

The influence of ABO blood group on mortality in major trauma

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Abstract

ABO blood group has a profound influence on hemostasis as it is a major determinant of plasma levels of von Willebrand Factor. In vitro studies suggest that blood group O is a risk factor for increased severe bleeding while blood group non-O is a risk factor for thromboembolic events. Yet, the impact of ABO blood group outcome after multiple trauma is unknown. Retrospective multicenter case-control study from three level-1 trauma centers in Germany from 2012-2015. Inclusion criteria were severe trauma with an Injury severity score ≥ 9 and admission to an intensive care unit. 1281 patients (69.5% male) were included. Mean Injury Severity Score (ISS) was 21.1 ± 12.4 ; mean age was 50.2 ± 22.4 years. Distribution of blood groups was: O: 37.4%; A: 44%, B: 12.7 and AB: 5.8%. Hospital mortality depending on blood group was 9.7 (A), 10.4 (B), 6.8 (AB) and 12.7 (O) %. Multivariate logistic regression for mortality revealed an Odds ratio of 0.79 (A), 0.60 (B) and 0.54 (AB) without statistical significance ($P=0.35$ (A), 0.17 (B), 0.33 (AB)). Thromboembolic events (blood group O vs. others) occurred in 2.8 (O) vs. 3.3 (others) %, $P=0.619$.

In this retrospective study on 1281 multiple injured patients, no relevant influence of ABO blood group on hemorrhage, thromboembolic events and mortality could be found.

Introduction

Normal blood coagulation is one of the physiological functions guaranteeing basic hemostasis and interacting with other fundamental body functions. Inherited or acquired coagulation disorders are associated with increased morbidity and mortality in otherwise healthy populations. Beside others, some data from the literature suggest that the ABO blood group system (BG) also influences coagulation and shows measurable adverse impact on patient's outcome. However, it is unclear so far if the BG has a major impact on mortality after major trauma.^{1,2} BG is a major determinant of plasma levels of von Willebrand factor (VWF) and consequently, since VWF acts as a specific carrier of factor VIII (FVIII) and protects it from proteolytic degradation of FVIII. Both procoagulant proteins are major determinants for bleeding and hemostasis.¹⁻⁴ VWF levels are 25-35% lower in BGO carriers.⁵ Therefore, some investigators assumed a relationship between BGO and increased severe bleeding.⁶⁻⁸ BGO was independently associated with a significant risk of severe post-partum hemorrhage (adjusted OR: 1.84, 95% CI: 1.32-2.57) in a French case-control study,⁹ and a recently published study found BGO to be an independent risk factor for mortality in severe injured patients.¹⁰ On the other hand, some studies found BG non-O as an independent risk factor for thromboembolic events (TE).¹¹⁻¹⁴

To the best of our knowledge, no study before investigated the influence of BG in major trauma patients on blood loss, incidence of TE and mortality and therefore we conducted this study. The objectives of this study were to 1) investigate the incidence of TE, 2) the amount of blood transfusion, and 3) the mortality depending on BG in major trauma patients.

Materials and Methods

This is a retrospective, multicenter study of three level-1 trauma centers in Germany. It is approved by all three local ethics committees (No. of approval 17-7605-BO). All patients admitted between 2012 and 2015, suffering from severe injury defined as ISS ≥ 9 , treated in the trauma room and admitted to an intensive care unit were included. Patient data was originally

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Key words: Hemorrhage; multiple trauma; coagulation; blood type.

Contributions: The authors contributed equally.

Conflict of interest: The authors declare no potential conflict of interest.

Funding: None.

Received for publication: 18 June 2019.

Accepted for publication: 14 August 2019.

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Orthopedic Reviews 2019;11:8214
 doi:10.4081/or.2019.8214

collected for the trauma registry of the German Trauma Society (Deutsche Gesellschaft für Unfallchirurgie, TR-DGU). The aim of this multicenter database was an anonymous and standardized documentation of severely injured patients for benchmarking of hospitals and health services research in the field of severe trauma. The inclusion criterion is admission to hospital with vital signs via the emergency room with subsequent intensive care treatment, including those who die before admission to the intensive care unit. Data are collected from four consecutive time phases from the site of the accident until discharge from hospital: (A) pre-hospital phase, (B) emergency room and initial surgery, (C) intensive care unit and (D) discharge and outcome. The documentation includes detailed information on demographics, injury pattern, pre- and in-hospital management, time course, relevant laboratory findings including data on transfusion and outcome of each individual. TE were defined as proven symptomatic deep venous thrombosis, pulmonary embolism, ischemic stroke or myocardial infarction during hospital stay. As the parameter "BG" is not included in the registry, standardized analysis of the whole registry is impossible and therefore this study is not a TR-DGU-project. Each of the three hospitals added the single parameter "BG" to their existing data set and brought them together.

Statistics

Statistical analysis was performed using SPSS statistical software (version 25; IBM Corp, Armonk, NY, USA) to calculate mean, median, mode, standard deviation and multivariate logistic regression. The revised injury severity classification, version II (RISC II) prognosis was calculated as described by Lefering *et al.*¹⁵

Multivariate logistic regression was performed to determine risk factors for mortality. Parameters of the RISC II-prognosis were used for adjustment. Parameters of the RISCII that are especially determined by patients' hemorrhage (Base Excess (BE), hemoglobin (Hb), and coagulation parameters) on arrival in the emergency department (ED) were not used for adjustment as they might be determined by our hypothesis that blood group influences these bleeding parameters. Fisher's exact test was used to compare incidence of TE.

Results

1281 patients were included, (male patients 69.5%). Mean Injury severity score (ISS) was 21.1 ± 12.4 . Mean age was 50.2 ± 22.4 . Distribution of BG was: O: 37.4%; A: 44%, B: 12.7% and AB: 5.8%.

Table 1 shows demographic data, blood gas and laboratory analysis on arrival in the emergency department (ED) and intensive care unit (ICU) given units of packed red blood cells (PRBC) in the ED and outcome.

Multivariate logistic regression showed no significant differences between injury pattern.

TE occurred in 39 of 1247 patients (3.1%). Comparing O BG vs. others, no significant difference was found (BG O: 13/467, 2.8 % vs. others: 26/779, 3.3%, P=0.619).

Multivariate logistic regression was performed to determine risk factors for mortality. Results of multivariate logistic regression are shown in Table 2.

O BG was the only group with a higher than predicted mortality (Mortality 12.7%, RISCII-Prognosis 11.4%) while all other four BG showed a lower than predicted mortality. In multivariate logistic regression, all other BG had an OR below 1 (BG A: 0.79, BG B: 0.61, BG AB: 0.54). When we adjusted for known risk factors for mortality, these differences were not significant, however.¹⁵ Post-hoc power analysis revealed a power of 41.3%.

Discussion

In this large multicenter cohort-study of 1281 severe injured patients, no relevant influence of ABO BG on hemorrhage, TE or mortality could be found.

We could neither observe differences in the number of PRBCs required by the patients nor in concentrations of hemoglobin or the results of coagulation tests on arrival in the ED or the ICU in a large cohort of 1281 patients. Patients were severely enough injured with a high risk of bleeding since they all had trauma team activation in the ED and were admitted to the ICU. Mean ISS was 21.1 ± 12.4 which is above the average ISS of 19.4, reported by the trauma registry of German trauma society.¹⁶ Distribution of BG equals data on distribution of BG in the German population.¹⁷ Since the severity of bleeding adds to some AIS codings (e.g. intraabdominal, intrathoracic, pelvic or intracranial hemorrhage) and thus contributes to the ISS and NISS calculation a higher injury severity might be expected when patients are bleeding more.

However, we observed no such difference.

Our hypothesis that BG O has a major impact on hemorrhage and mortality in severe injured patients was supported by a lot of laboratory and clinical studies. In 1964, Preston *et al.* first described differences in plasma concentrations of factor VIII in the normal population.¹⁸ Subsequently, more information on differences in coagulation factors especially VWF related to different BG could be observed in laboratory studies.¹⁴ Therefore some authors tried to identify BG O as an independent risk factor for bleeding.¹⁹ Garcia *et al.* conducted a study on patients under vitamin K antagonist treatment and showed that the risk for non-fatal major bleeding in O BG carries vs. non-O BG carriers was not statistically significant different (OR 0.7; 95%CI: 0.4-1.1).²⁰ In a single center survey, Franchini *et al.* found no increased risk of severe bleeding for BG O carriers in patients suffering cerebral hemorrhage.² In a case-control study carried out by Chauleur, O BG was independently associated with a significant risk of severe

Table 1. Demographic, laboratory and outcome data.

	A	B	AB	O
No. of patients (%)	565 (44)	163 (12.7)	74 (5.8)	479 (37.4)
Male patients (%)	68.0	76.1	70.3	68.7
Injury pattern				
Percentage of blunt injury (%)	95.5	96.3	96.0	96.0
ISS	20.83 ± 11.46	23.0 ± 14.4	20.26 ± 12.0	21.3 ± 12.2
NISS	25.76 ± 14.1	28.11 ± 16.3	25.88 ± 14.6	27.02 ± 15.1
AIS head >3 (%)	26	31	26	31
AIS chest >3 (%)	15.8	14.7	13.6	12.7
AIS abdomen >3 (%)	4.1	5.5	5.5	3.5
AIS extremities >3 (%)	9.2	10.5	6.8	9.8
ED				
Hemoglobin (mg/dl)	12.6 ± 2.0	12.6 ± 2.2	12.6 ± 1.9	12.6 ± 2.1
Thrombocytes (/nl)	218 ± 90	218 ± 71	205 ± 78	211 ± 86
PTT (sec)	25.3 ± 7.4	27.2 ± 18.3	24.5 ± 4.9	26.8 ± 11.2
PRBC (n)	0.45 ± 1.7	0.64 ± 2.1	0.86 ± 3.4	0.54 ± 1.9
BaseExcess	-1.05 ± 4.5	-1.26 ± 3.6	-1.14 ± 3.2	-1.06 ± 4.4
PT	88.2 ± 19.7	87.0 ± 19.0	84.5 ± 22.1	87.1 ± 21.0
ICU				
PTT (sec)	27.7 ± 11.0	28.0 ± 8.7	26.7 ± 4.9	26.8 ± 11.2
PT	86.9 ± 20.0	88.2 ± 19.0	85.2 ± 20.6	84.3 ± 20.0
Hemoglobin (mg/dl)	11.2 ± 2.1	11.46 ± 2.1	11.7 ± 1.8	11.4 ± 2.0
thrombocytes (/nl)	200 ± 94	200 ± 82	193 ± 76	191 ± 76
BaseExcess (mEq/l)	-0.52 ± 3.8	-0.92 ± 4.1	-1.14 ± 3.2	-0.80 ± 4.1
Outcome				
RISCII (%)	10.06	12.55	9.05	11.37
Mortality (%)	9.7	10.4	6.8	12.7
Total TE, n (%)	3.1	3.1	5.6	2.8
MI (%)	0.5	0	0	0.2
PE (%)	1.1	1.9	2.8	0.9
DVT (%)	0.9	0.6	2.8	1.1
Ischemic stroke (%)	0.4	0.6	0	0.4

Data presented as mean \pm standard deviation. Abbreviations: ISS: injury severity score, NISS: New injury severity score, PTT: partial thromboplastin time ,PRBC: packed red blood cells , RISCII: revised injury severity classification version II prognosis for mortality, ED: emergency department, ICU: intensive care unit; TE: thrombembolic complication; MI: myocardial infarction; PE: pulmonary embolism; DVT: deep venous thrombosis.

post-partum hemorrhage (adjusted OR: 1.84, 95% CI: 1.32-2.57).⁹

We did observe a trend towards more bleeding in O BG patients. First of all, O BG was the only group with a higher than predicted mortality (Mortality 12.7%, RISCII-Prognosis 11.4%) while all other four BG showed a lower than predicted mortality. Second, in multivariate logistic regression, all other BG had an OR below 1 (BG A: 0.79, BG B: 0.61, BG AB: 0.54). When we adjusted for known risk factors for mortality (15) these differences were not significant, however. Therefore, our sample size might have been too small to confirm ABO blood group as a risk factor.

On the other hand, we doubt whether a difference small enough not to reach the significance level in a homogenous group of over 1000 severely injured patients is of any clinical relevance in daily practice

Takayama *et al.* recently published the first study describing the influence on ABO BG in severely injured patients.¹⁰ They included 901 patients of two Japanese trauma centers, ISS > 15. BG O was associated with high mortality (28% in patients with BG O *versus* 11% in patients with another BG; P<0.001). Moreover, this association was observed in a multivariate model (adjusted OR = 2.86, 95%, CI 1.84-4.46; P<0.001), while no significant difference was observed in the transfusion volume between the two groups. Comparing their study population with ours, ISS for inclusion was higher (> 15 vs. ≥ 9) while mean ISS was lower (mean ISS 19 vs. 21). Severe (isolated) head injury was much more common in the Japanese study, while our patients suffered mostly from multiple injuries (median AIS head 4 *vs.* percentage of patients with AIS head > 3: 366/1281 = 28.5%). The role of the severe head injuries for mortality differences remains unclear. While it might have been the more severe intracranial bleeding of BG O patients there also might have been a different pattern of intracranial injuries. Recently, a study investigated the influence of ABO blood group on outcome subdural hematoma.⁷ Patients with blood type O that were found to have a decreased midline shift, a lower postoperative epileptic seizure incidence. In terms of rebleeding rate no significant difference between O and non-O patients were found (OR 0.65; 95% CI [0.23-1.82]; P=0.291) and morbidity outcome, expressed through the GOS (Glasgow Outcome Scale) at 3 months, showed no significant difference between O and non-O patients either (P=0.504 mean GOS 3).

We determined the incidence of thromboembolic complications to rule out that BG dependent mortality advantages with

Table 2. Multivariate logistic regression of potential risk factors for mortality.

	OR	95%-CI	P
Age			
55-64 years	1.7	0.7-3.7	0.21
65-74 years	2.8	1.4-5.7	0.003
75-84	5.5	2.8-10.5	0.000
85+	11.4	4.7-27.5	0.000
Blunt <i>vs.</i> penetrating trauma			
Blunt trauma	0.24	0.07-0.8	0.23
ASA			
ASA 3-4	1.81	1.04-3.14	0.036
Blood group			
A	0.79	0.49-1.29	0.35
B	0.60	0.29-1.25	0.17
AB	0.54	0.15-1.88	0.33
AIS most severe injury			
4	1.3	0.61-2.76	0.49
5	3.99	1.67-9.54	0.002
AIS second most severe injury			
3	1.7	0.94-3.15	0.08
4	6.07	2.99-12.32	0.000
5	8.20	3.60-18.68	0.000
AIS head			
3/4	2.43	1.22-4.85	0.012
5/6	5.6	2.61-12.02	0.000
Gender			
Male	0.98	0.6-1.59	0.98

respect to bleeding might have been counteracted by a higher rate of TE.²¹ However, we could not observe a significant difference in TE in our study population.

The limitation of this study is the retrospective nature. On the other hand, the strength of this study is the large study population from three different trauma centers.

Conclusions

In a large multicenter study on 1281 severe injured patients, a trend but no significant influence of ABO blood group on hemorrhage, TE and mortality could be found. Even if significance might be reached with an even larger group of patients, we question the clinical relevance of such a finding on the impact on daily practice in trauma care.

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DOI: 10.4081/or.2019.8214

URN: urn:nbn:de:hbz:464-20200107-103108-7



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