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The clinical impact of the shelf life of red blood cell concentrates intended for cardiac surgery patients

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INTRODUCTION AND ISSUE

On May 26, 2008, the Superior Health Council (SHC) received a request for advice from the Minister of Social Affairs and Public Health[1] on measures that may need to be taken regarding the shelf life of red blood cell (RBC) concentrates intended for cardiac surgery patients.

Following an expert meeting on the indications for the transfusion of red blood cells in November 2005, the SHC had already assessed the relevant literature on the potential clinical impact of the shelf life of RBC concentrates (Baele et al., 2008). Indeed, large-scale retrospective studies sometimes showed that the shelf life has an adverse effect on certain clinical parameters (Basran et al., 2006). However, the initially significant differences may disappear after adjustment for the confounding factors inherent in any retrospective approach (van de Watering et al., 2006). Although the two randomised clinical trials that existed at the time (Walsh et al., 2004; Hébert et al., 2005) did not provide any evidence in support of storage lesions having a potentially adverse effect on the clinical parameters, it should, however, be pointed out that the scope of these trials was too limited to allow for any definitive conclusions to be drawn on this issue. It should also be noted that, in their prospective pilot study (which included 66 patients), Hébert et al. (2005) drew a link between *short* RBC concentrate shelf lives and unfavourable patient outcomes. Thus, the SHC concluded that the results of the clinical trials are inconsistent and, with no appropriately powered randomised clinical trial available, do not allow for any recommendations to be issued for transfusion practice.

This request arises from the ominous conclusions drawn by Koch et al. (2008). The latter examined the outcome of RBC transfusions in adult patients who underwent cardiac surgery between 1998 and 2006 in the same hospital. These authors found that there is an increase in postoperative complications and mortality in patients who have only received such RBC concentrates as have been stored for over two weeks. The concerns raised by this extensive study (which involved 6,000 patients) are of paramount importance to the practice of transfusion medicine and cannot be ignored.

[1] Letter from Ms. L. Onkelinx, Minister of Social Affairs and Public Health (reference: FAGG/LM/30343) of 21/05/08, addressed to Mr. G. De Backer, SHC Chairman.

This advisory report therefore aims at examining the validity of the results and conclusions that tend to support the view that there are postoperative complications in cardiac surgery patients that are worsened by administering RBC concentrates that have been stored for several weeks.

This advisory report is based on the opinion of experts on transfusion medicine, haematology, clinical biology, microbiology, internal medicine, anaesthesiology, intensive care and cardiac surgery.

CONCLUSIONS

1. During storage, RBC concentrates intended for human transfusion undergo metabolic and structural alterations that grow increasingly significant over time, though they are more or less reversible depending on the case. The first retrospective studies led to the suggestion that these deteriorations are liable to worsen morbidity and increase the mortality rate of patients who have received a transfusion in various clinical settings, including cardiac surgery.

2. With no convincing facts available that could lead to the identification of one or several precise physiopathological mechanisms, the research carried out since, which has included but few controlled trials, has led to conflicting results, regardless of the clinical setting considered (cardiac surgery, intensive care, paediatrics, neonatology). In view of the many technical and practical difficulties encountered by the researchers as well as the methodological flaws found in the vast majority of these studies, it is not possible at the moment to provide a useful comparative study of the published trials, nor can an opinion be expressed on the relevance of the tested hypothesis. Middelburg *et al.* (2010) have recently advised that a certain number of stages be taken into account in order to reduce the impact of the most significant confounding factor (i.e. the indication for transfusion) at the clinical trial preparation stage.

3. Can the precautionary principle be invoked to suggest that the use of fresh concentrates should be preferred in spite of the lack of evidence in support of their being less harmful, as is done by several centres for acute cardiology and intensive care patients (Zubair, 2010)? The SHC takes the view that the precautionary principle can be applied when considering implementing a new technology with unknown potential adverse effects, or when such effects are observed without being able to establish a definite causal link with a suspected factor. As regards storage lesions, the discussion concerns a well-known practice and is not raised by indisputably observed clinical effects, but by partial and debatable theoretical and experimental considerations; some even take the view that it would be useless — unethical even — to carry out a RCT (Vamvakas, 2010). Not only does the evidence provided remain inconsistent, but implementing preferential use would be liable to result in problems in the supply of blood components for other patients. As a matter of fact, recipients of RBC concentrates with a *short* shelf life could face an unfavourable outcome. The SHC therefore takes the view that the precautionary principle should not be applied with respect to the question submitted. Conversely, the SHC finds it necessary to invoke the precautionary principle when deciding whether or not a given patient should receive a transfusion (SHC, 2010; Isbister *et al.*, 2011; Vamvakas, 2011).

4. It may be necessary to reassess the situation in the future, especially with respect to the results that are expected from planned RCTs and fundamental research projects that are currently being set up. Whilst RBCs are stored in blood banks, their structure and physiology are affected by many objective alterations. New good-quality experimental protocols therefore open the door to other pathogenic hypotheses. It follows that, from a scientific point of view, this debate cannot be put to rest yet. On the other hand, one should keep in mind that the progress that is continuously made with respect to preservation solutions, revitalisation (rejuvenation) protocols for stored concentrates, and other more or less sophisticated techniques such as freezing, the removal of red blood cells of advanced medullary age, RBC washing, donor selection (concerns haemolysis and haemoglobin recovery), the use of regenerating liposomes, alteration of the pH-level or anaerobic storage (Szymanski *et al.*, 2001; Draper et al., 2002; Hess & Greenwalt, 2002; Hess *et al.*, 2003; Lockwood *et al.*, 2003; Hess *et al.*, 2006; Högman *et al.*, 2006; Högman *et al.*, 2006b; D'Amici et al., 2007; Yoshida *et al.*, 2007; Zehnder *et al.*, 2008; Dumont *et al.*, 2009; Raat *et al.*, 2009; Burger *et al.*, 2010; Hess, 2010; McAteer *et al.*, 2010; Raval *et al.*, 2011; Yoshida & Shevkoplyas, 2010; Alfano & Tarasev, 2011; Ashenden & Mørkeberg, 2011; Meyer *et al.*, 2011) could provide a solution in the future that would make the current discussions superfluous, at least from a practical point of view and insofar as the currently authorised shelf life is applied.

RECOMMENDATIONS – ADVICE

The SHC advises that, for the moment, the shelf life of RBC concentrates should not be taken into account for blood transfusions that are to be administered to cardiac surgery patients or adults in any other clinical situation. The reasons are as follows:

- The recorded results are inconsistent;
- The upper shelf life limit is disputable, subjective and indefinable;
- The clinical effects mentioned have a limited impact as regards their clinical severity and the number of patients affected;
- There are methodological uncertainties regarding the manner in which the published positive studies were conducted and in which the statistical processing was carried out;
- There are technical differences regarding the production of RBC concentrates (preservation solution used, (no) leukocyte depletion, method used for leukocyte depletion), and
- There is a risk of disorganising the supply of and causing a shortage in blood components if more extensive use is made of RBC concentrates with a short shelf life.

From a medical point of view and pending a clear and univocal scientific answer to the question submitted, there is more to be gained from weighting the indication for transfusion very carefully than from introducing a selection process for RBC concentrates based on their shelf life.