Commentary

Effect of "old" versus "fresh" transfused red blood cells on patients' outcome: probably more complex than appears

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Provenance: This is an invited Commentary commissioned by the Section Editor Zhiheng Xu (State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, Department of Intensive Care, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China).

Comment on: Heddle NM, Cook RJ, Arnold DM, *et al*. Effect of Short-Term *vs*. Long-Term Blood Storage on Mortality after Transfusion. N Engl J Med 2016;375:1937-1945.

Submitted Dec 24, 2016. Accepted for publication Jan 04, 2017.
doi: 10.21037/jtd.2017.02.03
View this article at: http://dx.doi.org/10.21037/jtd.2017.02.03

The study recently published by Heddle *et al*. "*Effect of Short-Term vs. Long-Term Blood Storage on Mortality after Transfusion*" (1) is the last avatar of a series of studies examining whether extended red blood cell (RBC) storage in blood banks is detrimental or not to patients [for a detailed review, refer to: (2)]. The common sense would argue that "the freshest, the best", but extended storage may be rendered necessary for logistical reasons in blood banks for various reasons. Blood collection and storage creates so-called storage lesions, that are either reversible or non-reversible in transfused patients depending on blood component processing and patient condition (3,4). What remains uncertain is the actual effectiveness and also—eventually—the damage that allogeneous blood brings to a transfused patient. There are two main reasons for asking: (I) transfusion is "non-natural" and creates biological danger, manifested by a certain level of inflammation (5), thus, the superiority of fresh blood (i.e., as fresh as possible blood) may well be masked by the deployment of the recipient's innate or natural immunity; (II) some parameters related to the transport of oxygen by hemoglobin in RBCs—such as 2,3 DPG—are altered extremely rapidly after blood collection and processing (3,6), meaning that even the freshest possible blood losses certain oxygen restoration capacity in a disabled patient: to what extent does the freshest as possible blood do better than conventionally issued blood? Further, what does "fresh" and "old" really mean when related to stored blood, and more specifically when those terms are used in published clinical trials? There again, there are two main considerations: (I) the presence or (likely) absence of residual leukocytes as the latter affect the recirculation of transfused RBCs in microvessels (7): this point is seminal; as a matter of fact, all major clinical trials reported so far were performed using prestorage leukoreduced blood (2); (II) in most countries benefiting robust transfusion services, the mean age of the inventory is ~1,214 days, with variations depending e.g., on ABO, RH:1,2,3 and KEL:1 blood groups; the question could be: "is 10 to 12 day aged blood "old" or not?" Most published clinical trials comparing "fresh" *vs*. "old" blood actually compared the freshest as possible (~8±2 days old blood) *vs*. conventionally issued blood (~15–21 days old blood); some—but few—trials compared fresher blood (~2–3 days old) to conventionally issued blood. It seems difficult to actually compare very fresh to very old blood for ethical reasons (and likely medical reasons as well), as one can cast serious doubt on the safety of old blood (8). Thus, most trials compare medium ranges of aged blood: with no surprise, the selected readouts evidence no significant clinical difference. Meanwhile, to what extent the selected target populations and selected readouts are relevant is also questionable and, there again, there are a number of concerns: (I) most published series examined occurrences of events in critical care patients, either adults or neonates (2): though RBC transfusion is part of the current resuscitation

means, many other populations are fragile or exposed to a serious risk of alloimmunization in case they receive frequent transfusions (which happens to be the case of beta-thalassemia, sickle cell disease, myelodysplastic syndrome, bone marrow or organ transplanted patients, etc.); (II) a large body of experimental evidence stress out an increased risk of alloimmunization in relation with free or oxidized iron, microparticles/microvesicles, free oxygen radicals etc., which all happen to result from ageing (9). Alloimmunization is more complex than resulting solely from storage lesions (10) as it also depends on antigens and antigen presentation, recipient HLA etc. (11), but one cannot ignore the storage lesion responsibility. Most studies addressing the safety of old—compared to fresh—blood cells do not compare long-term events, but short-term mortality. Short-term mortality in complex patients is affected by numerous confounding factors; those confounding factor are in general taken into consideration by ad hoc statistical tests, but some are not, such as the impact of certain lipophilic drugs on RBCs etc. To conclude this part of the commentary, most reported clinical trials—and NM Heddle's as well—do not report that "old" blood does as well as "fresh" blood in transfused individuals, as often suggested by titles, or press advertisements, or commentaries, but—in general—that 3-week-old transfused RBCs do not increase 30-day mortality in critical care patients compared to 2-week-old RBCs.

The next comment reads as a question: "to what extent is it important to state that ~20-day-old RBCs carry no additional danger compared to ~10-day-old RBCs for patients who—for a large majority of them—do not have a very long life expectancy?" Wouldn't be questions addressing benefits rather than risks more valuable? It could thus be rephrased as follows: "to what extent do ~20-day-old RBCs carry oxygen to tissues similar to ~10-day-old RBCs in patients with longer life expectancy?" The latter issue questions some lacks in our understanding of the pathophysiology of foreign RBCs having suffered storage lesions with respect to: (I) a recipient's circulating cells (RBCs, but also platelets and leukocytes); (II) this recipient's vascular endothelial cells; (III) his/her tissues such as brain, heart, kidneys, liver and lungs? Lungs appear to be particularly sensitive to foreign RBCs and foreign platelets as two pathologies characterize transfusion hazards, namely transfusion related acute lung injury (TRALI; an immune-pathology involving an inflammatory state, possibly some infectious material such as lipopolysaccharides, anti-leukocyte antibodies and biological response modifiers, that altogether, assault leukocytes and especially lung infiltrating leukocytes) (12), and Transfusion Associated Circulatory Overload (TACO), which begins to be questioned as not being simply a matter of volume but perhaps also a matter or perfusion (13). In total, it appears that there is a lack of fine understanding of physiopathology of foreign transfused blood cells. This issue is far from being simple to address because it is physiology and immunology/inflammation all at the same time, with intricate relationships. It is physiology because it is all about—for what concerns RBC transfusions—carrying oxygen (plus—eventually—bringing hemoglobin and iron); it is immunity because all organic molecules are foreign and are perceived as such by sensors displayed in purpose on a large variety of circulating and vascular lining cells participating to natural (innate) immunity and inflammation (5). With regard to those issues, both fundamental and translational research is still necessary to increase our knowledge in microperfusion of normal and foreign blood cells, accompanied by derivatives that cannot be completely eliminated as inherent of the packed RBC collection and/or processing, but that can be mitigated by novel additive solutions or plastics or processes at large, allowing storage (extended or not). Microperfusion is central in certain pathologies such as cardiovascular and neurological pathologies: some clinical trials addressed the cardiovascular issue but remained inconclusive (14). Microcirculation is also an issue when old *vs.* fresh RBCs are transfused in septic patients (15,16). This is best exemplified by recent studies showing no specific benefit when liberal *vs.* restrictive RBC transfusion policies are applied (17).

The last part of this commentary will be medical and ethical. What is the actual relevance of such a question like the risk/benefit of transfusing fresh or less fresh—or, in other words—old or less old, RBCs? Is it universal or does it refer to what is now perceived as personalized medicine? It seem of utmost importance to not expose fetuses, neonates, young people with a long life expectancy to any drug-derived side effect which can be avoided: this is also the case for blood if blood is considered a drug or, to be more politically correct and universal, a "medicine" (18). It is also of utmost importance to maintain the capacity of benefiting transfusion programs of individuals prone to receive RBCCs regularly all life-long. The optimal use of blood in the most exposed or fragile populations is medically, ethically and economically sound. The optimal use of blood in all types of populations is medically and ethically sound: it may not be economically proficient but, in counterpart, it exposes to less chain errors and overall improves the safety and quality of blood transfusion systems. For a long time, medical progresses in pharmacology and transfusion medicine were made in parallel; they barely crossed; the dream that

transfusion could be replaced by engineered substitutes has somehow vanished and engineering is now applied to favor the generation of *ex vivo*—iPS or embryonic stem cell originating—RBCs or platelets (19); recently however, some teams sought out the design of drugs that either reduce or optimize the benefit of foreign transfused cells (20). Thus, if one tends to consider that the debate of "fresh" *vs.* "old" cells is over once and for all, he/she may well be wrong: it is just beginning on the contrary, as one will have—in my opinion—to precisely measure the pathophysiological effects of all novel derivatives (and storage lesion moieties), in each group age and patient category.

Acknowledgements

The author thankfully acknowledges fruitful and stimulating discussions on the topics with Prof. Jean-Daniel Tissot, Lausanne, CH, Dr. Alexander Vlaar, Amsterdam NL, and Prof. Jacques Lacroix, Montreal, CA.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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Cite this article as: Garraud O. Effect of "old" versus "fresh" transfused red blood cells on patients' outcome: probably more complex than appears. J Thorac Dis 2017;9(2):E146-E148. doi: 10.21037/jtd.2017.02.03

