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Perfluorochemical "Red Blood Cell Substitutes"

The Continued Search for an Indication

PERFLUOROCHEMICAL (PFC) liquids are hydrocarbon molecules of 8 to 10 carbons in length where the hydrogens have been replaced by fluorine. These liquids have several unique properties; they are immiscible in water, have a density of approximately twice that of water, are chemically inert, and have nearly twenty times the solubility for gases as does water. Because of their chemical inertness and high solubility for oxygen, emulsions of PFCs in normal saline have been studied over the past 30 yr as oxygen-carrying colloids that may temporarily supplement oxygen transport in lieu of erythrocytes.[1,2,3,4,5] Since PFCs carry oxygen by direct solubility, their contribution to oxygen content, like plasma, is directly proportional to the arterial oxygen tension (Pa_{O_2}) and requires a high Pa_{O_2} (>300 mmHg) to be effective. Another limitation of these emulsions is that they are cleared from the vascular space by the reticuloendothelial system relatively quickly, having a half-life in the range of 12–18 h.[3,4,5] Once out of the vascular space, the PFC remains in the liver and spleen for a prolonged period of time, with a half-life measured in weeks, thereby limiting the advisability of multiple doses over a short period of time.[5] Early emulsions in clinical trials suffered another limitation of emulsion instability, requiring the product to be stored frozen and only containing an "anemic" 10% PFC by volume.[3,4] These last two limitations have been overcome by a more recent product, although the primary limitations of requiring high inspired oxygen to carry limited amounts of oxygen for a short period of time remain.[6] Given these physical and physiologic constraints, using a PFC emulsion as a temporary replacement for erythrocytes in the traditional sense has not been found to be effective.[3,4] It has been demonstrated that treatment with a PFC emulsion does contributed to oxygen transport, but the contribution has not been sufficient to either change outcome or reduce the need for a blood transfusion.[3,4,6] In this current issue of the journal, Spahn *et al.* present a study attempting to demonstrate a reduced need for a erythrocytes transfusion by combining acute normovolemic hemodilution (ANH) and treatment with the PFC emulsion, perflubron.[7]

PFC (and plasma) pick up and release oxygen in direct proportion to oxygen partial pressure. Therefore, in spite of the fact they do not carry a large volume of oxygen; the oxygen they do carry will largely be released in the tissue. For example, if the Pa_{O_2} is 400 mmHg and the mixed venous P_{O_2} is 40 mmHg, 90% of the dissolved arterial oxygen will be released in the tissue, whereas only 25% of the hemoglobin bound oxygen will be released. Unfortunately with the doses of PFC used in this and other clinical studies, the maximum of obtainable fluorocrit (Fct) of 3%, (volume % of fluorocarbon in the blood, Fct, analogous to hematocrit), would contribute just under 1.0 volume percent (vol%) of oxygen content. One g/dl of hemoglobin (hematocrit ≅3%) will carry 1.34 vol% of oxygen. These comparisons would make PFC treatment seem analogous to blood treatment on a Fct *versus* hematocrit basis, given a Pa_{O_2} of less than 300 mmHg, except for the dosing limitations and short intravascular half-life of the PFC. It has been demonstrated, in animal and clinical studies, that treatment with PFC will produce an immediate rise in mixed venous oxygen tension (Pv_{O_2}) implying a contribution to oxygen delivery.[6,8,9] Understanding the limitations of dose, half-life, and relatively small contribution to oxygen transport, the authors have selected ANH as the clinical situation where a temporary supplementation to oxygen transport may ultimately reduce the overall need for erythrocytes.[7,9]

It is the authors supposition that treatment with PFC will allow patients to undergo a more severe degree of intraoperative anemia, due to ANH and surgical blood loss, resulting in a decreased need for red cell transfusions compared with a control group. Unfortunately, in this study the control group is not a parallel control. The treatment group undergoes ANH to a hemoglobin of 8 g/dl then receives 1.8 g/kg of PFC emulsion (about 0.9 ml/kg or 67 ml of PFC). During surgery the hemoglobin is then allowed to drop to 6 g/dl at which point another 0.9 g/kg of PFC is given. The patient's hemoglobin then is allowed to drop to 5.5 g/dl before they are transfused with the ANH blood. The patients randomized to the controls are transfused with blood when their hemoglobin reaches 8 g/dl. In addition, the PFC group has the F_{IO_2} increased to 1.0, whereas the control group has a F_{IO_2} of 0.4. At the end of surgery the target hemo-

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globin for both groups is greater than 8.5 g/dl. At 24-h the ANH/PFC group did receive fewer transfused units than the control group, (1.5 *vs.* 2.1 units). But by postoperative day 3 this difference is no longer significant. In a subgroup of patients whose intraoperative blood loss was greater than 20 ml/kg the difference remained significant throughout the hospital stay (3.4 units *vs.* 4.9 units at 21 days or day of discharge). It is not clear that these findings were due to the PFC emulsion for the results are predictable from the ANH alone.[10]

Both groups were transfused when they reached the protocol-defined hemoglobin level or if one of the following physiologic transfusion triggers was achieved: heart rate greater than 100 beats/min., mean arterial pressure less than 60 mmHg, P_{VO_2} less than 38 mmHg, or ST segment changes. One way of assessing safety may have been to determine how many of these physiologic transfusion triggers were encountered in each of the groups. If, for example, the PFC group noted more ST segment changes associated with lower hemoglobin levels it might bring into question whether the PFC treatment and the high F_{IO_2} indeed made the treatment group as safe as the control group. On the other hand, if more of these physiologic triggers were encountered in the control group it may help provide evidence that the PFC and high F_{IO_2} treatment allowed a lower hemoglobin with less physiologic consequence.

More adverse events were noted in the treatment group with respect to cardiovascular events, (40% *vs.* 30%), and digestive system events, (7% *vs.* 2%). The authors speculate that the cardiovascular events may have been due to the unfamiliarity of some of the study sites with the process of ANH. They then describe the technical issues regarding ANH and the subsequent retransfusion with associated volume shifts. This is indeed a risk associated with ANH, which should be taken into account when one is trying to lower the overall risk of perioperative blood and fluid management.

Ultimately the mortality was twice as high in the PFC group, (10 out of 195, *vs.* 5 out of 195), although this did not reach significance. Given the current risk of HIV is approaching 1:1,000,000 and Hepatitis C less than 1:100,000; it would take a very large study to determine if ANH/PFC treatment improves safety.[11,12]

It is always far easier to criticize a large complex clinical trial than it is to actually perform one, particularly one this large. The primary conclusion that the authors draw from their study, "that the use of perflubron emulsion as an intravenous oxygen therapeutic to augment autologous blood harvesting may represent a new alternative for. . .patients seeking to avoid or minimize the risks of allogeneic RBS transfusions. . .," is intriguing, but is likely to trigger disagreement and a skeptical response from many. However, regardless of such criticisms, the authors must be congratulated for what is clearly the largest and most thorough effort to date to examine the utility of these compounds in operative medicine. I am not yet convinced, but I remain hopeful that the broader utility of PFC emulsions may be proven. This study is a reasonable step in that direction.

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No Myth: Anesthesia Is a Model for Addressing Patient Safety

ANESTHESIA is an intrinsically hazardous undertaking and anesthesiologists have struggled for years to determine the incidence of catastrophic adverse outcomes. There is a wide belief that anesthesia is safer now than it was 30 or more years ago, and anesthesiology has been acknowledged by some for its nearly perfect safety record.[1] In this issue of ANESTHESIOLOGY, that belief is challenged.[2] Dr. Robert Lagasse, reviewing literature from the past 5 decades and presenting new data, claims provocatively that "the emperor is not wearing any clothes" and that "we must dispel the myth that anesthesia-related mortality has improved by an order of magnitude." Is this commonly held belief of markedly improved safety imaginary or does Lagasse's analysis miss the mark? The truth is somewhere in between. Assessing the contribution of anesthesia care to perioperative mortality and morbidity is notoriously difficult. Making fair comparisons across epochs in time is even more problematic. Yet, absence of unequivocal data is not evidence of absence of the effect. Even so, the available data may reflect several points: anesthesia for healthy patients is "safer" than it once was (but further progress may be possible); the rate of anesthesia-related mortality for all surgical patients is still higher than desired; and, safety levels can "plateau" or even diminish over time without constant effort at improvement.

Perhaps the last thorough peer-reviewed summary of anesthesia mortality studies was in 1987.[3] Fifteen years later, the issue is still plagued by confounding variation in definitions, relatively small sample sizes from selected institutions, and the lack of large population studies, especially in the United States. The new review in this issue by Lagasse of 23 studies, dating back to the mid-1950s, provides an interesting, but not totally clear perspective. The reported rates of anesthesia-related mortality vary widely by year and by country. Only four reports are from the United States and only one (The Confidential Enquiry into Perioperative Deaths)[4] is a systematic analysis of a large population. Lagasse's control chart suggests randomness in anesthesia-related mortality during the past 30 yr. As Lagasse asks, is this real or an artifact of varying techniques and definitions? There is no way to be certain. The definitions for deaths in which anesthesia was "associated," "related," "contributory," or "preventable" varied widely as did the time windows for the perioperative period (24 h to 30 days). The locales studied were disparate. Yet, even if we accept the definitions to be roughly comparable over the years, much else has changed that is not accounted for in the comparison of these studies.

Are the nature of surgical patients and the operations performed unchanged over time? It seems likely that, compared with the period before 1970, more complex procedures are now performed more readily on sicker patients. This phenomenon might be studied using large databases if they provide equivalent data far enough back in time. Moreover, while it might be possible to track changes over time in the distribution of patients' ASA physical status scores, we cannot determine whether there have been shifts in the way that scores would be assigned to the same patients in different epochs. It seems entirely possible that patients previously judged as ASA 3 or 4 may now be scored as ASA 2 or 3 as medical management for many diseases has improved and anesthetizing such patients has become routine.

Despite the difficulties, there are data to suggest on the order of a ten-fold improvement in anesthesia safety if the focus is on studies in the United States, the country for which claims of dramatic improvements have been made. Add to Lagasse's review the pioneering study of Beecher-Todd, which covered the period 1948–1952.[5] It reported a rate of 1:1560, for deaths in which anesthesia was at least "a very important contributing factor." Despite the caveats of interpretation, it's fair in definition and methods to compare this order of magnitude with that provided by Lagasse's new data, where the mortality rate was approximately 1:13,000. That's close to a ten-fold improvement. Considering differences in patient risk and complexity of surgery from 5 decades ago, it's easy to see why many claim a dramatic increase in safety from years past despite the absence of hard data. The reports of Marx and Memery, also from the United States, support this.[6,7]

The changing relative risk factor for anesthesiologists in malpractice insurance premiums provides different supportive evidence. The risk factor has dropped dramatically. Though many factors affect malpractice risk, changes of this magnitude would be unlikely without a substantial reduction in losses. The inflation-adjusted

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premium for Harvard Medical School insured anesthesiologists is approximately one-quarter of its rate in the mid-1980s (Personal communication between author J. Cooper and Robert Hanscom, Risk Management Foundation of the Harvard Medical Institutions, Cambridge, MA, August, 2002). That's not an order of magnitude, but it's a large change. Large claims are typically for major injury in relatively healthy patients; thus these data suggest that anesthesia care has become safer for that cohort.

Rather than the evolution of safety over time, consider the absolute risk of death related to anesthesia in the last 10–20 yr. Several studies indicate a very low mortality rate for ASA 1 and 2 patients. The quoted rate of one death per 200,000 anesthetics likely originated from Eichhorn's study of closed malpractice claims, which counted mostly healthy patients.[8] Two periods were studied, before and after the institution of monitoring standards. The rates of anesthesia mortality for ASA 1 and 2 patients was 5 in 757,000 (1/151,000) patients in the first period (1976– June, 1985) and 0/244,000 patients from July, 1985 through June, 1988. A recent study by Arbus *et al.* of 869,000 anesthetics in the Netherlands during 1995–1997, reported 7 deaths solely attributable to anesthesia, a rate of 1:124,000.[9] Yet another recent study, which appears to be comprehensive in its collection of perioperative adverse events in a Canadian hospital from 1996–2000, reports only 1 anesthesia contributory death in 84,000 patients, including patients in all ASA classifications.[10] Finally, in the two hospitals studied by Lagasse, there were no deaths solely attributable to anesthesia among approximately 184,000 patients of all ASA physical status. Anesthesia had a major contribution in only one of 126,000 ASA 1 and 2 patients.[2] As hazardous undertakings go, anesthesia's track record for healthy patients is indeed a model for health care. Carefully examining the Beecher-Todd study, we see that for "good risk patients" anesthesia was the primary or major contributing factor to death in approximately 4.1 per 10,000 surgical procedures between the years 1948 and 1952.[5] Compared with today's data, that is more than an "order of magnitude" improvement that many have suggested.

But, it's not good enough. The goal of the Anesthesia Patient Safety Foundation, expanding from that articulated by Macintosh[11] 50 yr ago, is that *no patient* shall be harmed by anesthesia.‡

Lagasse appropriately reminds us that anesthesia is not yet completely safe for ASA 1 and 2 patients (whose main risks may be iatrogenic) and less so for sicker patients. Anesthesia still contributes to serious adverse events and avoidable deaths.

Has anesthesia safety reached a plateau? Lagasse's data from hospitals in the 1990s contain too few patients for a definite conclusion, but such a plateau is possible. Negative outcomes related to anesthesia-care might end up being traded off against chances for successful surgical treatment of serious diseases. The low probability of anesthetic mortality for healthy patients may force safety goals to compete inappropriately against efficiency and cost considerations. Lagasse's paper emphasizes a need to improve anesthesia and system safety for all patients, including a growing cohort of ASA 3 and 4 patients.

The theory of organizational safety teaches that "safety" is a never-ending process whose success may not be measured strictly by epidemiologic methods.[12] The profession of anesthesiology itself is a model concerning patient safety *processes*.[13] Anesthesiologists have played important leadership roles in addressing organizational safety in all of health care. Anesthesiology was the first medical profession to treat patient safety as an independent problem. Anesthesiology has implemented widely accepted guidelines on basic monitoring, conducted long-term analyses of closed malpractice claims, addressed fatigue of residents serving in-house call, developed patient simulators as meaningful training tools, and tackled problems of human error. Most importantly the profession has institutionalized safety in its scientific and governing bodies, creating the ASA's Patient Safety and Risk Management Committee and the Anesthesia Patient Safety Foundation. Yet we should not be complacent, believing that we have won the war. Lagasse, in this review and in his prior work, has made valuable contributions to this effort. We all agree that the war must continue. Nonetheless, we believe there is no "myth" as to improvement in anesthesia patient safety. There are semantic disagreements, differences about what are the epochs being compared and little good data to be found. Anesthesiologists should remain aware of the hazards they still face, take pride in having been the leaders in patient safety efforts, and stay motivated to continue the pursuit of "no harm from anesthesia" with the passion it still demands.

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