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I. D. Duzhiy[1],
S. M. Kobyletskyi[1,2],
S. V. Kharchenko[1],
[1]*Sumy State University, Medical Institute, Department of General Surgery, Radiology and Phthisiology, 31 Sanatorna str., Sumy 40018, Ukraine;*
[2]*Sumy Regional Clinical Hospital, Regional Gastrointestinal Bleeding Center, 48 Troitska str., Sumy 40022, Ukraine*

INDICATIONS FOR THE FIRST ERYTHROCYTE TRANSFUSION IN PATIENTS WITH UPPER GASTROINTESTINAL BLEEDINGS DEPENDING ON THE GENETIC CONSTITUTION

Abstract

Background. Today a personified approach may penetrate in a daily transfusion practice. Every patient with upper gastrointestinal bleeding should have a clear and individually selected indication for transfusion therapy.

Objective – to develop indications for the first erythrocyte transfusion for patients with upper gastrointestinal bleedings of different origin.

Materials and methods. A total of 10 patients with acute with upper gastrointestinal bleeding were studied in Sumy Regional Clinical Hospital and Sumy State University. The polymerase chain reaction method for ESR1/rs2234693 gene polymorphism of patients and the *post hoc* analysis were implemented.

Results. A new transfusion scheme was presented. The first erythrocyte transfusion was indicated to compensate ulcer and variceal bleedings, if diagnostics of haemostasis control, cardiovascular history and genotyping information were appropriately fixed and considered.

Conclusion. The first erythrocyte transfusion under the haemoglobinemia between ≤ 70 and 100 g/L may be individually effective when the clinical decision-making process for transfusion indication includes genotyping assessment. This strategy should be assessed in a future clinical trial.

Keywords: bleeding, transfusion, erythrocyte, gene polymorphism.

Corresponding author: *info@dgs.sumdu.edu.ua*

І. Д. Дужий[1],
С. М. Кобилецький[1, 2],
С. В. Харченко[1],
[1]*Сумський державний університет, Медичний інститут, кафедра загальної хірургії, радіаційної медицини та фтизіатрії, вул. Санаторна, 31, м. Суми, 40018;*
[2]*Сумська обласна клінічна лікарня, Обласний центр шлунково-кишкових кровотеч, вул. Троїцька, 48, м. Суми, 40022*

ПОКАЗАННЯ ДО ПЕРШОГО ПЕРЕЛИВАННЯ ЕРИТРОЦИТІВ У ХВОРИХ НА ВЕРХНЮ ШЛУНКОВО-КИШКОВУ КРОВОТЕЧУ ЗАЛЕЖНО ВІД ЇХ ГЕНЕТИЧНОЇ КОНСТИТУЦІЇ

Резюме

Вступ. Сьогодні персоніфікований підхід проникає у щоденну трансфузійну практику. Кожний хворий на верхню шлунково-кишкову кровотечу повинен одержати окреме індивідуально підібране показання до трансфузійної терапії.

Мета роботи – розробити показання до першого переливання еритроцитів у хворих на верхню шлунково-кишкову кровотечу різної етіології.

Матеріали і методи. 10 пацієнтів з гострими верхніми шлунково-кишковими кровотечами було вивчено у Сумській обласній клінічній лікарні та Сумському державному університеті. Використано аналіз *post hoc* та полімеразну ланцюгову реакцію для генного поліморфізму ESR1/rs2234693.

Результати. Нова трансфузійна схема подана. Перша трансфузія еритроцитів показана для компенсації виразкових та варикозних

кровотеч, якщо діагностика гемостатичного контролю, серцево-судинний анамнез та інформація генотипування були відповідно визначені та оцінені.

Висновки. Перша трансфузія еритроцитів при гемоглобінемії між ≤ 70 та 100 г/л є індивідуально ефективною, якщо клінічний висновок для трансфузії включає оцінювання генотипу. Таку стратегію необхідно оцінити у майбутніх клінічних випробуваннях.

Ключові слова: кровотеча, трансфузія, еритроцит, генний поліморфізм.

Резюме

И. Д. Дужий[1],
С. Н. Кобылецкий[1, 2],
С. В. Харченко[1],
[1]Сумский государственный университет, Медицинский институт, Кафедра общей хирургии, радиационной медицины и фтизиатрии, ул. Санаторная, 31, г. Сумы, 40018;
[2]Сумская областная клиническая больница, Областной центр желудочно-кишечных кровотечений, ул. Троицкая, 48, г. Сумы, 40022

ПОКАЗАНИЯ К ПЕРВОМУ ПЕРЕЛИВАНИЮ ЭРИТРОЦИТОВ У ПАЦИЕНТОВ С ВЕРХНИМИ ЖЕЛУДОЧНО-КИШЕЧНЫМИ КРОВОТЕЧЕНИЯМИ С УЧЕТОМ ИХ ГЕНЕТИЧЕСКОЙ КОНСТИТУЦИИ

Введение. Сегодня персонифицированный подход проникает в ежедневную трансфузионную практику. Каждый пациент с верхним желудочно-кишечным кровотечением должен иметь определенное индивидуально подобранное показание для трансфузионной терапии.

Цель работы – разработать показания к первой трансфузии эритроцитов для пациентов с верхними желудочно-кишечными кровотечениями различной этиологии.

Материалы и методы. В Сумской областной клинической больнице и Сумском государственном университете изучено 10 пациентов с верхними желудочно-кишечными кровотечениями. Использован для пациентов метод анализа *post hoc* и полимеразной цепной реакции для полиморфизма гена ESR1/rs2234693.

Результаты. Новая трансфузионная схема представлена. Первое переливание эритроцитов показано для компенсации кровотечения язвенной или варикозной этиологии, если диагностика относительно гемостатического контроля, сердечно-сосудистый анамнез и информация о генотипировании соответственно определены и рассмотрены.

Выводы. Первое переливание эритроцитов при гемоглобинемии между ≤ 70 и 100 г/л является индивидуально эффективным, когда клиническое принятие решения о трансфузии включает генотипирование и его оценку. Такая стратегия должна быть оценена в клинических испытаниях.

Ключевые слова: кровотечение, трансфузия, эритроцит, генный полиморфизм.

Автор, відповідальний за листування: *info@dgs.sumdu.edu.ua*

Introduction

Currently threshold haemoglobinaemia remains questionable towards a start of an erythrocyte transfusion for a patient with acute upper gastrointestinal bleeding (AUGIB) (1). In a view of post-transfusional complications we lately observe a public development of restrictive transfusion policy that aims to minimize use of blood components therapy or even more to release blood-free strategy in practice (2–4). Nonadequate approach to a blood transfusion, especially erythrocyte units, in treatment of AUGIB can yield death or recurrence outcome (5) that's why high and important need exists to precise threshold haemoglobinaemia related to first-time erythrocyte transfusion. This precision may optimize the transfusion support of a patient with AUGIB.

Taking into account a variety of clinical scenarios associated with AUGIB the definitive choice of first time erythrocyte use is hard individualized up to clinical presentation of every single patient. Patients with a variceal origin of bleeding the evidence-based approach for transfusions is unclear (6, 7). According to the National protocols of some countries for ulcer bleedings, which epidemiologically are the most prevailing, the erythrocyte transfusion begins with the haemoglobinaemia ≤80 g/L (6,8). However these requirements do not assess risks in pressure increase in the patient's portal vein system after transfusion which can impact stability of haemostasis (9). It implicates a need for lowering haemoglobin thresholds on erythrocyte transfusions for bleedings of variceal or mixed origins (9, 10).

The diagnostics of the patient's genetic constitution presents a new scientific role to threshold precision. Considering genetic traits of the patient with AUGIB in case of transfusion treatment are not mutually involved but carriers of some traits are more sensible to cardiovascular events and mortality during a bleeding development (1, 11–13).

The study's aim: to develop precise indications for first erythrocyte transfusion in patients with AUGIB considering ESR1 gene polymorphism rs2234693.

Methods

Study design

A retrospective study of 10 patients with AUGIB took place at the Surgical Unit "Gastrointestinal Bleeding Center" of Sumy Regional Clinical Hospital, the Department of General Surgery, Radiology with Phthisiology and the Scientific Laboratory of Molecular and Genetic Studies of the Sumy State University Medical Institute. The inclusion criteria were patient's age of > 18 years old, in-patient treatment and informed consent of study participants. The study was done with respect to local ethical conduct and institutional rules of Sumy Regional Clinical Hospital and Sumy State University Medical Institute.

Patient sample and its characteristic

The patient sample included five patients with duodenal ulcer disease complicated by bleeding (Forrest class IB – IIC), four patients with hepatic cirrhosis, complicated by variceal bleeding and one patient with Mallory – Weiss syndrome (Table 1).

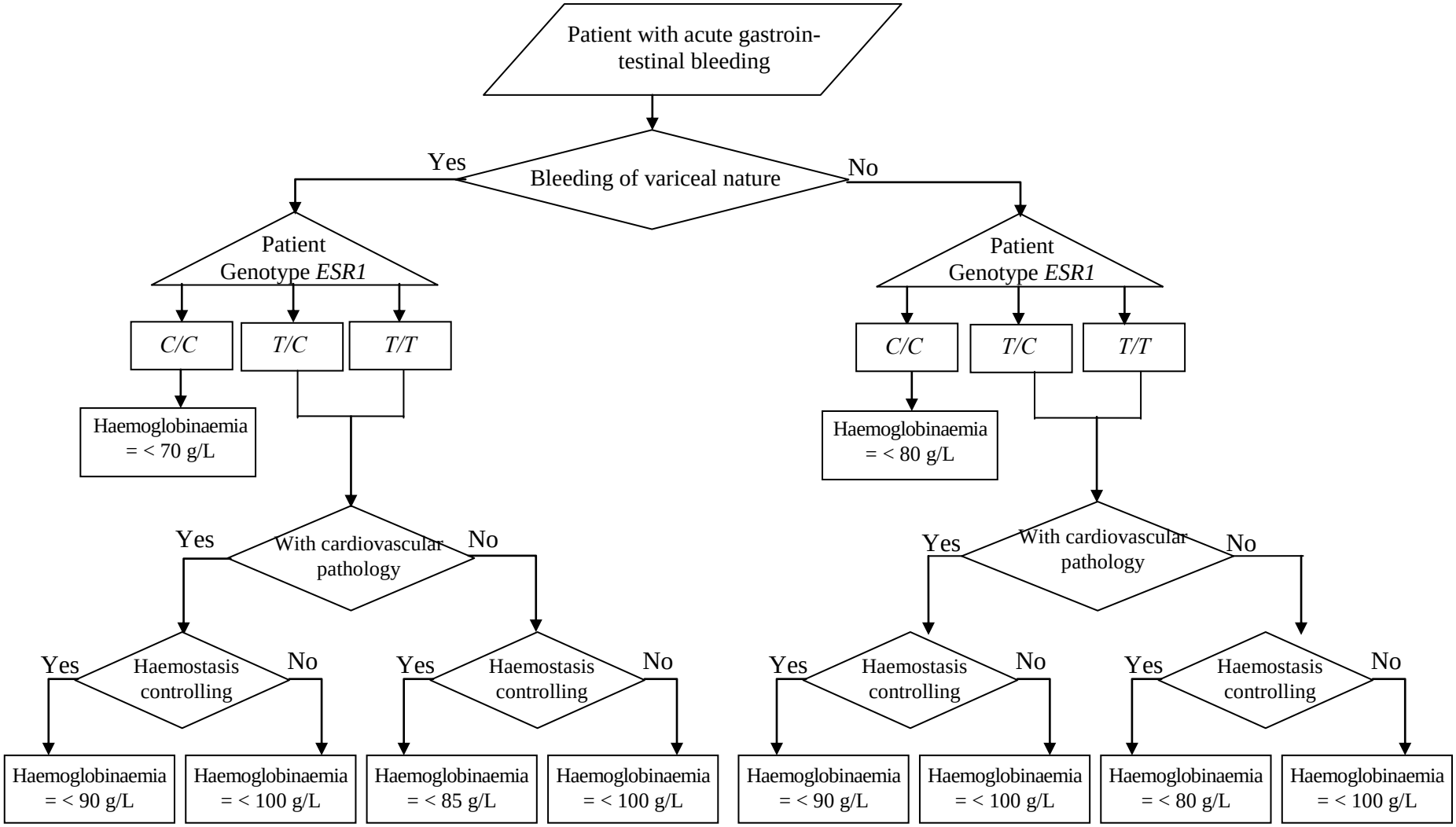
TABLE 1 – Clinical characteristics and therapeutic features of the studied patients

Parameters	Patients with ulcer bleedings (n = 5)	Patients with variceal bleedings (n = 5)
Age, years (mean, range)	60 (22–76)	48 (34–65)
Sex, male/female	3/2	3/2
Gene ESR1 frequencies (T/T; T/C; C/C)	3;1;1	1;3;1
Haemoglobinaemia, g/L, (mean, range):		
on admission	77 (69–100)	78 (68–87)
on discharge	101 (86–127)	95 (85–110)
Haemotocrit, % (mean, range):		
on admission	23 (13–32)	26 (20–28)
on discharge	30 (27–37)	29 (25–33)
Erythrocyte count, $\times 10^{12}$ (mean, range):		
on admission	2.37 (1.75–3)	2.4 (1.8–2.64)
on discharge	2.83 (2.3–3.56)	2.71 (2.3–3.1)
Erythrocyte transfusion, mL (mean, range)	800 (500–1290)	1020 (220–2220)
Blood plasma transfusion, mL (mean, range)	160 (0–280)	740 (510–1000)
Infusion of normal saline, mL (mean, range)	1800 (1000–2800)	1700 (1200–2510)
Hospital stay, days (mean, range)	9 (6–12)	8 (5–11)

Genotyping method and clinical assessment

We collected 0.1 ml venous patient blood to define ESR1 gene polymorphism rs2234693 with following application of the PCR-restriction fragment length polymorphism. We identified ESR1 gene localized in position 6q25.1 of the nuclear DNA in blood leukocyte. The lengths of restriction fragments were 392 nucleotide pairs C/C genotype, 392, 342 and 50 nucleotide pairs for C/T genotype, 342, 50 for T/T genotype using the *Pvu*ll restrictase (Thermo Fisher Scientific, USA). The site of restriction were 5'...CAG↓CTG...3' and 3'...GTC↑GAC...5'. The PCR conducted in the thermal cycler GeneAmp PCR System 2700 (Applied Biosystems, USA).

Scheme 1 – Differentiation of the haemoglobinaemia values and indications post hoc for leukocyte-depleted erythrocyte transfusion under consideration of ESR1 gene polymorphism



The diagnostic conclusion to genotype was the following three polymorphic variants: T/T (homozygote, normal), C/T (heterozygote, normal), C/C (homozygote, conditionally considered as pathological polymorphic variant).

All the patients had consultation with a cardiologist after electrocardiographic diagnostics for assessment of the cardiovascular system. In patients with ulcer disease we diagnosed an ischemic heart disease (n = 1), a periphery obliterating arteritis (n = 1) and a nephrogenic hypertension (n = 1); in patients with variceal lesion we constated an ischemic heart disease (n = 1) and a metabolic myocardiopathy (n = 1).

The laboratory control of paraclinical parameters we administered once on admission, after each 12 hours. If the patient's clinical state demonstrated severity signs (melaena, haematomesis, syncope) presented we referred a new haemoglobinaemia check. Once the haemoglobinaemia reached the thresholds, we transfused erythrocytes to the patients. After clinical observation and transfusion we monitored each hour during first 6 hours, following it each 12 hours.

The criteria of bleeding continuation and noncotrolled haemostasis were a presence of clinical and paraclinical signs of the patient. Clinical signs included melaena, haematomesis, syncope, meanwhile paraclinical ones were the haemoglobinaemia value. Also, the haemostasis controlling added 2-time endoscopic monitoring during first 4 hours from the admission time, after this the endoscopy procedure used on demand and on discharge. If the Forrest class I B-II B or stigmata (blood in the stomach lumen) visualized, we assessed the haemostasis as a noncontrolled form.

Results

The transfusion scheme consisted in categorizing patients in two groups. In the first group we included patients with T/T and C/T genotypes, the second one was C/C genotype. Considering the genotypes and assessment of the patient's clinical state the transfusion decision respected to threshold haemoglobinaemia also. The value ≤ 100 g/L of haemoglobinaemia was threshold to compensate noncontrolled bleeding in patients with T/T and C/T genotypes. Despite the bleeding nature, the patients with an associated cardiovascular disease and T/T and C/T genotypes had the threshold ≤ 90 g/L. For C/C carriers the first transfusion started from the threshold within ≤ 70–80 g/L depending on the origin of bleeding. If the last was variceal, the threshold limited to ≤ 70 g/L, if there was data of ulcer origin, the threshold reached ≤ 80 g/L. If the cardiovascular history was absent in the patient with T/T and C/T genotypes, the threshold estimated ≤ 85 g/L for the variceal bleeding, however, the same genotypes patient with ulcer bleeding transfused under ≤ 80 g/L (Scheme 1).

The visualization shows that the scheme personified approach to the first erythrocyte transfusion. After the conservative therapy all the patients discharged on the ambulatory follow-up of gastroenterologist and surgeon.

Discussion

The scheme was created post hoc and it creates interest to universal differentiation of transfusion support for patients with AUGIB. We could conclude results during 48 hours using the PCR-restriction fragment length polymorphism. This time renders impossible a large implementation of this technique. In near future automatic genotyping methods accelerate practicability of diagnostics based on the genetic constitution which economizes the burden on public medical resources. Unfortunately, the genetic testing stays aside of the practice routine and it doesn't regulated positively in the developed countries because of big data problems, common clinical consensus and its diagnostic accuracy (14).

The majority of patients (more than 85 %) with AUGIB arrest spontaneously (15, 16), but Halland M. et al., declared 59 % patients needed a transfusion therapy (17). In this light, the scheme is oriented for the majority of patients with AUGIB of different risks. Nevertheless the scheme didn't involve many patient categories: fatal patients, recurrent in-patients, operated patients, bleeders of mixed origin or combined with other ulcer complications, we should pay attention to these bleeders in future gene-association studies. We present the scheme as a conceptual background for a new diagnostic trial

separation on haemoglobinaemia range between ≤ 70 g/L and ≤ 100 g/L, assessment of cardiovascular risk and ESR1 genotype constitution of the patient. Further studies are required.

Conclusion

Thus, the precision of leukocyte-depleted erythrocyte transfusion treatment for patients with acute upper gastrointestinal bleeding may objectively personified with help of an appropriate haemostasis control, including differential

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