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This week

Blood doesn't always save lives

Transfusions can be a lifeline, but concerns are growing that they can sometimes be harmful too

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"FOR the life of the flesh is in the blood. No soul of you shall eat blood." So says the Bible's book of *Leviticus*, and it is for this reason that Jehovah's Witnesses shun blood transfusions. They do not, however, shun surgery. As long as surgeons use special techniques, Jehovah's Witnesses can have surgery – including operations with the greatest potential for blood loss, such as open-heart surgery – without ever receiving a drop of someone else's blood.

Now some surgeons and anaesthetists are questioning whether every patient shouldn't get the same treatment. Over the past decade a number of studies have found that, far from saving lives, blood transfusions can actually harm many patients.

The problem is not the much-publicised risk of blood-borne infectious agents, such as HIV, but the blood itself. Study after study has shown that transfusions, particularly those containing red blood cells, are linked to higher death rates in patients who have had a heart attack, undergone heart surgery, or who are in critical care. The exact nature of the link is uncertain, but it seems likely that chemical changes in ageing blood, their impact on the immune system, and the blood's ability to deliver oxygen are key.

In fact, most experts now agree that the risk posed by the transfused blood itself is far greater than that of a blood-borne infection. "Probably 40 to 60 per cent of blood transfusions are not good for the patients," says Bruce Spiess, a cardiac anaesthesiologist at Virginia Commonwealth University in Richmond.

Such claims have led this week to the US National Institutes of Health issuing a call for proposals to study the problem. Also this week, the Joint Commission in Chicago, which accredits US hospitals, is holding the first of several meetings to look for ways to reduce the risks. It is expected to at least conclude that hospitals should be more selective in the use of transfusions.

Blood transfusion became a mainstay of medicine during the two world wars, where it was used as a last resort to save soldiers who had suffered massive blood loss. But now, far from being restricted to catastrophic bleeding, transfusions are routinely used as an optional treatment, most commonly for patients in intensive care or undergoing major surgery. In these situations, mostly small volumes of red cells are transfused, usually after they have been stored at 4 °C for anything up to 42 days.

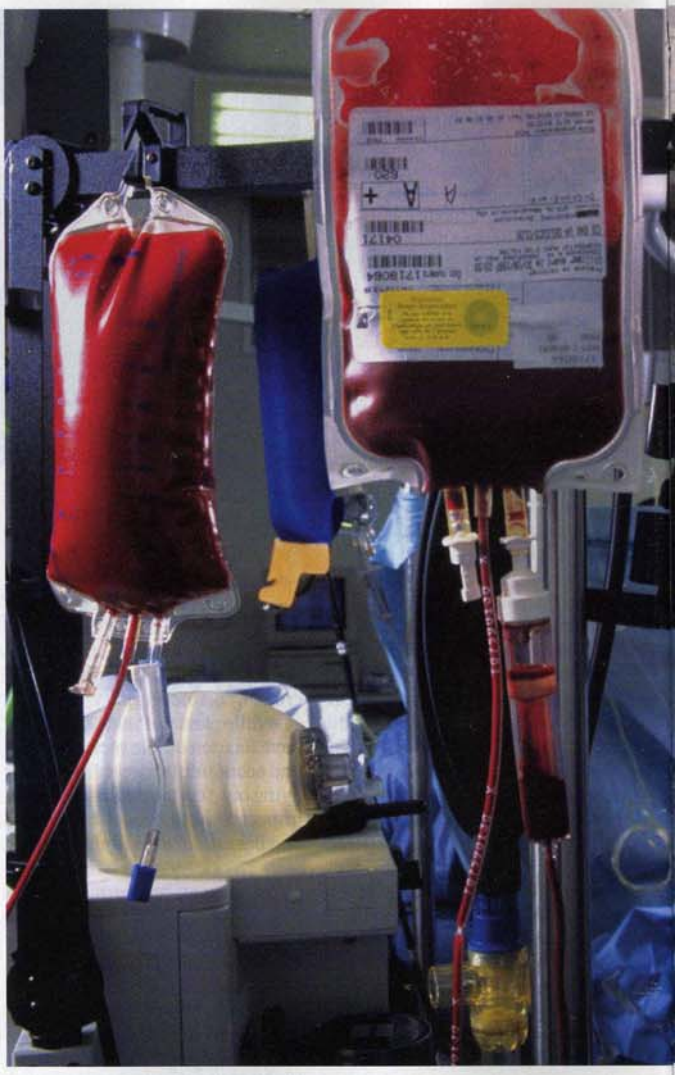
"For heart-surgery patients in the UK, a red cell transfusion was associated with three times the risk of dying within the year"

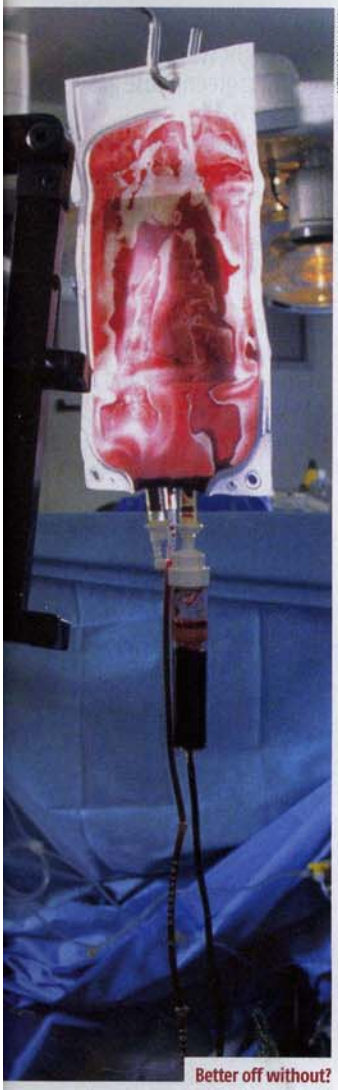
The rationale behind such blood transfusions seems incontrovertible. Red cells deliver vital oxygen to tissues, and seriously ill patients who are also anaemic fare less well, so a transfusion should help. Those assumptions went untested for the better part of a century.

Things started to change in 1999 with a randomised controlled trial on 838 critical care patients in Canada that used haemoglobin levels to determine when a blood transfusion was given. Normal levels of haemoglobin, the oxygen-carrying protein in red cells, range from 120 to 170 grams per litre. A normal haematocrit – the proportion of red cells in the blood – ranges from 36 to 50 per cent. Doctors decide whether to give a transfusion based on a number of factors, including haemoglobin levels and haematocrit, and the patient's overall robustness. Many guidelines exist, and practice varies from one hospital or doctor to another, but it is common for patients to receive transfusions when their haemoglobin dips to between 70 and 100 g/l or their haematocrit to 21 to 30 per cent.

But the Canadian study found significantly fewer patients died in hospital, 22 versus 28 per cent, if they received transfusions only when their haemoglobin fell below 70 g/l rather than when it fell below 100 g/l.

A more recent study has found that in heart attack patients with haematocrits of over 25 per cent, a transfusion is associated with

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Better off without?

more than three times the risk of death or a second heart attack within 30 days compared with not having a transfusion (*Journal of the American Medical Association*, vol 292, p 1555).

For almost 9000 patients who had heart surgery in the UK between 1996 and 2003, receiving a red cell transfusion was associated with three times the risk of dying in the following year and an almost sixfold risk of dying within 30 days of surgery compared with not receiving one. Transfusions were also associated with more infections and higher incidences of stroke, heart attack and kidney failure – complications usually linked to a lack of oxygen in body tissues (*Circulation*, vol 116, p 2544).

"There is virtually no high-quality study in surgery, or intensive or acute care – outside of when you are bleeding to death – that shows that blood transfusion is beneficial, and many that show it is bad for you," says Gavin Murphy, a cardiac surgeon at the Bristol Heart Institute, who ran the UK study.

> "Within hours of being collected, red cells become stiff, making them less able to squeeze into narrow capillaries"

Organisations such as the American Society of Anaesthesiologists have started recommending that doctors be more conservative about ordering transfusions. But many experts worry that the recommendations are being ignored, and don't go far enough. Transfusion, they say, should only be used as a last resort, and far greater effort should go into preventing blood loss in the first place and ensuring patients are not anaemic before surgery (see "Bloodless surgery").

"Usually when there is any clinical uncertainty about a treatment you don't give it, but with transfusions we do," says James Isbister of the Royal North Shore Hospital in Sydney, who is an adviser to the Australian Red Cross Blood Service.

A priority is to find out how transfusions can be harmful. One possibility is that they affect the patient's immune system. Blood transfusions are typically teeming with cytokines – chemicals that modify immune cells – and both the cytokines and white blood cells in donated blood have been shown to affect the action of "recipient" immune cells in the lab. Before modern immunosuppressant drugs were developed, blood transfusions were sometimes used to achieve immunosuppression during kidney transplants.

Several of the recent studies have found an association between contracting infections in hospital and transfusions, which seems to support the theory. "The more units of blood patients receive, the more likely they are to get infections," says Mary Rogers at the University of Michigan in Ann Arbor, who has studied transfusions in US heart surgery patients.

Infections are not the whole story, however. Within hours of being collected, red cells become stiff, making them less able to squeeze into narrow capillaries – essential if they are to deliver oxygen to organs. The changes are triggered in part by white cells, although it is not known how they might do this. Blood banks in the UK routinely filter blood to remove any white cells, something which is not done everywhere in the US or Australia.

Chemical changes also take place that limit the ability of red cells to deliver oxygen to the tissues. For example, levels of nitric oxide (NO), which signals blood vessels to open, drop dramatically within a day of collection. "We are now working on the best way to put NO back into blood on a large scale," says Jonathan Stamler of Duke University in North Carolina.

Another study, published last month, suggests the longer red cells are stored, the poorer their quality (*The New England Journal of Medicine*, vol 358, p 1229). It found patients who received blood more than two weeks old were almost 70 per cent more likely to die within a year than those who got newer blood.

"If all blood had to be used within two weeks, it would cause a major inventory problem," says Isbister, adding that the finding highlights the need to look for better ways to store blood. Just as important is the need for clinical trials to work out who benefits from transfusions and who doesn't. "We need 60 or 70 randomised clinical trials right now," says Spiess.

But people should not stop donating blood, stress experts. "Transfusion is critical in several situations such as severe haemorrhage. We also need blood for essential products such as antibodies and clotting factors for people with haemophilia," says Isbister. ●

BLOODLESS SURGERY

"Reduce, reuse, recycle" is usually a mantra for the environment, but it applies to "bloodless surgery" too.

It was originally developed to enable Jehovah's Witnesses, who shun transfusions, to undergo major surgery. But as safety concerns have spread so has its use. It may involve little more than treating any anaemia prior to surgery, reducing the blood taken for tests, and meticulous surgery.

"Most general surgery patients who receive a transfusion get one or two units of blood. With careful surgery you can avoid losing that amount in the first place," says Nicolas Jabbour at the Baptist Medical Center in Oklahoma City.

Special techniques can also be used. For example, at the New Jersey Institute for the Advancement of Bloodless Medicine and Surgery at Englewood Hospital, patients who have lost a lot of blood may spend time in a hyperbaric chamber after surgery in an attempt to load their remaining red cells with oxygen. More commonly, during or after surgery, spilt blood is collected, cleaned and reinfused. The process has the disadvantage that it removes proteins that stimulate clotting and is also unacceptable to some Jehovah's Witnesses. An alternative is to remove some blood before surgery and replace it with saline or another fluid. After surgery, the patient's blood is returned.

Bloodless surgery works, suggests a 2006 study comparing 49 Jehovah's Witnesses and 196 non-Jehovah's Witnesses undergoing cardiac surgery, which found comparable death rates during surgery (*The American Journal of Cardiology*, vol 98, p 1223).