

Pain control in neonates

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An infant is, quite naturally, one who is unable to speak (Latin: in = not +fans, speaking, from fari, to speak).'

Most parents have little difficulty in recognising their newborn infant's cry of pain. But there has been a prolonged debate among doctors about the reliability and importance of this signal. The debate has reflected discordant medical attitudes about pain and suffering that surfaced in the mid-1800s when the vapours of sulphuric or diethyl ether, nitrous oxide, and chloroform were found to abolish the pain of surgery.

Martin Pernick has reviewed the introduction and spread of the use of the first anaesthetic agents in America; he found, surprisingly, a selective pattern of application. 'Many, if not most mid-nineteenth-century practitioners anaesthetised some of their patients and not others: 'The issue for them: Pernick noted, 'was not whether to use anaesthetics, but when and on whom.' Medical textbooks of the time taught that doctors should 'consider a patient's sex, race, age, ethnicity, economic class, personal habits, and temperament ... before using anaesthetic agents.' For example, Pernick cited the opinion of Henry Bigelow, who published the first article on the use of anaesthesia in 1848: 'The new technique is unnecessary for infants, because they lack the anticipation and remembrance of suffering.' In 1852, Doctor Abiel Pierson of Massachusetts observed that infants could sleep 'insensibly' even while undergoing surgery. Pierson and others who believed in infant insensibility were convinced that the ability to experience pain was related to intelligence, memory and rationality. 'Like lower species: the doctors held, 'babies lack the mental capacity to suffer.' Pernick reported that in an operation performed in 1854, Samuel Cabot Jr., a colleague of Bigelow, wrote, 'the child patient was rolled firmly in a sheet, as a substitute for ether.'

Others believed that the 'constitutions' of small children were such that 'the nervous power is ... easily affected by stimuli: and that babies were extremely sensitive to pain. Pernick noted that some surgeons, notably Samuel D. Gross and Eliza L.S. Thomas of the Women's College of Pennsylvania in the 1850s, favoured the use of anaesthesia for infant patients. 'The young,' Doctor Thomas wrote, 'are innocents, unconscious of the motive for the surgery, and they should be 'saved from suffering.'

A modern debate about the need for anaesthesia in very young babies undergoing surgical procedures erupted in 1986 with the publication of a letter in the US from a mother charging mistreatment of her premature infant. Thoracotomy and patent ductus ligation had been performed without anaesthesia, the mother asserted; only oxygen and paralysing agents were administered during the 1 1/2 hour surgical procedure. Pain relief had been withheld, the mother was told, because 'it had never been demonstrated that babies can feel pain.' In answer to her complaint, an official of the American Medical Association wrote, 'Giving a premature infant the best chance to live is the primary medical objective; freedom from temporary pain is important, but it must be a secondary medical consideration.' These public arguments had the laudable effect of revealing that the practice of giving little or no analgesic and anaesthetic drugs to young babies undergoing surgery was very common in the US. According to the conventional wisdom, the risks of pain-relieving medications were 'greatly multiplied' in infants-especially so in very small neonates.

A similar dispute exploded in Britain in 1987, following publication of an article by Anand and co-workers.⁵ The paper had been awarded a prize the previous year as the best presentation by a young paediatrician at the annual scientific meeting of the British Paediatric Association. The prize-winning study, carried out in Oxford, was a small randomised trial (n = 16) of conventional anaesthesia (nitrous oxide and curare) compared with a new regimen (conventional anaesthesia plus intravenous fentanyl-a narcotic analgesic drug) for preterm infants undergoing ligation of a patent ductus. The researchers reported an important blunting of detrimental hormonal and catabolic responses to surgery in 8 infants who were operated on under the new anaesthetic regimen. And, Anand's group postulated, 'prevention of the massive stress response of preterm infants may lead to an improvement in their clinical outcome following surgery.'

The BPA6 and other admirers of this ethically-sound, rigorously designed, and very important challenge of a previously untested conventional practice, were astonished by loud charges of 'inhumane treatment' that followed publication of the article. The disapproval was voiced in letters to the editor (How [could] an ethics committee approve [such] a study.... ?), in newspapers (Pain-killer shock in babies operations'), and in a press release signed by 14 MPs (Inhumane baby operations slammed'). Although the furor was distressing to the investigators, the complaints served a very useful purpose by calling public attention to the fact that long-accepted anaesthetic practices for small neonates must be questioned in considerable detail. (In a survey of British paediatric anaesthesiologists, 80% stated that they believed neonates were capable of feeling pain, and yet 48% never used narcotic analgesics and a further 41% seldom did so.) The 1987 uproar also provided an unequalled opportunity to instruct members of Parliament about the propriety and validity of the modern randomised clinical trial format. Sir John Walton, president of the General Medical Council, replied to the Parliamentary group's charge that the study in question had been 'barbarous:' 'I am persuaded after careful examination of the evidence before me that your concern is based upon certain serious misconceptions and a consequential failure to understand the true purpose and nature of this project and the treatment by anaesthesia, which it involved.' After a detailed rebuttal of each of the claims of impropriety, Sir John concluded, in unequivocal support of parallel-comparison studies of untested interventions, 'In my view, it would have been much more unethical for fentanyl to have been introduced without being submitted to the test of [a] randomised clinical trial.' On 17 September 1988, a public apology to the researchers was issued by a member of Parliament speaking for the Pro-Life critics. 'It is now

clear to me: the spokesman stated, 'that the [trial] I criticised, far from being barbarous and unnecessary, [has] in fact been a valuable contribution to more humane treatment of preterm infants.'

The confidence in the serious intentions of the researchers and in the practical importance of the studies, expressed by supporters and, in the end, critics of the anaesthesia trial, has now been amply rewarded. Anand, now working with American co-workers in Boston, has reported the results of further studies of the dangerous responses of neonates triggered by major surgical operations. He and his associates have demonstrated that the hormonal and catabolic stress reactions of babies under-going surgical procedures is substantially greater than those of adult surgical patients. And they have now completed a new randomised trial comparing the stress responses under two anaesthetic-analgesic protocols, of 45 critically ill neonates undergoing surgical repair of cardiac defects that required the use of cardiopulmonary by-pass and hypothermic circulatory arrest. The two contrasting regimens of pain control were relatively light anaesthesia -analgesia (the conventionally-treated group received the usual doses of halothane and morphine) versus deep anaesthesia- analgesia (the experimental group received high doses of sufentanil [a potent opioid drug] and morphine). The very large hormonal-metabolic stress responses to cardiac surgery measured in the patients assigned to the light anaesthesia-analgesia regimen, were substantially reduced in the babies allotted to receive deep opiate anaesthesia- analgesia. Although pre-trial calculation of sample-size-needed was based on predicted difference in hormone and metabolic variables, the observed difference in clinical outcome (increased number of postoperative complications and number of deaths among infants assigned to the light anaesthesia- analgesia group) suggests that relatively deep levels of anaesthesia and analgesia may be required to improve postoperative outcome in critically ill neonates.

These disturbing findings confirm the darkest fears of many parents and nurses. The results cry out for additional observational and experimental studies by others to determine the extent to which the Oxford and Boston results can be generalised -particularly as they relate to the control of pain in all of the life-prolonging procedures carried out in neonatal intensive care. Anand and his co-workers, and now-Quinn et al, have let the genie out of the bottle: the issue of unrelieved pain and suffering in neonates can no longer be 're-bottled' and labelled 'a secondary medical consideration.'

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Quinn and co-workers (above) found that premature infants requiring ventilation and allotted to receive morphine by continuous drip, experienced reduced concentrations of adrenaline during the first 24 hours of treatment (as compared with an increase of adrenaline and noradrenaline among placebo-treated randomised controls). The observation that catecholamine concentrations were initially high and then fell in infants receiving opiate treatment, suggested to the authors that excessive stress, and perhaps pain, experienced by these infants, had been ameliorated by treatment. But no other differences in important outcomes were observed between the two groups in this trial; moreover, clinical signs of pain were similar in treated infants and in concurrent controls. Although the authors acknowledged that their findings did not make a strong case for routine use of morphine infusions in neonates undergoing ventilation, they concluded, as no significant adverse effects were found, 'it is humane to use a morphine infusion in babies who have to undergo ventilation for longer than 24 h.'

Wolf pointed out other studies in infants and in adults, which demonstrated that 'stress responses are not directly linked to pain, and [therefore] stress hormones cannot be used as an indicator of adequate analgesia.' 'Limiting the stress response seems sensible: he acknowledged, 'but the benefit in terms of outcome is difficult to prove: Although opioids appear to be 'remarkably safe in critically ill babies,' he continued, 'tolerance develops rapidly.' 'Treatment of babies with large effective doses [of opiates] at times of major stress may therefore be more appropriate,' Wolf advised, 'than continuous infusions as long-term sedatives....'

More trials are needed to settle the opiate -for-ventilated-neonates debate, nonetheless, the dramatic increase in awareness of the need for pain control in all neonates, indeed in all children, is both remarkable and heart-warming. A recent example of this modern avowal is seen in a survey of the use of opioid analgesia in one neonatal intensive care unit. when life support in critically-ill neonates was withdrawn or withheld. Despite the potential of respiratory depression, the authors reported, neonatologists used these agents to relieve suffering in most of the dying infants (101 of 120 = 84%). Another example of the new sensitivity is found in a randomised trial testing the efficacy and safety of an analgesic cream used to control the pain of circumcision. Similarly, 'pain services' have been established in some paediatric departments. One such multidisciplinary group was formed to review the impediments to adequate pain management in childhood (dubbed 'The Ouchless Place'). The committee developed protocols for management of postoperative pain, uniform pain assessment, and for the blunting of pain in all needle procedures. The continued oversight, the authors pledge, will 'dramatically decrease the burden that illness imposes on hospitalised children and their families....'

The importance of these humane and long overdue advances cannot be overemphasised.