Theseus, the Labyrinth, and the Minotaur of anaesthetic-induced developmental neurotoxicity

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When Theseus set sail to slay the mighty Minotaur, he likely spared a thought for the difficulty in navigating the Labyrinth that surrounded his foe. The search for therapies for anaesthesia-induced developmental neurotoxicity shares a similar mythical context. In our version of these events, Prince Theseus is the cure (potentially played by dexmedetomidine), the Minotaur is sevoflurane-induced neurotoxicity and the Labyrinth (a maze of confounding factors) is represented by physiological aberrations. In this issue of the British Journal of Anaesthesia, two reports1,2 appear to arrive at contradictory conclusions regarding the success of dexmedetomidine in combating sevoflurane-induced developmental neurotoxicity in neonatal rat pups. The two research teams are to be congratulated for reporting the results in a manner that enables the reader to appreciate the entire gamut from protection against organ toxicity to toxicity to the entire organism because of the clarity and detail in their reports. However, the physiological derangements observed in these studies, and their contradictory findings, lead to labyrinthine interpretation. Readers should also refer to the accompanying editorial on the same studies by Vutskits and Sall3 when considering these issues.

Both studies1,2 reported that adding increasing doses of the sedative dexmedetomidine4 to surgical anaesthetic doses of sevoflurane led to progressive physiological disturbances and mortality. These teams have previously drawn attention to the disparity between preclinical studies—in which physiological control is limited—to the operating theatre wherein the skilled paediatric anaesthetist carefully controls physiological functions.5–7 As it is highly improbable to maintain homeostasis in neonatal rodent pups under anaesthesia, these two reports1,2 add to the chorus of those seeking more relevant animal models such as piglets8–9 and non-human primates10–12 in which physiological monitoring and support are possible. Indeed, given that the physiological derangement in these studies was so profound as to induce mortality, we find it remarkable that dexmedetomidine was still able to exert protection in one of the studies. Perez-Zoghbi and colleagues1 confirm previous findings13–15 that 1 μg kg−1 of dexmedetomidine provides protection against volatile anaesthetic-induced developmental neurotoxicity, although in the current report the offending volatile anaesthetic is sevoflurane rather than isoflurane.16 A crucial difference with our prior work with isoflurane14 is that Perez-Zoghbi and colleagues1 demonstrated higher mortality with escalating doses of dexmedetomidine (≥5 μg kg−1) in the presence of sevoflurane, possibly because of the surgical dose of volatile anaesthetic used. While the investigators assessed depth of anaesthesia, they performed this in a semi-quantitative manner in which it was not possible to determine the depth of the anaesthetic that occurred when dexmedetomidine was added to the surgical plane of anaesthesia produced by sevoflurane 2.5%. An alternative approach might have included equi-anaesthetic doses of sevoflurane and/or dexmedetomidine such that in the presence of a MAC-reducing dose of dexmedetomidine, sevoflurane concentration would be titrated down. However, in such a study it would not be possible to determine whether any neuroprotective effect with the equi-anaesthetic combination was a result of a reduction in the dose of the neurotoxic sevoflurane rather than a protective action of dexmedetomidine. Nonetheless, the potential benefits of dexmedetomidine could be due both to its neuroprotective effects (protecting against anaesthetic injury) as well as its anaesthetic-sparing effect (reducing the anaesthetic dose of injury). This dual effect is being leveraged in the ongoing TREX randomized controlled trial.16

Given the concerns over physiological derangement and mortality, we agree with the approach of Perez-Zoghbi and colleagues1 to focus their analyses on groups that were not so physiologically deranged as to result in death of 100% of the neonatal rat pups. In those groups, the authors showed neuroprotective effects of dexmedetomidine at 1 and 5 μg kg−1 in the surviving rat pups. Not only have Perez-Zoghbi and colleagues1 confirmed previous findings with isoflurane,13–15 but this work is also compatible with other data suggesting that dexmedetomidine protects against ketamine17–18 and propofol19 injury while appearing relatively safe itself.13–14,17–20 However, we would have greater confidence in these findings if they were repeated in animal models where physiological control, more analogous to clinical care, is achieved.

How do we reconcile the findings of Perez-Zoghbi and colleagues1 and Sanders and colleagues4 with the new findings of Lee and colleagues2 that 1 μg kg−1 of dexmedetomidine is not protective against sevoflurane-induced neurotoxicity? Because these studies were performed under the auspices of a SMART TOTS-inspired collaboration, these groups used very similar methodology while working independently. However, there are subtle differences in methodology including a difference in statistical analytical methods that begs closer scrutiny. As described above, Perez-Zoghbi and colleagues1 focused on lower doses of dexmedetomidine, excluding higher doses because of 100% mortality. Conversely, Lee and colleagues2 pursued their a priori designed statistical analytical plan in which all groups, including...
the physiologically deranged, are considered for analysis. The physiological derangements included significant prolonged decreases in peripheral oxygen saturation to 60–75% in animals receiving sevoflurane plus dexmedetomidine ≥1 μg kg⁻¹. Under this scenario, a putative benefit (or toxicity) of low doses of dexmedetomidine in preventing sevoflurane-induced neurotoxicity might now be lost because of the correction for multiple analyses. While it is laudatory to both provide and adhere to a prospectively written statistical analytical plan for preclinical trials (a gold standard for randomized clinical trials), we do see merit in the reasoning of Perez-Zoghbi and colleagues4 that higher doses of dexmedetomidine (≥5 μg kg⁻¹) plus sevoflurane induce such a severe physiological derangement to be considered the same injury as for lower doses (e.g. combining anaesthetic-induced neurotoxicity with hypoxia-induced neurotoxicity); indeed, hypoxia can enhance isoflurane-induced neurotoxicity.21

More generally for the field, it would have been valuable for Lee and colleagues2 and Perez-Zoghbi and colleagues4 to have conducted similar statistical analyses. In this context, it would have been better if both groups had conducted a direct statistical comparison of sevoflurane with sevoflurane plus dexmedetomidine 1 μg kg⁻¹.

The dose of dexmedetomidine 1 μg kg⁻¹ is clinically relevant for sedation,4 hence, it is reassuring that a sedative had been identified that does not provoke significant cell death itself. Given that prolonged sedation can require for critical illness, dexmedetomidine could prove to be a safer alternative than other sedatives in the intensive care unit. However, this benefit has yet to be tested in paediatric clinical studies. Also, dexmedetomidine has side-effects including bradycardia and hypotension that could adversely affect the very young and could negate any neuroprotective benefit.22–24 But as an adjunct to caudal anaesthesia (without general anaesthesia) for infant inguinal hernia repair receiving dexmedetomidine loading dose of 3 μg kg⁻¹ over 30 min, no significant bradycardia or hypotension was observed.25

While use of dexmedetomidine as part of a general anaesthetic regimen in the very young is being tested for both its anaesthetic sparing and neuroprotective effects (in the TREX trial),26 further preclinical study is required. Beyond addressing concerns related to the lack of physiological control in these studies, noxious stimuli27 and simulated hernia surgery28 exacerbate anaesthetic injury, perhaps through inflammatory pathways.8 As we have previously argued,13 for clinical translation neuroprotective strategies should be tested in anaesthesia + surgery models. After all this represents the major patient population we seek to protect. It remains unknown whether dexmedetomidine provides neuroprotection against anaesthesia + surgical stimulation. Whether ‘TREX’ can slay the Minotaur remains unclear.

The fact that recent clinical studies have failed to identify meaningful outcomes associated with anaesthetic-induced developmental neurotoxicity27,28 begs the question: are we chasing a myth? If there is no Minotaur (neurotoxicity), do we need Theseus (a cure)? At the very least, removing the confound of physiological disturbance (analogous to destroying the Labyrinth) should help us identify if there is a Minotaur. Use of animal models in which physiology can be controlled will improve the science, enhance the face validity and improve the potential for clinical translation of the work. However, the Minotaur is not our only enemy. Regardless of whether anaesthetics induce neurotoxicity, protective strategies to prevent perioperative brain injury, including ischaemia and other insults, remain important.16,29 With the ability of dexmedetomidine to protect against anaesthetic- and ischaemic-induced neuronal death,30 trials focusing on perioperative brain injury are warranted. Yet in the absence of a defined clinical problem of anaesthetic-induced developmental neurotoxicity, justification for further animal studies is becoming increasingly difficult. Eliminating confounding physiological derangement will help clarify if we are chasing a (clinical) myth. In order to find the Minotaur, and even Theseus, we at least need to destroy the Labyrinth.

Declaration of interest
None declared.

References

As animal evidence continues to mount, we face a real dilemma regarding the clinical relevance of anaesthesia-induced developmental neurotoxicity. In December 2016, the US Food and Drug Administration (FDA) issued an announcement stating that commonly used general anaesthetics could potentially be detrimental to very young and rapidly developing brains. This announcement was based on an extensive body of animal research.3–24 Now we must grapple with the FDA’s official recommendation that potential risks should be balanced with the benefits of appropriate anaesthesia in young children. More importantly, as we deal with the official expectation that potential risks should be discussed with families and health-care providers, we are reminded how crucial it is to deepen our understanding of the pertinent mechanisms and potential long-lasting behavioural outcomes relating to the exposure of the young brain to anaesthesia.

Although initial studies were focused on different rodent models of anaesthesia-induced developmental neurotoxicity, certain limitations were undeniable, thus affecting their translational value. For example, rodent brain development is substantially shorter than human brain development (weeks as opposed to years).23 The majority of rodent models used exposures considered to be lengthy (4–6 h).3–4 6–8 11 Most importantly, the

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Anaesthesia-induced developmental neurotoxicity: reality or fiction?

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