serious acute (allergic) transfusion reactions (grade 3 and 4).

[i]Case reports of anaphylaxis within a few seconds to minutes after the start of transfusion.

[j]Total number of blood components issued from the transfusion services (RBCs, FFP, PC).

[k]Reporting to the haemovigilance database is mandatory.

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registration method, and when comparing the Danish incidence with the incidence found in Holland and Norway from 2008 to 2010, one would expect in the region of 10 to 50 cases of TAA per year in Denmark. However, only 1–2 cases were reported to DART during this period. In most countries, there has been an increase in the reporting of TAA between 2005 and 2010, whereas the incidence in Denmark is unchanged. The incomplete knowledge of the aetiology and pathogenesis involved in TAA and the different haemovigilance schemes makes it difficult to determine the true incidence of TAA [15, 27]. We were not able to find any previous studies describing the incidence or the degree of reporting of TAA in surgical settings. Our study only deals with possible TAA's seen during anaesthesia and surgery, and TAA's appearing in other clinical settings may have a different reporting pattern. However, the overall TAA frequency in DART is more than 3 times lower than in SHOT and 50 times lower than in the NHO (National Haemovigilance Office) database of Ireland, which altogether suggests that TAA is underreported in Denmark.

There is no proven explanation for the insufficient and variable reporting of TAA, and it may be a combination of several factors such as a lack of awareness, lack of standardized criteria, difficulty in making the diagnosis, differences in reporting methods as well as differences in whether the reporting is mandatory or not and lack of time for reporting and registration [15, 22, 27]. Education and research into the symptoms and aetiology of TAA to make standardized diagnostic criteria could maybe, in addition to an improved and accessible reporting system, improve the report of TAA. The report to DART and to other haemovigilance databases may also be improved by making reporting to the haemovigilance database mandatory. A qualitative study of reporting among the transfusing staff could help identifying possible knowledge gaps and/or practical barriers to successful haemovigilance. Participation in the comparable international reporting system ISTARE is expected to facilitate knowledge sharing internationally in the future [28].

To our knowledge, we have identified and described the hitherto largest group of possible TAA cases occurring during anaesthesia and surgery. The study is based on patients with thoroughly evaluated perioperative allergic reactions. It is also the study of TAA with the highest number of s-tryptase measurements so far.

The study has several limitations: first of all, this is a retrospective study, with a relatively small sample size and highly selected patients, making it impossible to estimate the risk of developing TAA occurring during surgery or attribute it to a specific type of blood component. Also data rely in part on data extraction from anaesthetic charts, which may be subject to inaccuracy due to human error in the registration process during anaesthesia and surgery. Even though the standardized DAAC investigation found no conclusive evidence in favour of a specific agent eliciting the reactions in any of the TAA cases, we still cannot completely rule out other unregistered agents/causes than the blood transfusions. We therefore consider them to be *possible* cases of TAA according to the imputability assessment of the ISBT. However, the six cases with elevated levels of s-tryptase might even be considered *probable* TAA cases.

Due to these limitations, there is no conclusive evidence of a causal link, but the findings in this study support the hypothesis that blood transfusion may have caused these reactions. Taken together with the severe nature of these anaphylactic reactions, this warrants further studies into the risk of TAA during surgery and its causes.

In conclusion, we identified a number of cases of possible TAA not registered by the Blood Bank haemovigilance systems or DART, suggesting that the incidence of TAA in Denmark is underestimated. As described above, the 'true' incidence of TAA in Denmark is likely to be considerably higher than 1:300 000 transfusions registered by DART. However, based on the highly selected population in this study, and the present nature of both the DAAC and the DART reporting systems, it is not possible to provide a reliable estimate as to what could be the real incidence in Denmark. One could, however, speculate that the incidence should be 5–25 times higher, as in Norway or Holland. Although still rare, TAA and acute transfusion reactions constitute an increasing proportion of all reported transfusion complications in many countries. This is due to an increase in the actual number of reports and thus not caused by inflation by a decrease in the report of other transfusion reactions [7, 8, 9, 24]. TAA should therefore be a subject of focus regarding transfusion safety according to literature and recommendations of the international haemovigilance systems [8, 9, 15, 29]. Considerations of risks and benefits should always be made before transfusing blood components. This requires accurate knowledge of the incidence and characteristics of adverse events such as TAA and emphasizes the importance of an effective haemovigilance system [30, 31].

Conflict of interest

The authors have no competing interests.

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