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Monitoring of nociception: is more always more?

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In this edition of the *British Journal of Anaesthesia* (*BJA*), Funcke and colleagues[1] describe the results of a trial in which 96 subjects were randomly assigned to have intraoperative remifentanil administration adjusted based on clinical judgement (control) or the output of one of three monitors of nociception: surgical pleth index (SPI), pupillary pain index (PPI), or nociception level index (NOL). The authors found that titration based on the PPI or NOL was associated with a significantly reduced dose of remifentanil when compared with guidance by the SPI or clinical judgement. In fact, when these monitors were used to guide remifentanil administration, the infusion was temporarily discontinued in 75% and 48% of the patients in the PPI and NOL groups, respectively. The authors also describe higher intraoperative levels of plasma stress hormones (adrenocorticotropic hormone and cortisol) in the PPI and NOL groups; more frequent intraoperative patient movements (not statistically significant); and, consequently, higher doses of neuromuscular blocking agents in these groups. Analgesia guidance with the SPI did not result in any such events. None of the described differences had a significant influence on patient outcomes in the PACU.

These results are even more remarkable when compared with those of another recent publication in the *BJA*. Meijer and colleagues[2] investigated NOL-guided versus standard administration of intraoperative opioids in 50 subjects, and found lower plasma stress hormone levels and less pain in the PACU after NOL-guided analgesia in.

Within a month, two studies that investigated the same monitors and obtained remarkably different results have been published within the same journal. Readers seeking scientific evidence to guide their practice might understandably be confused.

However, in the context of monitoring of nociception, contradictory findings may not only be explained by differences in study protocols or data analysis. Fundamental unknowns, such as the lack of a gold standard to quantify nociception, the lack of a consensus on meaningful clinical outcomes, and the lack of a standard best practice for analgesic therapy during general anaesthesia, are more than likely to obscure conclusions one might be able to draw from the available trials.

Funcke and colleagues[1] observed different performance for each of the three 'validated' monitors. Unsurprisingly, a quick literature search reveals multiple citations containing the term 'validation' for each of these monitoring devices. The value of these validation studies is, however, undermined by the fact that validation of a nociception monitor has remained an undefined process.

Apart from these fundamental problems, these two trials simply prove that intraoperative pain regimes are not universally comparable. The control group of Funcke and colleagues[1] received significantly higher opioid doses than the NOL group, likely resulting in lower intraoperative levels of plasma stress hormones. In the study of Meijer and colleagues,[2] the control group received lower opioid doses than the NOL group at several intraoperative time points, which, in the end, is associated with higher intraoperative levels of plasma stress hormones in the control group. Hence, the take-home message might simply be that lower intraoperative opioid doses may lead to a greater humoral stress response. However, the question of whether monitor-guided analgesia results in an actual clinical benefit remains unanswered. The true potential of nociception monitoring may well be defined by the way such devices are integrated into clinical processes. Benefits may be more likely obtained when monitors do not aim to replace, but to assist the clinician's experience.

Importantly and in stark contrast, a scenario in which clinicians place more trust in a monitor than in their own clinical experience may be fraught with danger. This phenomenon is well known in the airline industry, a setting frequently compared with anaesthesia. In a publication relating to over-reliance on (unfamiliar) monitors, the Australian Civil Aviation Safety Authority (CASA) points out that the introduction of Global Positioning System (GPS) navigation systems resulted in airplane pilots and motor vehicle drivers making many grotesque errors.[3] The case of a Belgian woman meaning to pick up a friend in Brussels, Belgium (144 km from her home), but being instead guided by GPS to Zagreb, Croatia (1300 km from her home) without apparently raising her suspicion may serve as an extreme example. The CASA points out that familiarity with any monitoring device and its limitations is of utmost importance before any in-flight use. Where the airline industry clearly appreciates the dangers of distraction and misguidance by monitoring devices, anaesthetists seem at times only too happy to place more trust in such tools than justified by any evidence.

A clear expert consensus about how to validate nociception monitors using clearly defined clinical outcomes is needed. This, combined with development of a detailed body of knowledge of the limitations and pitfalls of the underlying technologies, should be seen as an essential prerequisite before anaesthetists prematurely embark on more fanciful journeys guided by monitors that may, in fact, guide them farther off course.

Declarations of interest

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Importance of proper conduct of clinical trials

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Clinical trials provide the evidence that forms one of the cornerstones of modern evidence-based medicine, together with clinical judgement and patient values and preferences.[1] The US National Institutes of Health defines a clinical trial as, 'a research study in which human subjects are prospectively assigned to one or more interventions (including placebo or control) to evaluate the effects of those interventions on health-related biomedical or behavioural outcomes'.[2] Clinical trials have a long history. Arguably, the first description of one can be found in the 'Book of Daniel' in The Bible.[3] In approximately 600 Before the Common Era, the Babylonian King Nebuchadnezzar ordered his people to eat meat and drink wine, which was a diet that he believed would keep them in good physical condition. Daniel of Judah and his friends (Shadrach, Meshach, and Abednego, who were convinced vegetarians) refused the royal diet and proposed to the royal steward the first recorded clinical trial protocol: 'Test your servants for 10 days; let us be given vegetables to eat and water to drink. Then let our appearance and the appearance of the youths who eat the king's rich food be observed by you, and according to what you see deal with your servants'. Daniel and his youthful friends who ate a vegetarian diet and drank water were found in better physical condition than the 'meat and wine group', and so the king issued a new edict allowing his subjects to also eat legumes and drink water. This first open-label unblinded trial presented methodological issues that remain important in contemporary research: equipoise, selection bias, inadequate controlling for confounders and sample size, unclear outcomes definitions and assessment, but it did lead to an important change in routine practice (i.e. the diet as a form of preventive measure). Interestingly, the trial report was short and effective, even though it was only published 400 yr after study completion.[4]

Clinical trials are usually conducted to evaluate the efficacy, safety, or cost-effectiveness of an intervention with an acceptable margin of uncertainty. The ultimate goal is still the same: improving patient care. RCTs, the randomised evaluation of an intervention against a control, are currently considered the most reliable source of data in medical practice and are widely considered 'the gold standard' of hypothesis testing. However, RCTs are time and effort consuming for patients, investigators, and the healthcare system in general. Moreover, clinical application of their results is not straightforward, as they derive from an experiment on an intervention that is conducted under well-defined circumstances and rigorous criteria in a specific cohort of patients. All of these aspects can be different from those present in clinical practice when physicians decide whether or not to apply an intervention to an individual patient. Indeed, interpretation of results can be difficult for clinicians, and many study questions cannot be tested in clinical trials, in most cases for ethical reasons. Clinicians are not only faced with questions about generalisability; there are also problems with differences in quality of study methodology and evidence. Some of these barriers can be overcome with standardised assessment of the quality and strength of the body of evidence for a clinical question. This is the aim of the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach used in clinical practice guidelines, where evidence from clinical trials and expertise from content experts are merged to provide recommendations.[5] It is interesting to note that, although the importance of clinical trials for improving medical care is largely recognised, the body of literature evaluating their impact in comparison with other sources of evidence is still small. Since the initial growth of the use of clinical trials in the late 1960s and 1970s, researchers have developed more