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Discovering Pain in Newborn Infants

Kanwaljeet J. S. Anand, M.B.B.S., D.Phil.

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Until the 1980s, it was widely believed that newborn babies do not perceive pain. This was a remnant from decades ago, when Myrtle B. McGraw, Ph.D., had reported that neonatal responses to pin pricks were absent or inconsistent,[1] anesthesiologists had noted that anesthetic complications occurred more frequently in infants,[2] and reliable monitors, vaporizers, or infusion pumps were not available.

Kanwaljeet J. S. Anand, M.B.B.S., D.Phil., F.A.A.P., F.C.C.M., F.R.C.P.C.H.

Randomised Trial of Fentanyl Anesthesia in Preterm Babies Undergoing Surgery: Effects on the Stress Response. By Anand KJ, Sippell WG, and Aynsley-Green A. Lancet 1987; 1:243–8. Reprinted with permission.

Abstract: In a randomised controlled trial, preterm babies undergoing ligation of a patent ductus arteriosus were given nitrous oxide and D-tubocurarine, with (n = 8) or without (n = 8) the addition of fentanyl (10 μg/kg intravenously) to the anesthetic regimen. Major hormonal responses to surgery, as indicated by changes in plasma adrenaline, noradrenaline, glucagon, aldosterone, corticosterone, 11-deoxycorticosterone, and 11-deoxycortisol levels, in the insulin/glucagon molar ratio, and in blood glucose, lactate, and pyruvate concentrations were significantly greater in the nonfentanyl than in the fentanyl group. The urinary 3-methylhistidine/creatinine ratios were significantly greater in the nonfentanyl group on the second and third postoperative days. Compared with the fentanyl group, the nonfentanyl group had circulatory and metabolic complications postoperatively. The findings indicate that preterm babies mount a substantial stress response to surgery under anesthesia with nitrous oxide and curare and that prevention of this response by fentanyl anesthesia may be associated with an improved postoperative outcome.

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To compromise, surgery was often performed on paralyzed, unanesthetized infants,[3–5] although the Liverpool technique (nitrous oxide and curare) promoted by Gordon Jackson Rees, F.F.A.R.C.S., in the 1950s[6] was used more commonly.[7] This was state-of-the-art neonatal anesthesia at the John Radcliffe Hospital (Oxford, United Kingdom) when I arrived there in October 1982 (Supplemental Digital Content, http://links.lww.com/ALN/B962).

Inspired by the work of David P. Cuthbertson, C.B.E., F.R.S.E., Frederick A. Moore, M.D., F.A.C.S., M.C.C.M., Kurt George M.M.Alberti, F.R.C.P., F.R.C.P.E., F.R.C.Path., F.K.C., and guided by my mentor Albert Aynsley-Green, K.T., M.R.C.S., F.R.C.P., F.R.C.P.E., F.R.C.P.C.H., F.Med. Sci., F.R.S.A. (fig. 1), our initial studies focused on documenting the hormonal–metabolic stress responses of term and preterm neonates undergoing surgery.[8,9] Stress hormones triggered severe catabolism particularly in preterm neonates, which led to a search for defining its impact on clinical outcomes. We performed among the first meta-analyses in pediatrics[10] and found high postoperative mortality rates in preterm neonates undergoing surgical ligation of a patent ductus arteriosus. These aggregate data also suggested a trend toward improving outcomes with greater use of patent anesthesia.[10]

We hypothesized that anesthetic approaches providing deeper anesthesia than the Liverpool technique may

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Fig. 1. Dr. Anand (*left*) with his mentor, Sir Albert Aynsley-Green (*right*), *circa* 1985.

reduce the surgical stress responses of preterm neonates, but how could we prove it? Two unexpected encounters occurred at this point to influence our thinking. First, while riding a bus to central Oxford, the person sitting next to me enquired about my research and encouraged me to meet with Richard Peto, F.R.S., to learn about clinical trial design. Another serendipitous meeting occurred after a surprise visit by Harvard University Professor Edward Lowenstein, M.D. As we walked the grounds of Blenheim Palace together, Ed heard my story and suggested fentanyl as the best anesthetic option for preterm babies undergoing patent ductus arteriosus ligation.[11] He was later instrumental in attracting me to Harvard Medical School for a postdoctoral fellowship and has remained a lifelong friend. Were it not for these two chance encounters, as well as my mentor's unreserved support, we could not have designed this blinded, randomized, placebo-controlled trial of fentanyl anesthesia in preterm neonates.[12]

Implementing a randomized clinical trial was itself a challenge, but convincing the 56 British anesthetists from the Oxford University Nuffield Department of Anaesthetics to abandon their decades-old routine clinical practice and follow the study protocol dictated by a turbaned *Indian* house officer (one with no previous training in anesthesia) was a bigger challenge! Few preterm neonates required patent ductus arteriosus ligation, some were ineligible based on our study criteria, and some were deemed "too sick to be randomized" by their attending anesthetists. My clinical colleagues and I were familiar with the processes for implementing a blinded randomized trial, although a seminar and personal advice from William Silverman, M.D., helped to overcome most of the initial difficulties.[13] To obtain consent, complete study data forms; personally collect the precious neonatal blood samples before and after surgery and at 6, 12, and 24 h postoperatively for this trial (and having another randomized trial ongoing at the time[14]); and then assay all hormones and metabolites myself (while also continuing my clinical duties) taught me that sustained effort is the secret sauce of success.

Results of this randomized trial showed major differences in the hormonal–metabolic stress responses between the two randomized groups (fig. 2), coupled with a trend toward relatively fewer postoperative complications in the fentanyl anesthesia group (table 1).[12] Our study design did not include recording vital signs or arterial blood gases during anesthesia and surgery or recording their severity of illness before surgery; these deficiencies were identified later. Despite such obvious deficiencies, this study received the Dr. Michael Blacow Award for the best paper presented at the 58th Annual Meeting of the British Paediatric Association (1986), and it was published twice by *The Lancet* (January 10 and 31, 1987).

The mothers of two premature babies, Helen Harrison in California and Jill Lawson in Washington, D.C., had already questioned the medical practices denying or discounting pain in premature newborns.[4,15] Later that year, *Redbook* magazine reported that this study was an "experiment" to test whether premature babies react to pain. A popular British tabloid, *The Daily Mail* took this up and made it front-page news. The ensuing media storm, together with a press release from the British Parliamentary Pro-Life Group[16] and an official investigation by the United Kingdom General Medical Council ensured that

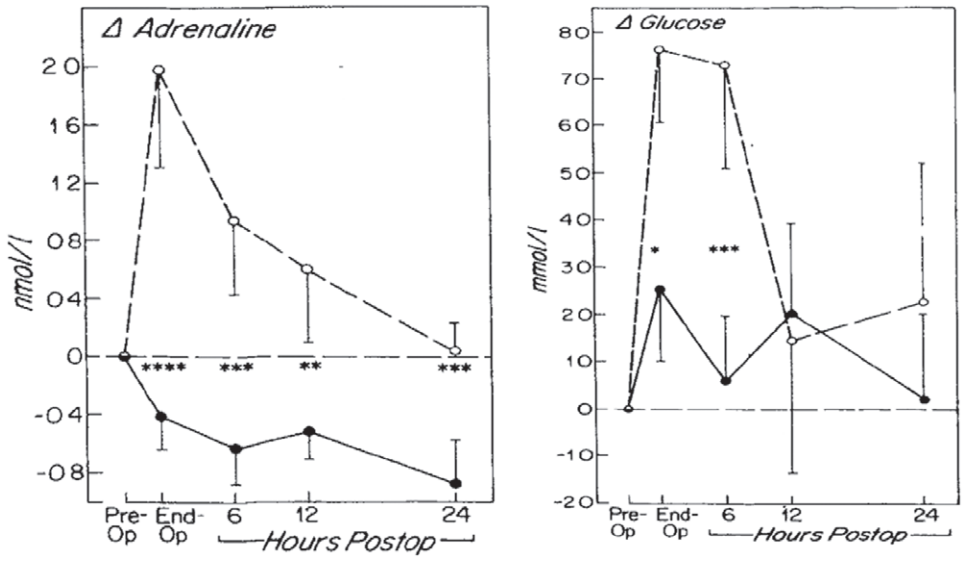

Fig. 2. Comparison of perioperative changes in the plasma adrenaline and blood glucose concentrations between the fentanyl (*solid line*, n = 8) and nonfentanyl (*dashed line*, n = 8) anesthesia groups. Modified and reprinted with permission from Anand KJ, Sippell WG, Aynsley-Green A: Randomised Trial of Fentanyl Anesthesia in Preterm Babies Undergoing Surgery: Effects on the Stress Response. Lancet 1987; 1:243–8.

Table 1. Clinical Complications during the Postoperative Period in the Fentanyl and Nonfentanyl Groups

	Fentanyl (n = 8)	Nonfentanyl (n = 8)
Increased ventilation requirements	1	4
Frequent attacks of spontaneous bradycardia	1	4
Hypotension	0	2
Poor peripheral circulation	0	2
Glycosuria	0	1
Metabolic acidosis	0	2
Intraventricular hemorrhage	0	2
Temperature variability	6	0

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most practitioners had heard about this research. Forfar and Campbell[17] captured this whole story in brief narrative, and leading pediatric anesthesiologists added their support.[18–21]

David Hatch, M.B.B.S., F.F.A.R.C., reviewed the recent research on pain and nociception in neonates and questioned the options available for neonatal analgesia.[18] Frederick A. Berry, M.D., and George A. Gregory, M.D., refuted the rationale for avoiding anesthesia in neonates and presented evidence for using volatile (halothane, isoflurane) and intravenous (opioid) anesthetics safely in all neonates.[19] Peter D. Booker, M.B.B.S., M.D., F.R.C.A., reported the proceedings of an earlier workshop where I had presented these data and helped develop a rationale justifying postoperative analgesia in neonates.[20] Myron Yaster, M.D., summarized the recent data on using intravenous fentanyl or local anesthetics (infiltration or nerve blocks) for surgical procedures in neonates.[21]

Interactions with such established figures in this field fueled my intense curiosity to learn more about the developing pain system in the human fetus and neonate. These efforts, then guided by my postdoctoral mentor Paul R. Hickey, M.D., ultimately led to a scientific framework for pain perception in the newborn.[22] We were not the first to propose such a rationale[23,24] but, because of the ongoing research of many others at that time, could present a more persuasive argument for pain perception in human newborns.[22] With the intense research activities in this area, as well as the public controversy related to neonatal pain, this appeared to become the zeitgeist of the late 1980s, propelling our novel synthesis to much greater heights than we had ever expected.[25] It is most humbling to watch the multiple lines of investigation that have emanated over more than 30 yr, just from a small randomized trial that included only 16 preterm neonates.

Correspondence

Address correspondence to Dr. Anand: Stanford University School of Medicine, Stanford, California 94304. anandam@stanford.edu. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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