

I am supported by grants from the National Institute of Health (K08 HL097029, R01 HL113264) and the Alpha-1 Foundation. I declare no other competing interests. The content is solely my responsibility and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health. I thank Edwin K Silverman, Peter J Castaldi, and Craig P Hersh for their helpful comments.

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Negotiating the dilemma of anaesthesia and sedation in NICUs



Anaesthetics kill neurons in the brains of neonatal animals, including non-human primates, and cause permanent and progressive neurocognitive deficits.¹ The results of translational studies in people have raised concerns that the findings in animals might be true for human infants as well—ie, anaesthetic exposure during a susceptible period of development can lead to neuronal cell death and, more importantly, neurocognitive decline.² However, as Ricardo Carbajal and colleagues,³ the investigators of the EUROPAIN study, note in *The Lancet Respiratory Medicine*, there is also compelling evidence that untreated neonatal pain leads to poor cognition and motor function, impaired brain development, and altered pain responses.⁴ Negotiating this dilemma is becoming an increasing challenge for clinicians. As one of the investigators of the EUROPAIN study previously described, “the acute and long-term effects of unrelieved pain or surgical stress, justify the continued clinical use of potent anaesthesia for neonates and infants...until further empirical evidence becomes available.”⁵

With their large and thorough study, the EUROPAIN group provide some of this valuable, needed evidence by describing the current bedside use of sedation and analgesia and associated factors in 6680 newborn babies in neonatal intensive care units (NICUs) from 18 European countries. 1746 (82%), 266 (18%), and 282 (9%) neonates in the tracheal ventilation (TV), non-invasive ventilation (NIV), and spontaneous ventilation (SV) groups, respectively, were given sedation or analgesia as a continuous infusion, intermittent doses,

or both ($p < 0.0001$). A clear understanding of how sedatives and analgesics are being used in neonates is crucial to understanding how, or if, to change the way these drugs are given.

The use of anaesthetics in children is under close scrutiny. Organisations like the American Academy of Pediatrics and American Society of Anesthesiologists are urging physicians to disclose the possible neurological risks of these drugs to parents and suggest caution when considering elective surgery in children younger than 3 years.^{2,6} Perhaps not surprising is that consciousness-altering drugs that render people in an insensate state could have neurotoxic side-effects. The effects of maternal exposure to narcotics, alcohol, and other consciousness-altering medications on the developing fetus are already well established.⁷ Research on fetal alcohol syndrome, a known and permanent neurotoxic exposure, was the genesis behind investigation of the potential neurotoxicity of anaesthetics and sedatives.⁶ The results of a landmark study in 2000 showed that administration of ethanol (a known N-methyl-D-aspartate [NMDA]-receptor antagonist and γ -aminobutyric-acid [GABA]-receptor agonist) to rodent pups resulted in neuroapoptosis.⁸ Because most anaesthetics are thought to work through NMDA-receptor and GABA-receptor mechanisms, follow-up studies were done with established anaesthetics. Neurodegeneration was noted after anaesthetic exposures.¹ In 2003, Jevtovic-Todorovic and colleagues⁹ presented their sentinel findings of developmental implications, showing that a combined



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Published Online
September 24, 2015
[http://dx.doi.org/10.1016/S2213-2600\(15\)00368-9](http://dx.doi.org/10.1016/S2213-2600(15)00368-9)
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anaesthetic (midazolam, nitrous oxide, and isoflurane) administered to 7-day-old rats for 6 h kills neurons in the developing brain and causes long-term impairment of brain function.⁹ The cellular findings have been subsequently reproduced in every animal species tested, including primates.¹⁰

Attempts to duplicate these findings in studies in human beings have been limited by ethical concerns about prospective randomised study designs, difficulty translating doses and periods of neurodevelopmental susceptibility from animal species to human beings, and the obvious feasible confounders (prolonged hospital admission and serious illness) that could cause the cognitive deficits rather than the drugs. Separation of the potential effects of anaesthesia, sedation, and narcotics from factors such as the physiological and psychological stresses of surgery or prolonged intensive care, which can also affect a child's development, is difficult.⁶ None of the studies, alone or in combination, form a basis for informing clinical practice. Whether a safe anaesthetic, narcotic, or sedative exists is unclear.^{2,6}

As a consequence, clinicians face a problem. Neonates are sentient, capable of feeling pain. Treating their pain is an ethical obligation and part of providing humane, compassionate care.¹¹ However, particularly with concerns being raised about anaesthetics, sedatives, and narcotics, no guidelines exist for prolonged sedation, anaesthesia, and analgesia in the NICU (possibly explaining some of the practice variation noted in the EUROPAIN findings, for example, sufentanil was mostly used in France and Poland and Cyprus provided continuous sedation in all tracheally ventilated patients, whereas Norway only provided continuous sedation for 5.7% of neonates) or how to most safely and compassionately use these drugs.

Interesting concerns emerge from the EUROPAIN results. The investigators describe an association between infants exposed to anaesthetics, sedatives, and narcotics, and increased duration of intubation. In the univariate analysis, neonates given opioids, sedatives-hypnotics, or general anaesthetics in neonates (O-SH-GA) in the TV group needed a longer duration of TV than did those who were not given O-SH-GA (mean 136.2 h [SD 173.1] vs 39.8 h [94.7]; $p < 0.0001$). Most of the intubated neonates included in the study were intubated before their admission to the NICU, suggesting

that these neonates were already unwell in the delivery suite. Despite the propensity score matching, the data captured in the study might not fully indicate gradations of illness severity or the clinical factors that compelled the initial treating clinician to escalate care. Also possible is that severity of illness confounds in subtle ways—ie, the perception of increased illness in a particular patient might make clinicians prolong the duration of intubation (and consequently sedation) for that patient. Unfortunately, what does seem apparent is that the sicker neonates, and likely more vulnerable to the undesirable effects of O-SH-GA, have more exposure to anaesthetics, sedatives, or narcotics. The implications of these findings need further study.

The EUROPAIN results provide a detailed and valuable snapshot of contemporary NICU sedation, anaesthesia, and analgesia across Europe. Much research still needs to be done to interpret the implications of the findings from EUROPAIN and translate them into safe care for neonatal patients.

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I declare no competing interests.

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