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Beyond the Hospital: Continuous Peripheral Nerve Blocks at Home

PROVIDING extended analgesia after painful surgery remains one of the main barriers to expanding the types of cases performed on an ambulatory basis. This fundamental obstacle also hampers the compassionate care we provide to many current outpatients because they suffer from inadequate analgesia. Chung *et al*. helped quantify failure of outpatient pain management and noted that after some orthopedic, urologic, and plastic surgeries, the incidence of severe pain postoperatively was between 40 and 70%.[1] Although the introduction of short-acting sedatives, anesthetics, and analgesics has improved the reliability of prompt emergence from anesthesia, postoperative pain and narcotic-related side effects, such as nausea and vomiting, remain major sources of patient dissatisfaction, lead to extended hospital stays, and hamper our ability to progress. Typical regional anesthetic techniques like spinal and epidural blockade that can be used intraoperatively provide little postoperative analgesia to aid recovery in the ambulatory patient. The use of outpatient peripheral nerve blocks is frequently criticized because of the intense pain that may ensue after resolution. As perioperative physicians we are challenged to develop a method of analgesia that is site specific, has few side effects, and can facilitate economic yet compassionate care. Continuous peripheral nerve blocks combined with a simple disposable infusion device that can be used at home may offer a novel solution to part of this problem. In initial nonrandomized reports and comparative trials it has provided excellent analgesia for numerous upper and lower extremity outpatient procedures.[2–6] In this issue of ANESTHESIOLOGY, Rawal *et al.*[7] and Ilfeld *et al.*[8] provide two prospective randomized studies designed to examine the effectiveness of ambulatory continuous peripheral nerve blocks. The results are compelling because both studies found a reduction in pain scores, low opioid consumption, high patient satisfaction, and few logistical obstacles when home continuous peripheral nerve blocks were implemented or compared with standard oral pharmacologic management of postoperative pain.

Continuous peripheral nerve catheters have been an integral part of acute and chronic pain management since first being described by Ansboro[9] in 1946. Over the ensuing half-century, numerous clinicians have developed techniques to facilitate catheter placement and manage inpatient treatment. These techniques have been gradually refined, enabling a small group of skilled clinicians to incorporate continuous peripheral nerve catheters into their practice with a high degree of success. Continuous peripheral nerve blocks have been associated with sustained, effective, postoperative analgesia[10–12]; opioid-sparing,[13–16] improved rehabilitation[17]; and improved patient well-being with minimal side effects. It is only natural that with the reevaluation of healthcare spending and the increased interest in expanding ambulatory surgery that this method would be tried on an outpatient basis. This is especially true given the economic success and low morbidity and mortality rates that have accompanied the transition of other hospital-based techniques to the ambulatory environment. Making this next transition successfully, on a larger scale, goes beyond the successful placement of individual catheters. It requires further data, improved training, and careful attention to the discharge and follow-up process.

Discharging patients with an insensate extremity and relying on the patient to self-administer local anesthetic remains controversial. Concerns about patient injury from an insensate extremity, catheter migration, and the potential for local anesthetic toxicity persist. Despite the encouraging results in these two randomized prospective trials, further data with larger patient samples will be necessary to confirm safety. In both studies in this issue, the investigators instituted several mechanisms to maximize patient safety that have been prevalent in the initial nonrandomized trials of home perineural infusions. Both Rawal *et al.*[7] and Ilfeld *et al.*[8] required study participants to display comprehension of the verbal and written instructions they were provided, and both teams required the presence of a chaperon. A common theme in several case reports is the careful attention paid to avoidance of inadvertent vascular catheter placement. This is typically done by injecting a large test dose of local anesthetic with epinephrine *via* the catheter before discharge to ensure the catheter tip is not misplaced. Perhaps more importantly, both groups used

◆ This Editorial View accompanies the following two articles: Rawal N, Allvin R, Axelsson K, Hallén J, Ekbäck G, Ohlsson T, Amilon A: Patient-controlled regional analgesia (PCRA) at home: Controlled comparison between bupivacaine and ropivacaine brachial plexus analgesia. ANESTHESIOLOGY 2002; 96: 1290–6; and Ilfeld BM, Morey TE, Enneking FK: Continuous infraclavicular brachial plexus block for postoperative pain control at home: A randomized, double-blinded, placebo-controlled study. ANESTHESIOLOGY 2002; 96:1297–1304.

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diluted concentrations of local anesthetic that have already been found to be safe in inpatients. These concentrations ideally should minimize motor block and provide a margin of safety if delivered intravascularly. This strategy is well articulated in the Rawal *et al.*[7] discussion. In addition, both teams provided an available physician to answer questions by telephone. The importance of this was emphasized by Ilfeld *et al.*[8] who reported that 30% of patients exercised this resource, despite being discharged with verbal and written instructions. Finally, daily telephone calls were placed to each patient to obtain data and to confirm safety.

While both sets of authors in this journal use different catheter insertion techniques, each with their individual advantages, both groups have developed expertise and a system that allows for effective economic use. Centers that do not have the capacity or the physicians to develop this infrastructure or expertise may not feel comfortable using peripheral nerve catheters or transitioning from inpatient catheter use to outpatient implementation. Clearly, competency must be gained first, and currently, these techniques are not widely taught. Large differences exist among training programs for effectiveness in teaching regional anesthesia. Most centers continue to provide adequate training in centroneuraxial techniques, but the majority still does not provide adequate training for peripheral nerve blocks, despite their increased use in outpatient surgery.[18] This was demonstrated by Kopacz and Neal[19] who documented that the median number of peripheral nerve blocks performed in residency is only 45, and most are associated with pain procedures and not operative anesthetics. This compares with epidural anesthesia, which relies on a similar complexity of equipment, takes similar organization to efficiently place, and relies on dexterity, but is performed 175 times (median) during residency.[19]

Given this disparity in teaching peripheral nerve blocks it is no wonder that some practitioners report intermittent success with continuous techniques and find them too time-consuming, while others achieve excellent results and continue to expand their use. As specialists, we should be wary of new claims and insist on data to ensure safety. But we must also be cautious not to discount new techniques that may greatly augment our treatment capability because they seem difficult or beyond our initial training. It is interesting to note that similar difficulties, resistance, and observations accompanied the transition of spinal anesthesia into mainstream acceptance and had to be rigorously defended by its pioneers. Sixty-eight years after the introduction of spinal anesthesia, Drs. Moore and Bridenbaugh at the Mason Clinic still had to defend the technique's efficacy and devote time to proving paralysis was unlikely.[20]

Although more research defining the limits for outpatient use of peripheral nerve catheters is necessary to fully characterize the indications, limitations, infusion rates, and delivery devices, the work of Rawal *et al.*[7] and Ilfeld *et al.*[8] demonstrates the potential for these techniques to become routine aspects of anesthesia care. But further training of both residents and established practitioners will be essential.

Continuous outpatient peripheral nerve catheters have the advantage of providing site- specific, dense, extended analgesia with systems and solutions that are readily available.[21] Developing this area of anesthesia is essential to increasing the scale and scope of surgery that is compassionately performed on an outpatient basis. It is also crucial to enhancing the quality of care for surgical procedures that are already considered appropriate for ambulatory centers. Given the anesthetic and economic success of ensuring rapid turnover and quick emergence in ambulatory surgery, refocusing perioperative attention beyond the hospital toward extended analgesia and broader economic concerns seems an appropriate path for our profession to follow. The authors of the studies in this issue should be commended, not only for their evidence demonstrating that continuous outpatient catheters are feasible, but also for looking beyond the operating room and scientifically exploring a technique that promises to improve the overall perioperative experience.

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References

1. Chung F, Mezei G: Adverse outcomes in ambulatory anesthesia. Can J Anaesth 1999; 46:R18–26

2. Rawal N, Axelsson K, Hylander J, Allvin R, Amilon A, Lidegran G, Hallen J: Postoperative patient-controlled local anesthetic administration at home. Anesth Analg 1997; 86:86–9

3. Klein SM, Greengrass RA, Gleason DH, Nunley JA, Steele SM: Major ambulatory surgery with continuous regional anesthesia and a disposable infusion pump. ANESTHESIOLOGY 1999; 91:563–5

4. Klein S, Grant S, Greengrass R, Nielsen K, Speer K, White W, Warner D, Steele S: Interscalene Brachial Plexus Block With a Continuous Catheter Insertion System and a Disposable Infusion Pump. Anesth Analg 2000; 91:563–5

5. Ganapathy S: Elastomeric pumps for ambulatory patient controlled regional analgesia. Can J Anesth 2000; 47:897–902

6. Chelly J, Gebhard R, Coupe K, Greger J, Khan A: Local anesthetic PCA via a femoral catheter for the postoperative pain control of an ACL performed as an outpatient procedure. Am J Anesthesiol 2001; 28:192–4

7. Rawal N, Allvin R, Axelsson K, Hallen J, Ekback G, Ohlsson T, Amilon A: Patient-controlled regional analgesia (PCRA) at home: Controlled comparison between bupivacaine and ropivacaine brachial plexus analgesia. ANESTHESIOLOGY 2002; 96:1290–6

8. Ilfeld B, Morey T, Enneking F: Continuous infraclavicula brachial plexus block for postoperative pain control at home: a randomized, double-blinded, placebo-controlled study. ANESTHESIOLOGY 2002; 96:1297–1304

9. Ansboro F: Method of continuous brachial plexus block. Am J Surgery 1946; 71:716–22

10. Selander D: Catheter technique in axillary plexus block. Acta Anaesth Scand 1977; 21:324–9

11. Tuominen M, Pitkanen M, Rosenberg P: Postoperative pain relief and bupivacaine plasma levels during continuous interscalene brachial plexus block. Acta Anaesthesiol Scand 1987; 31:276–8

12. Rosenblatt R, Pepitone-Rockwell F, McKillop M: Continuous axillary analgesia for traumatic hand injury. Anesthesiology 1979; 51:565–6

13. Dahl J, Christiansen C, Daugaard J, Schultz P, Carlsson P: Continuous blockade of the lumbar plexus after knee surgery-postoperative analgesia and bupivacaine plasma concentrations. A controlled clinical trial. Anaesthesia 1988; 43:1015–8

14. Singelyn F, Deyaert M, Joris D, Pendeville E, Gouverneur J: Effects of

intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous three-in-one block on postoperative pain and knee rehabilitation after unilateral total knee arthroplasty. Anesth Analg 1998; 87: 88–92

15. Borgeat A, Schappi B, Biasca N, Gerber C: Patient-controlled analagesia after major shoulder surgery: patient-controlled interscalene analgesia versus patient-controlled analgesia. ANESTHESIOLOGY 1997; 87:1343–47

16. Bolt S, Teiken P, Pitcher D, Johnstone F, Davis G: Use of a psoas compartment catheter and sciatic nerve block during femur reconstruction. Anesth Analg 1995; 80:S1-S581

17. Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F: Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. ANESTHESIOLOGY 1999; 91:8–15

18. Klein S, Pietrobon R, Nielsen K, Warner D, Greengrass R, Steele S: Peripheral nerve blockade with long-acting local anesthetics: a survey of the society for ambulatory anesthesia. Anesth Analg 2002; 94:71–6

19. Kopacz D, Neal J: Regional anesthesia and pain medicine: residency training-the year 2000. Reg Anesth Pain Med 2002; 27:9–14

20. Moore D, Bridenbaugh L: Spinal (Subarachnoid) Block. JAMA 1966; 195: 123–8

21. Grant S, Neilsen K: Continuous Peripheral Nerve Catheters for Ambulatory Anesthesia. Current Anesth Reports 2000; 2:304–7

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NO-body's Perfect

THE search for a selective pulmonary vasodilator that might improve, rather than worsen, arterial oxygenation has produced dozens of possible therapies and thousands of research reports. Over the past 10 yr, this search finally has been fruitful, and has brought several new therapies into clinical use. One such therapy is inhaled nitric oxide (iNO). In this issue, Stuart Lowson reviews some important alternatives to iNO therapy.[1] Nitric oxide is a lipophilic, endogenous, free radical molecule with biologic activity identical to endothelium-derived relaxing factor (EDRF). It acts as an important messenger throughout the body by increasing local concentrations of guanosine 3',5'-cyclic monophosphate (cGMP), by nitrosylation of proteins, and by interacting with many blood elements and cell types.[2] When inhaled, NO is delivered to areas of the lungs that are best ventilated, and, because it is rapidly bound to hemoglobin and inactivated in the circulation, can selectively vasodilate ventilated lung regions with increased vascular tone. It therefore can provide selective pulmonary vasodilation, improve arterial oxygenation, and through the NO-cGMP pathway and direct effects, modulate function within blood elements as well as at distant sites.[3–5]

Currently, substantiated indications for iNO include the treatment of hypoxic respiratory failure of the newborn (PPHN),[6–9] and the assessment of pulmonary vascular reactivity in patients with pulmonary hypertension.[10] To date, the U.S. Food and Drug Administration has approved nitric oxide only for the treatment of term and near-term (more than 34 weeks of gestational age) neonates with hypoxic respiratory failure associated with pulmonary hypertension. Inhaled NO clearly is effective for this indication and reduces the severity of subsequent lung disease and the necessity for extracorporeal membrane oxygenation in these infants. Off-label clinical use is widespread, and includes using inhaled NO to treat acute respiratory distress syndrome (ARDS); complications of lung and cardiac transplantation; pulmonary hypertension associated with congenital and acquired heart disease, as well as chronic pulmonary diseases; and to produce desirable direct effects on blood elements, specifically during the treatment of acute chest syndrome in sickle cell disease.[11]

Lowson describes several alternatives to inhaled NO, and focuses his review on inhaled prostacyclin (PGI_2). Why do we need additional drugs if we have nitric oxide? Expense is only one criterion for drug selection. Efficacy, safety, availability, and ease-of-use are other important considerations.

Efficacy of inhaled NO for its off-label uses has been difficult to demonstrate. Placebo-controlled trials of iNO to treat ARDS have been disappointing, demonstrating only transient improvements in oxygenation and no effect on outcome.[12,13] While in many patients inhaled NO provides selective pulmonary vasodilation, large multicenter trials examining the effect of inhaled NO therapy on clinical course and outcome of patients with diverse causes of pulmonary hypertension have not been performed.

Physiologically, it seems reasonable that a selective pulmonary vasodilator might be effective in treating ARDS. Reduced pulmonary capillary pressure should decrease the extent of pulmonary edema; should improve lung compliance; and might speed resolution of lung injury. Improved oxygenation should permit a reduction of the inspired oxygen concentration and airway pressure. But these effects may be insufficient to alter outcome. Usually, pulmonary artery pressure is only modestly elevated in ARDS. Even in severe cases, the mean pulmonary artery pressure is usually about 30 mmHg.[14] This degree of pulmonary hypertension is well tolerated, and few patients with ARDS die of their pulmonary hypertension. Rather, the survival of patients with ARDS appears to depend more on the occurrence of sepsis and multiple organ failure than on blood gas tensions or pulmonary artery pressure.[15–17]

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The effect of iNO varies among patients. Approximately one-third of patients fail to demonstrate improved oxygenation or decreased pulmonary artery pressure.[12,18] The cause of hyporesponsiveness remains under investigation. We cannot predict which patients may benefit and why pulmonary vasodilation does not occur in others.

Consequently, the search for ways of improving the efficacy of iNO and designing effective alternative therapies continues. Combinations of therapies have been developed that aim to improve the matching of ventilation-to-perfusion or increase the biologic activity of inhaled NO. Alternative therapies have been suggested that may provide equivalent pulmonary vasodilation. While such therapies are attractive, whether they will affect clinical outcome is unknown.

Ventilatory techniques that increase alveolar recruitment, such as the use of high-frequency oscillation in neonates,[7] or prone positioning of ARDS patients,[19] may improve the response to inhaled NO. Recruiting lung volume, by adding PEEP[20] or by the use of partial liquid ventilation with perfluorocarbons,[21] has been used to augment the response to iNO. The coadministration of vasoconstrictors, such as almitrine and norepinephrine, may enhance pulmonary vasoconstriction and accentuate the improvement in Pa_{O_2} observed during inhaled NO therapy, presumably by improving the matching of ventilation to perfusion.[22,23] Inhibition of the phosphodiesterase (PDE) enzymes that hydrolyze cGMP can also increase the efficacy and duration of action of iNO.[24,25]

Even if efficacy were improved, however, iNO therapy still has several drawbacks. It is expensive, cumbersome devices are necessary to administer the drug safely, and continuous administration is required. Especially for chronic treatment of pulmonary hypertension, therapies that are inexpensive, available in convenient forms (such as a tablet or simple multidose inhaler), and allow for intermittent dosing would be advantageous.

Does inhaled prostacyclin fulfill these goals? First, and probably most importantly, the efficacy of inhaled PGI_2 has been tested inadequately. Randomized, double-blind, multicenter trials that assess the effect of inhaled PGI_2 on clinical outcomes (*i.e.*, survival, severity, or duration of disease) have not been performed. It would be unwise to substitute an untested therapy for one that has been proved effective, such as the use of iNO for the treatment of PPHN. While it is an effective vasodilator, the biochemical effects of PGI_2 are quite different from those of NO. They affect different pathways and mechanisms. Whether PGI_2 can be used to treat the underlying disease state and modify the extent of cellular injury in diseases such as ARDS is unclear. Second, little is known of the toxicity of inhaled PGI_2. Long-term toxicity testing has yet to be performed in humans. Third, administration of inhaled PGI_2 is also cumbersome, requiring continuous administration *via* a gas-powered nebulizer.

So, our work is not yet done, and our search for the ideal molecule, or combination of molecules, continues. Areas of research include the use of inhaled Type V phosphodiesterase inhibitors, such as sildenafil,[25–27] administration of NO-donor compounds that can release predictable amounts of NO at specific rates,[28,29] and directly manipulating the genes controlling the NO-cGMP pathway.[30] These might be administered by intermittent inhalation, intravenous infusion, or even oral routes. We also may find other prostacyclin analogs that can be administered orally[31] or subcutaneously[32] to be effective.

When examining alternatives to iNO therapy, it is crucial to not lose sight of what is supported by evidence and what is suggested by anecdote. The pharmacologic and toxicologic profiles of these compounds remain incomplete. Clearly, selective pulmonary vasodilation can be life-saving, and this work must be continued. But while expensive and time-consuming, there can be no substitute for testing these new compounds in randomized placebo-controlled trials and in carefully defined disease states.

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References

1. Lowson SM: Inhaled alternatives to nitric oxide. ANESTHESIOLOGY 2002; 96: 1504–13
2. Ignarro L: Biological actions and properties of endothelium-derived nitric oxide formed and released from artery and vein. Circ Res 1989; 65:1–21
3. Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM: Inhaled nitric oxide for the adult respiratory distress syndrome. N Engl J Med 1993; 328:399–405
4. Adrie C, Bloch KD, Moreno PR, Hurford WE, Guerrero JL, Holt R, Zapol WM, Gold HK, Semigran MJ: Inhaled nitric oxide increases coronary artery patency after thrombolysis. Circulation 1996; 94:1919–26
5. Head CA, Brugnara C, Martinez-Ruiz R, Kacmarek RM, Bridges KR, Kuter D, Bloch KD, Zapol WM: Low concentrations of nitric oxide increase oxygen affinity of sickle erythrocytes in vitro and in vivo. J Clin Invest 1997; 100:1193–8
6. Clark RH, Kueser TJ, Walker MW, Southgate WM, Huckaby JL, Perez JA, Roy BJ, Keszler M, Kinsella JP: Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. Clinical Inhaled Nitric Oxide Research Group. N Engl J Med 2000; 342:469–74
7. Kinsella JP, Truog WE, Walsh WF, Goldberg RN, Bancalari E, Mayock DE, Redding GJ, deLemos RA, Sardesai S, McCurnin DC, Moreland SG, Cutter GR, Abman SH: Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. J Pediatr 1997; 131:55–62
8. Neonatal Inhaled Nitric Oxide Study Group: Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. The Neonatal Inhaled Nitric Oxide Study Group. N Engl J Med 1997; 336:597–604
9. Roberts JD, Jr, Fineman JR, Morin FC, 3rd, Shaul PW, Rimar S, Schreiber MD, Polin RA, Zwass MS, Zayek MM, Gross I, Heyman MA, Zapol WM: Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. N Engl J Med 1997; 336:605–10
10. Fishman AP, McGoon MD, Chazova IE, Fedullo PF, Kneussel M, Peacock AJ, Torbicki A: Diagnosis and assessment of pulmonary hypertension, Primary Pulmonary Hypertension: Executive Summary from the World Symposium. Edited by Rich S. World Health Organization, 1998. Available at http://www.who.int/ncd/cvd/pph.html. Accessed March 21, 2002.
11. Hurford WE, Steudel W, Zapol WM: Clinical therapy with inhaled nitric

oxide in respiratory diseases, Nitric Oxide Biology and Pathobiology. Edited by Ignarro LJ. San Diego, Academic Press, 2000, pp 931–45
12. Dellinger RP, Zimmerman JL, Taylor RW, Straube RC, Hauser DL, Criner GJ, Davis K, Hyers TM, Papadakos P, and the Inhaled Nitric Oxide in ARDS Study Group: Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Crit Care Med 1998; 26:15–23
13. Zimmerman JL, Taylor RW, Dellinger RP, Straube RC, et al.: A double-blind, randomized placebo controlled study of 5 ppm inhaled nitric oxide in acute respiratory distress syndrome (ARDS), Society of Critical Care Medicine. Orlando, Florida, 2000
14. Zapol WM, Snider MT: Pulmonary hypertension in severe acute respiratory failure. N Engl J Med 1977; 296:476–80
15. Montgomery AB, Stager MA, Carrico CJ, Hudson LD: Causes of mortality in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 1985; 132:485–9
16. Suchyta MR, Clemmer TP, Elliott CG, Orme JF, Jr, Weaver LK: The adult respiratory distress syndrome: A report of survival and modifying factors. Chest 1992; 101:1074–9
17. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000; 342:1301–8
18. Manktelow C, Bigatello LM, Hess D, Hurford WE: Physiologic determinants of the response to inhaled nitric oxide in patients with the acute respiratory distress syndrome. ANESTHESIOLOGY 1997; 87:297–307
19. Papazian L, Bregeon F, Gaillat F, Thirion X, Gainnier M, Gregoire R, Saux P, Gouin F, Jammes Y, Auffray JP: Respective and combined effects of prone position and inhaled nitric oxide in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 1998; 157:580–5
20. Johannigman JA, Davis K, Jr, Campbell RS, Luchette FA, Frame SB, Branson RD: Positive end-expiratory pressure and response to inhaled nitric oxide: changing nonresponders to responders. Surgery 2000; 127:390–4
21. Houmes RJ, Hartog A, Verbrugge SJ, Bohm S, Lachmann B: Combining partial liquid ventilation with nitric oxide to improve gas exchange in acute lung injury. Intensive Care Med 1997; 23:163–9
22. Payen DM, Gatecel C, Plaisance P: Almitrine effect on nitric oxide inhalation in adult respiratory distress syndrome. Lancet 1993; 341:1164
23. Papazian L, Bregeon F, Gaillat F, Kaphan E, Thirion X, Saux P, Badier M, Gregoire R, Gouin F, Jammes Y, Auffray JP: Does norepinephrine modify the effects of inhaled nitric oxide in septic patients with acute respiratory distress syndrome? ANESTHESIOLOGY 1998; 89:1089–98
24. Ichinose F, Adrie C, Hurford WE, Zapol WM: Prolonged pulmonary vasodilator action of inhaled nitric oxide by Zaprinast in awake lambs. J Appl Physiol 1995; 78:1288–95
25. Bigatello LM, Hess D, Dennehy KC, Medoff BD, Hurford WE: Sildenafil can increase the response to inhaled nitric oxide. ANESTHESIOLOGY 2000; 92:1827–9
26. Weimann J, Ullrich R, Hromi J, Fujino Y, Clark MW, Bloch KD, Zapol WM: Sildenafil is a pulmonary vasodilator in awake lambs with acute pulmonary hypertension. ANESTHESIOLOGY 2000; 92:1702–12
27. Ichinose F, Erana-Garcia J, Hromi J, Raveh Y, Jones R, Krim L, Clark MW, Winkler JD, Bloch KD, Zapol WM: Nebulized sildenafil is a selective pulmonary vasodilator in lambs with acute pulmonary hypertension. Crit Care Med 2001; 29:1000–5
28. Saavedra JE, Southan GJ, Davies KM, Lundell A, Markou C, Hanson SR, Adrie C, Hurford WE, Zapol WM, Keefer LK: Localizing antithrombotic and vasodilatory activity with a novel, ultrafast nitric oxide donor. J Med Chem 1996; 39:4361–5
29. Adrie C, Ichinose F, Holzmann A, Keefer L, Hurford WE, Zapol WM: Pulmonary vasodilation by nitric oxide gas and prodrug aerosols in acute pulmonary hypertension. J Appl Physiol 1998; 84:435–41
30. Ullrich R, Bloch KD, Ichinose F, Steudel W, Zapol WM: Hypoxic pulmonary blood flow redistribution and arterial oxygenation in endotoxin-challenged NOS2-deficient mice. J Clin Invest 1999; 104:1421–9
31. Nagaya N, Uematsu M, Okano Y, Satoh T, Kyotani S, Sakamaki F, Nakanishi N, Miyatake K, Kunieda T: Effect of orally active prostacyclin analogue on survival of outpatients with primary pulmonary hypertension. J Am Coll Cardiol 1999; 34:1188–92
32. Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, Keogh A, Oudiz R, Frost A, Blackburn SD, Crow JW, Rubin LJ: Continuous Subcutaneous Infusion of Treprostinil, a Prostacyclin Analogue, in Patients with Pulmonary Arterial Hypertension. A double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 2002; 165:800–4

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Intraoperative Use of Recombinant Activated Coagulation Factor VII

IN the current issue of ANESTHESIOLOGY, two case reports and a letter describe the perioperative use of recombinant activated coagulation factor VII (rFVIIa; NovoSeven®, NovoNordisk, Copenhagen).[1–3] The letter by Svartholm *et al*. reports that rFVIIa diminished intraoperative bleeding associated with severe necrotizing pancreatitis after standard therapeutic measures had failed[3]; the case report by Slappendel *et al*. reports that rFVIIa appears to have decreased postoperative bleeding after hip arthroplasty in a patient with alcohol-induced cirrhosis[2]; while Tobias appears to have used rFVIIa during dilutional coagulopathy.[1] These are not the first anecdotal reports of using rFVIIa to control bleeding for disorders for which rFVIIa is not approved; indeed, several others have been published. One such report details the dramatic cessation of bleeding in a victim of major trauma with apparently irremediable hemorrhage and coagulopathy, which had caused the clinicians to cease further attempts to achieve hemostasis.[4] Subsequent reports have described the successful treatment of patients who sustained severe trauma,[5] absence of blood loss from laparoscopic liver biopsy in patients with cirrhosis,[6] and reduction of blood loss in a swine model of liver trauma.[7]

Coagulation factor VII is an integral component of the coagulation system, and normally small amounts of the activated form (FVIIa) are present in the circulation.[8] Under the initiation and direction of Dr. Ulla Hedner,[9] rFVIIa was developed for the prevention of spontaneous bleeding episodes and for diminution of intraoperative blood loss for the 15–25% of patients with hemophilia

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who have inhibitors (antibodies) of clotting factors VIII or IX. The development of these inhibitors can occur as a consequence of therapy with replacement coagulation factors, or in patients with previously normal coagulation (acquired hemophilia). For these indications rFVIIa has been shown to be efficacious[10,11] and safe, and is now an approved and accepted therapy. The theoretical possibility of induction of systemic pathologic thrombosis could not be found in rabbits,[12] and has thus far not been a clinically important problem. The research and development of rFVIIa for its approved indication has expanded our knowledge about normal and abnormal coagulation paradigms. Progress in knowledge and therapy of coagulation disorders is planned to be the subject of a forthcoming article in the "Clinical Concepts and Commentary" section of ANESTHESIOLOGY.

Circulating FVIIa accounts for approximately 1% of circulating FVII,[8] and is enzymatically inactive until a complex with tissue factor (TF) is formed. Coagulation factor VII initiates hemostasis by combining with tissue factor (a membrane-bound glycoprotein expressed by subendothelial cells) at the site of injury, forming a TF–FVIIa complex at the local site. The complex activates other factors, which eventually results in limited thrombin generation, which activates platelets. Activated platelets are essential, together with factors II, IX, and X for the development of a full thrombin burst, which is necessary for the development of a stable, solid fibrin plug; one that is resistant to fibrinolysis. Therapy with doses of rFVIIa that achieve supraphysiologic concentrations saturate TF binding sites, provide for platelet activation and development of clinically significant thrombin production despite an absence of coagulation factors VIII or IX, or in the presence of antibodies to these factors.[13] Thrombin formation is impaired in thrombocytopenia and some types of platelet dysfunction.[14] rFVIIa increases thrombin generation in thrombocytopenia.[15] Thus, it is not surprising that there have been case reports of success in achieving hemostasis after administration of rFVIIa for thrombocytopenia,[16] thrombocytopenia refractory to platelet transfusion owing to antibodies to platelet antigens,[17] or in some states of platelet dysfunction.[18] Inasmuch as FVII is the first coagulation factor to decrease in hepatic dysfunction,[19] rFVIIa has been used in patients with cirrhosis, with normalization of prothrombin time.[20]

However, rFVIIa should not be regarded as the universal solution for disorders of coagulation; there are limitations to its rational use. Each dose of the protein is currently exceedingly expensive. The clearance of rFVIIa is approximately 30–35 $ml \cdot kg^{-1} \cdot h^{-1}$ in adults and greater in children,[21] requiring repeated dosing approximately every 2 h for maintenance of efficacy. Furthermore, availability of this recombinant protein is limited.

Although rFVIIa has been reportedly used to treat a wide variety of coagulation defects, it is important to note that its only clinically proven efficacy, by double-blinded, randomized clinical trials, has been for hemophilia. Trials of the use of rFVIIa for treating several clinical conditions are in progress. Indeed, a recent National Institutes of Health (NIH) request for applications (RFA) specifically expressed interest in clinical trials with rFVIIa. Efficacy for rFVIIa has not been demonstrated for patients without a preoperative coagulation disorder, in whom abnormal intraoperative bleeding develops, such as that resulting from a dilutional coagulopathy. Diagnosis of the specific defect, and therapy with specific coagulation factors, plasma, or platelets, remain the appropriate therapies for these patients. It would not be appropriate, at this time, to attempt to replace standard diagnostic measures and standard accepted therapy with use of rFVIIa. When these measures truly fail, it may be reasonable to use rFVIIa as an attempted "rescue" therapy. However, as with any new therapeutic agent, rational use should follow appropriate demonstration of efficacy and safety.

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References

1. Tobias JD: Synthetic factor VIIa to treat dilutional coagulopathy during posterior spinal fusion in two children. ANESTHESIOLOGY 2002; 96:1522–5

2. Slappendel R, Huvers FC, Benraad B, Novàkova I, van Hellemondt GG: Use of recombinant factor VIIa (NovoSeven®) to reduce postoperative bleeding after total hip arthroplasty in a patient with cirrhosis and thrombocytopenias. ANESTHESIOLOGY 2002; 96:1525–7

3. Svartholm E, Annerhagen V, Länne T: Treatment of bleeding in severe necrotizing pancreatitis with recombinant factor VIIa (letter). ANESTHESIOLOGY 2002; 96:1528

4. Kenet G, Walden R, Eldad A, Martinowitz U: Treatment of traumatic bleeding with recombinant factor VIIa (letter). Lancet 1999; 354:1879

5. Martinowitz U, Kenet G, Segal E, Luboshitz J, Lubetsky A, Ingerslev J, Lynn M: Recombinant activated factor VII for adjunctive hemorrhage control in trauma. J Trauma 2001; 51:431–8

6. Jeffers L, Bernstein DE, Erhardtsen E, Reddy KR, Glazer S, Squiban P, Bech R, Hedner U, Schiff ER: The use of recombinant factor VIIa in laparoscopy liver biopsy: A pilot trial (abstract). Gastroenterology 1998; 114:L0275

7. Martinowitz U, Holcomb JB, Pusateri AE, Stein M, Onaca N, Freidman M, Macaitis JM, Castel D, Hedner U, Hess JR: Intravenous rFVIIa administered for hemorrhage control in hypothermic coagulopathic swine with grade V liver injuries. J Trauma 2001; 50:721–9

8. Wildgoose P, Nemerson Y, Hansen LL, Nielsen FE, Glazer S, Hedner U: Measurement of basal levels of factor VIIa in hemophilia A and B patients. Blood 1992; 80:25–8

9. Hedner U: Recombinant coagulation factor VIIa: From the concept to clinical application in hemophilia treatment in 2000. Semin Thromb Hemost 2000; 26:363–6

10. Shapiro AD, Gilchrist GS, Hoots WK, Cooper HA, Gastineau DA: Prospective, randomised trial of two doses of rFVIIa (NovoSeven) in haemophilia patients with inhibitors undergoing surgery. Thromb Haemost 1998; 70:773–8

11. Key NS, Aledort LM, Beardsley D, Cooper HA, Davignon G, Ewenstein BM, Gilchist GS, Gill JC, Glader B, Hoots WK, Kisker CT, Lusher JM: Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (Novoseven) in haemophiliacs with inhibitors. Thromb Haemost 1998; 80:912–8

12. Diness V, Bregengaard C, Frhardtsen F, Hedner U: Recombinant human factor VIIa (rFVIIa) in a rabbit stasis model. Thromb Haemost 1992; 67:233–41

13. Monroe DM, Hoffman M, Oliver JA, Rogerts HR: Platelet activity of high-dose factor VIIa is independent of tissue factor. Br J Haematol 1997; 1997:542–7

14. Béguin S, Keularts I: On the coagulation of platelet-rich plasma. Haemostasis 1999; 29:50–7

15. Kjalke M, Ezban M, Monroe DM, Hoffman M, Roberts HR, Hedner U: High-dose factor VIIa increases initial thrombin generation and mediates faster platelet activation in the thrombocytopenia-like conditions in a cell-based model system. Br J Haematol 2001; 114:114–20

16. Kristensen J, Killander A, Hippe E, Hellegerg C, Ellegard J, Holm M, Kutti J, Mellqvist U, Johansson J, Glazer S, Hedner U: Clinical experience wtih recombinant factor VIIa in patients with thrombocytopenia. Haemostasis 1996; (suppl 1):26

17. Vidarsson B, Onundarson PT: Recombinant factor VIIa for bleeding in refractory thrombocytopenia (letter). Thromb Haemost 2000; 83:634–635

18. Tengborn L, Petruson B: A patient with Glanzmann thrombastenia and epistaxis successfully treated with recombinant factor VIIa. Thromb Haemost 1996; 75:981–2

19. Manzano ML, Arocena D, Tomás JA, Hedner U, Quiroga JA, Carreno V: Measurement of the procoagulant activity of factor VII in patients with liver cirrhosis and normal prothrombin activity: evaluation of the bleeding risk, Blood Coagul Fibrinolysis 2000;11(suppl 1):S95–9

20. Bernstein DE, Jeffers L, Erhardtsen E, Reddy KR, Glazer S, Squiban P, Bech R, Hedner U, Schiff ER: Recombinant factor VIIa corrects prothrombin time in cirrhotic patients: a preliminary study. Gastroenterology 1997; 113:1930–7

21. Erhardtsen E: Pharmacokinetics of recombinant activated factor VII (rFVIIa). Semin Thromb Hemost 2000; 26:385–91