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Physiologic Transfusion Triggers

Do We Have to Use (Our) Brain?

WE have all learned that 2,3-diphosphoglycerate (2,3-DPG) progressively decreases during storage of erythrocytes,[1] resulting in an increase of the affinity of hemoglobin for oxygen.[2] As a consequence, these erythrocytes seem to be less capable of releasing large amounts of oxygen to the tissue.[3] Therefore, it has been proposed to transfuse fresh rather than stored erythrocytes. For example, in a model of sepsis, only fresh (and not stored) erythrocytes could restore oxygen consumption.[4] Also, in septic patients with increased lactate levels, oxygen consumption did not increase after erythrocyte transfusions,[5] and gastric mucosal pH even decreased after the transfusion of erythrocytes older than 15 days.[5] Therefore, it is surprising that Weiskopf *et al.*[6] in this issue of ANESTHESIOLOGY found that transfusion of autologous erythrocytes stored for approximately 3 weeks is as efficacious as the transfusion of fresh (3–4 h) erythrocytes in reversing anemia induced cognitive dysfunction.

This finding is particularly surprising because the expected decrease in 2,3-DPG and the increase in the affinity of hemoglobin for oxygen was observed in the stored erythrocytes that reversed cognitive dysfunction.[6] Does this indicate that the retransfused stored erythrocytes had regained—at least partially—their 2,3-DPG levels at the time of testing? This is possible because Beutler and Wood[7] have shown that 1 h after transfusion, approximately 25–30% of prestorage 2,3-DPG was restored in donor erythrocytes. This does not necessarily mean that fresh and stored erythrocytes result in an equal increase of cerebral tissue oxygenation, which is the likely mechanism responsible for the reversal of the cognitive dysfunction after isovolemic hemodilution.[8–10] Perhaps the stored erythrocytes improved cerebral oxygenation sufficiently to reverse the cognitive dysfunction, whereas the fresh erythrocytes may have increased cerebral oxygenation to a greater extent. However, this did not translate into measurably better cognitive function. A more gradual increase of the hemoglobin concentration from 5 to 7 g/dl with intermittent neuropsychological testing might have resulted in a detectable difference in favor of fresh *versus* stored erythrocytes. In addition, it is important to note that the study subjects were healthy young volunteers. Storage changes of erythrocytes may have had less impact on tissue oxygenation in these individuals than in patients with underlying diseases such as sepsis or coronary artery disease. Last but not least, a recent study has challenged the common understanding that 2,3-DPG levels in stored erythrocytes are the key factor for oxygen off-loading capacity of transfused erythrocytes.[11] In this study, human erythrocytes stored for 2–3 weeks and containing almost no 2,3-DPG were equally efficacious in maintaining intestinal microvascular oxygen partial pressure as erythrocytes that were stored for 2–6 days. Only erythrocytes stored for 5–6 weeks were less efficacious.[11] Although undoubtedly there are differences between the oxygenation of the intestine and the brain, both studies indicate that 2,3-DPG levels of transfused erythrocytes may not play a major role with respect to their capacity for tissue oxygenation.

Apart from their contribution to the discussion of old *versus* fresh erythrocyte transfusions, Weiskopf *et al.*[8,9,12] have opened the "window to the brain" with respect to monitoring the adequacy of cerebral oxygenation during acute anemia. Monitoring the effect of acute anemia on the cerebral function is essential because most experts would agree that erythrocyte transfusions are indicated to "treat or prevent imminent inadequate tissue oxygenation."[13] Current monitoring assesses the heart for development of myocardial ischemia by electrocardiogram and transesophageal echocardiography. Also, the entire circulation can be evaluated by measuring mixed venous hemoglobin saturation in the presence of a pulmonary artery catheter and by calculating oxygen consumption using indirect calorimetry. With circulatory monitoring only, however, we have no direct access to the state of oxygenation and function of other organs. Monitoring the function of the brain in relation to the hemoglobin concentration is an important step toward physiologic transfusion triggers. However, cognitive testing with horizontal addition, digit symbol substitution, and memory tests[6,8,9,12] requires the cooperation of the patient and thus is unpractical during major operations or after trauma when patients normally are anesthetized. Anemia sensitive neurologic monitoring during general anesthesia is an area that requires further development,[10,12,14–16] *e.g.*, analysis of evoked potentials aimed at central processing may in the future enable on-line monitoring of the adequacy of cerebral oxygenation.

◆ This Editorial View accompanies the following article: Weiskopf RB, Feiner J, Hopf H, Lieberman J, Finlay HE, Quah C, Kramer JH, Bostrom A, Toy P: Fresh blood and age stored blood are equally efficacious in immediately reversing anemia-induced brain oxygenation deficits in humans. ANESTHESIOLOGY 2006; 104:911–20.

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The current study by Weiskopf *et al.*[6] is therefore remarkable for several reasons. First, it is challenging the evolving way of thinking, that fresh erythrocytes are universally better than old erythrocytes. Second, it adds weight to the hypothesis that the 2,3-DPG level may not be the key factor determining the oxygen off-loading capacity of transfused erythrocytes. Finally, in conjunction with previous studies,[8–10,12] it suggests that on-line monitoring of the functional adequacy of cerebral oxygenation in relation to the hemoglobin concentration during acute anemia may be a valuable tool. Importantly, this study has established a very sensitive human model to monitor the early functional signs of oxygen supply–demand mismatch of the brain. This test can further be used to evaluate therapies that presumably increase oxygen delivery and tissue oxygenation such as hyperoxic ventilation[9,10,17,18] and artificial oxygen carriers.[19]

After developing the capacity to monitor the functional adequacy of the oxygenation of the heart, the circulation, and the brain during acute anemia, physiologic transfusion triggers will progressively replace arbitrary hemoglobin based transfusion triggers. This will render allogeneic erythrocyte transfusions more efficacious because physicians will be capable of using goal-directed erythrocyte transfusions.

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Is There Value in Obtaining a Patient's Willingness to Pay for a Particular Anesthetic Intervention?

WHEN we were anesthesia residents in Palo Alto and New Haven two decades ago, patients on the morning of the surgery would often say, "I'm worried I won't wake up after the operation." Except for the sickest patients undergoing complex surgery, we do not hear these concerns anymore. The public now believes that anesthesia is extraordinarily safe from catastrophic outcomes, including major organ dysfunction and death. In 2006, many patients are concerned about pain and postoperative nausea or vomiting (PONV). This is especially true for the majority of patients undergoing less invasive surgery.

What is the value of interventions directed toward such transient outcomes? In this issue of ANESTHESIOLOGY, Kalkman *et al.*[1] add to the growing scientific literature supporting not only the patient's desire to avoid pain and PONV, but the monetary valuation of relief from pain and PONV. Their 808-patient study found that the

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median willingness to pay (out of pocket) for a pill that completely prevents pain after surgery amounted to $35 (interquartile range, 7–69), whereas patients were willing to pay $17 (interquartile range, 7–69) for a pill that completely prevents PONV.

Upon hearing such results, practitioners often ask, "How can those dollar numbers be useful? Willingness to pay will depend on the patient's wealth or income, and patients are rarely asked to pay for health care."

The goal of this editorial is to explain why willingness-to-pay studies are done. To some extent, the answer is straightforward: Economic evaluations such as the cost–utility analyses traditionally used to assess chronic care are not directly transferable to acute conditions such as pain and nausea because these typically only last for a few hours or days.

Our second goal is to challenge the specialty of anesthesiology to also emphasize the patient's desire to eliminate pain and PONV from clinical practice in the same way safety was emphasized during the past several decades.

Although the willingness-to-pay research methodology is conceptually simple and intuitive, it remains controversial. Its theoretical underpinning is from welfare economics, which aims to maximize social welfare by examining the economic activities of individuals, as opposed to communities or societies. This branch of economics assumes individuals are the best judges of their own welfare and are able to measure welfare adequately either in monetary terms or as a preference.

In a free market, shopping decisions are based on the commodity's price and the individual's reservation price, or the maximum perceived worth of that commodity. However, this does not occur in healthcare systems with third-party payors because patients are shielded from the true costs of care. With willingness to pay, benefits (including nonhealth attributes such as convenience) are valued in monetary terms so that outcomes are comparable across all interventions.

In general, willingness-to-pay data are useful in three settings:

1. Helping a company set the price for a new service or intervention (*e.g.*, drug or device) that is paid fully by the patient (*e.g.*, an over-the-counter medicine).
2. When a health system has decided to offer a new service or intervention but wants to charge the patient some amount of money to recover some of the costs. As an example, this was done in Tanzania to determine what rural populations were willing to pay for cataract surgery.[2]
3. Offer guidance in selecting which rival interventions are preferred by patients as criteria for payment (coverage) by the payor. For example, diabetic patients may prefer inhaled insulin over subcutaneous insulin.[3]

The willingness-to-pay values of $35 for analgesia and $17 for PONV relief reported in the study[1] are lower than those in previous studies performed in North America and may be related in part to income differences. The annual median household income for the Dutch patients studied was approximately $25,000. In contrast, 66 patients studied at Stanford in 2001, with incomes roughly twice as high, reported being willing to pay $110 to avoid pain and $100 for PONV relief. Also, the methodology used at Stanford was different, because these patients were asked how much money they were willing to pay to prevent an outcome that would hypothetically last for 6 h postoperatively.[4] Outcome descriptions were created using patients' own words.

As far back as 1992, Fred Orkin, M.D., published an abstract reporting that patients were willing to pay $15 out of pocket to avoid any immediate postanesthetic side effect and $50 to avoid emetic episodes. A separate study of 80 patients in North Carolina from 2001 determined $56 as the median willingness to pay to avoid PONV.[5] A Canadian study found that 86% of patients were willing to pay at least $50 and as much as $200 for patient-controlled analgesia after surgery.[6]

Certainly how you ask the questions (*e.g.*, having patients fill out a paper questionnaire in their living room while trying to think about pain *vs.* being interviewed at the bedside in the postanesthesia care unit while experiencing pain) or whether the issue is defined as prevention or treatment may affect the willingness-to-pay answers. So how should we interpret these dollar amounts? First, they support the importance of reducing the incidence of common but less serious side effects of surgery and anesthesia. A survey of 56 anesthesiologists around the United States revealed that the five items considered most important to patients were incisional pain, nausea, vomiting, preoperative anxiety, and discomfort from intravenous line insertion.[7] Patients concurred.[8]

Because burgeoning healthcare costs are straining budgets in all countries, there is pressure to define the value of interventions (*e.g.*, PONV prophylaxis, processed electroencephalographic signal monitoring, antiinfective-coated central venous catheters, continuous nerve blocks) by assessing their costs and benefits, including long-term health and complication risks. As anesthesiologists, we care for a wide spectrum of patients and procedures, from patients with complex medical conditions undergoing major cardiovascular procedures to healthy individuals undergoing routine surgery.

Economic analyses do not necessarily require that less money should be spent. Typically, an economic evaluation of a new medical intervention would take the form of a cost–utility analysis. A cost–utility analysis measures the incremental net cost of performing an intervention (expenditures for the intervention minus savings from future healthcare costs) and compares it with the marginal, or incremental, benefit obtained.

For such cost–utility studies, quality of life must be quantified, *i.e.*, converted into units that can be compared among different health conditions, which are typically chronic (*e.g.*, renal failure requiring dialysis, heart failure). Utilities are numerical ratings or "preference weights" of the desirability of health states that reflect a person's preferences, on a linear scale from 0.00 (death) to 1.00 (perfect health). Preference values for health states are commonly obtained using valuation techniques such as the standard gamble, the time trade-off, or the visual analog scale.

Quality-adjusted life years (QALYs) reflect both quality of life and duration of survival. QALYs are obtained by multiplying the utility value for a given health condition by its duration. For example, an additional year of survival for an individual in perfect health (with a utility of 1.0) is considered equivalent to a patient having two additional years but with a health state with a utility of 0.5. The QALYs equal 1 in both cases.

The incremental cost–utility ratio is equal to $(C_2 - C_1)/(QALY_2 - QALY_1)$, or incremental costs divided by incremental QALYs. The output of a cost–utility analysis is reported as $/QALY. Medical interventions are considered to be cost effective when they produce health benefits at a cost comparable to that of other commonly accepted treatments. Although no consensus has been reached, many commonly used interventions cost less than $50,000 per QALY gained. These are considered cost effective and should be performed. Those that cost $50,000–100,000 per QALY are questionable, and those above $100,000 per QALY are not considered cost effective. Prevention of a perioperative myocardial infarction, renal failure, or major infection may fall within this framework and be deemed cost effective. As anesthesiologists, we continue to study and implement new strategies to reduce these complications.

However, many anesthesia side effects are so short lasting that it is not possible for an intervention with transient effect to have an incremental cost–utility ratio smaller than the commonly accepted threshold of $50,000. An example follows to illustrate this important notion. Let us assume that the surgery health state without any anesthesia has a utility weight of 0.1 (on the 0–1 scale). If the surgery lasted an hour, the general anesthetic that allows the patient to be analgesic, amnestic, and unconscious (assume a utility to the patient of 1) would result in a utility gain of 0.9 (1 minus 0.1), multiplied by its duration in years (0.000114 yr = 1 h/8,760 h in a year), for a total QALY gain of 0.0001. That is, the QALY gain is the difference in QALY weight (1.0 *vs.* 0.1) multiplied by the number of years for which the health state is experienced.

Based on a threshold of $50,000, the maximum amount that the society should be willing to pay for an anesthetic for an hour-long surgery requiring general anesthesia should be $5. However, most people in the United States would readily place the value of an anesthetic to be much more than that, in part because patients perceive that major complications are averted. This example indicates that cost–utility methodology commonly used for chronic diseases can lead to less than optimal economic decisions for acute illness.

Because translating the value of healthcare benefits (*e.g.*, decreased pain and suffering) into monetary terms is tricky, the need arises for willingness-to-pay values. These then theoretically could feed into a cost–benefit analysis (a second, different type of economic assessment), which forces an explicit decision about whether the benefit is worth the cost.

Contingent valuation involves querying individuals directly regarding the *maximum* amount they are willing to pay to have the commodity in question or the *minimum* amount they would be willing to accept in compensation for being deprived of it. Willingness to pay is a primary tool that health economists have for valuing the effect of acute conditions on patients. Outside of anesthesia, and for purposes of illustration, patients reported a willingness to pay of $1,200 for benefits of ultrasound in an uncomplicated pregnancy (*e.g.*, reassurance of normal fetal anatomy and growth),[9] $100 per month for a new treatment of advanced non–small-cell lung cancer,[10] and $50 to avoid the minor side effects of intravenous contrast dye using nonionic agents.[11]

In most industries, the quality of the product is assessed by the customer, in our case the patient. The quality of medical decisions, patient satisfaction, and clinical outcomes can be improved by eliciting patient preferences. For example, the choice of an opiate to relieve postoperative pain may actually reduce the quality of the recovery period of a postoperative patient who considers nausea more objectionable than pain. In this patient, a less emetogenic, nonopioid analgesic may provide the patient with the postoperative outcome that he or she desires. For many patients undergoing outpatient surgery, it may also justify prescribing a new brand-name pharmaceutical that is more efficacious than the current standard, or convincing industry to develop new agents that the patient would be willing to pay for out of pocket.

In the same way the specialty of anesthesiology focused on developing drugs, devices, knowledge, and protocols to dramatically reduce catastrophic events related to anesthesia in the operating room, postanesthesia care unit, and intensive care units, anesthesiologists are now challenged to bring similar quality improvement efforts to pain and nausea, and practically eliminate those as well. Continuous peripheral nerve blocks reduce pain compared with opioids for certain surgeries,[12] but not all eligible patients get them. Why not? Multimodal PONV prevention based on *a priori* risk scores also reduce PONV.[13] But not all high-risk PONV patients get prophylaxis. The current article by Kalkman *et al.*[1] fur-

ther highlights the importance of pain and PONV treatment from the patient's perspective.

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Perspectives on the Genetic Basis of Opioid-induced Hyperalgesia

OPIOID analgesics represent one of the few classes of pharmacologic agents used to treat persistent pain conditions. In this issue of ANESTHESIOLOGY, Liang *et al.*[1] evaluated the pain-promoting effects of repeated doses of opioids in 15 strains of inbred mice. As noted by the authors, there is increasing recognition that acute and chronic opioid use can result in opioid-induced hyperalgesia (OIH), a syndrome characterized by increased sensitivity to noxious stimuli and increased clinical pain report. The clinical observation that only a subset of individuals is susceptible to this phenomenon strongly suggests a genetic influence. Furthermore, the observation that OIH is more common in patients with a history of opioid abuse suggests that OIH and opioid abuse may share common underlying genetic and neurobiologic mechanisms. The results of the current study are potentially of substantial clinical relevance because they directly illustrate the importance of β_2-adrenergic receptor (ADRB2) in mediating OIH.

The authors used newly developed *in silico* murine genetic approaches to provide evidence that ADRB2 stimulation induces a hyperalgesic state that contributes to OIH. They demonstrated that *in silico* genetic analyses, coupled with pharmacologic experiments, provide an extremely powerful approach for the dissection of genetic factors and biologic pathways that contribute to complex pain behaviors, traits, and phenotypes. The use and further development of these methodologies promise to accelerate our understanding of the underlying processes that contribute to pathologic pain states as well as the pharmacologic actions of opioids and other analgesics.

Although there is evidence that opioid receptor stimulation increases the expression of ADRB2s,[2,3] the identified functional role of *ADRB2*s in OIH is a novel and unexpected finding. Previous studies have identified brain and spinal cord facilitatory mechanisms in the genesis of OIH.[4–6] However, there is growing evidence that peripherally located ADRB2s contribute to both basal pain sensitivity and the development of persistent pain states. For example, Khasar *et al.*[7,8] provided substantial pharmacologic and behavioral evidence that the stimulation of peripheral ADRB2s produces a hyperalgesic state in rats. Diatchenko *et al.*[9] recently reported that the three major haplotypes of the human *ADRB2* are strongly associated with the risk of developing a common human chronic pain condition, temporomandibular joint disorder. Consistent with these observations, recent studies have shown that decreased activity of catechol-*O*-methyl transferase (an enzyme that regulates the bioavailability of the endogenous ADRB2 agonist epinephrine) is associated with enhanced sensitivity to pain and the risk of temporomandibular joint disorder.[10] Fur-

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thermore, reductions in catechol-*O*-methyl transferase activity enhance pain sensitivity in animal models *via* the activation of β-adrenergic receptors.[11] Therefore, the outcomes of the current study have identified a new mechanism whereby the ADRB2 contributes to heightened pain states.

The outcomes of this study also point the way to several future studies. Although the association between *ADRB2* haplotypes and OIH is clear, the specific biologic mechanisms that contribute to this association remain to be elucidated. In humans, the three common ADRB2 haplotypes differ with respect to signaling properties, expression, and agonist-induced internalization. [9,12, 13] Thus, the finding that ADRB2s mediate OIH in a strain- and haplotype-specific manner in mice suggests that the capacity of ADRB2s to mediate OIH in humans is also genotype specific. Therefore, human association studies that examine the relationship between genetic variants of ADRB2 and clinically observed OIH are required. It is also highly probable that other genes and associated proteins will have an equal or greater influence on OIH. The authors note that only a small fraction of murine genes have been optimally resolved. As the information in the murine and human genomic databases expands, it is highly likely that many more genes and biologic pathways will be identified that contribute to OIH and persistent pain states.

The current findings have important clinical implications, suggesting that ADRB2 antagonists will be effective in attenuating OIH and in treating a variety of other persistent pain conditions. Furthermore, the findings suggest that genotyping will prove useful in identifying (1) responders and nonresponders to opioid analgesics, (2) individuals at risk for developing persistent pain conditions, and (3) novel pharmacologic strategies for treating persistent pain conditions. We await the outcomes of studies that examine the clinical significance of these intriguing findings.

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