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Perioperative glucocorticoid supplementation for patients undergoing endoscopic transsphenoidal pituitary tumour surgery: using a sledgehammer to crack a nut?

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Pituitary tumours can be categorised as either producing or non-producing based on their endocrine function.[1–3] When excision of a pituitary tumour is required, the endoscopic endonasal transsphenoidal route is commonly used, and in many parts of the world, perioperative steroid supplementation is standard. The goal of steroid supplementation is to provide sufficient steroid concentrations should intraoperative adrenal insufficiency, postoperative adrenal insufficiency, or both occur. The latter can cause impaired cortisol levels, which can lead to an Addisonian crisis, a serious and life-threatening condition that in the early stages can present with fatigue, nausea, and vomiting, and eventually can lead to shock.[4,5]

There are two situations in which perioperative steroid supplementation is clearly indicated. The first is when the patient has an adrenocorticotropic hormone (ACTH)-producing tumour causing hypercortisolism (Cushing's disease), which can produce hypertension, skin abnormalities, and weight gain.[6] After removal of the tumour, ACTH production declines abruptly. This causes a rapid decline in cortisol concentrations, which cannot be counteracted because of central adrenal insufficiency.

A second clear indication is the presence of a non-producing tumour that has caused hypopituitarism owing to a mass effect, which results in hypocortisolism and requires prolonged preoperative steroid supplementation. These patients are dependent on exogenous steroid supplementation. They have pre-existing secondary adrenal insufficiency and are at risk of adrenal crisis because of surgical stress.

In the remaining patients, those with a properly functioning hypothalamic–pituitary–adrenal (HPA) axis, there is always a risk that the surgical procedure itself may injure the preoperatively intact anterior lobe of the pituitary, causing (iatrogenic) secondary adrenal insufficiency.[7] It is for this reason that perioperative steroid supplementation is commonly given to all patients undergoing pituitary surgery, regardless of their preoperative endocrine status.[8,9]

Hattori and colleagues[10] presented an interesting retrospective study on the relationship between perioperative steroid administration and complications among 1813 patients who underwent transsphenoidal pituitary tumour surgery in Japan. They compared the incidence of complications between patients who received prophylactic steroid administration on the day of the operation only, and those who did not receive any steroid supplementation. Patients with Cushing's disease and those who had received preoperative steroid therapy were excluded. The authors found no significant difference between the groups in the incidence of secondary adrenal insufficiency. Thus there was no difference in the incidence of iatrogenic (surgically induced) adrenal insufficiency. This led them to conclude that prophylactic steroid supplementation might not be necessary for patients who have an intact HPA axis before transsphenoidal pituitary surgery.[10]

As the number of manuscripts submitted for publication continues to increase, so has the threshold for publication. Single-centre retrospective observational studies seldom reach the required priority for publication as a full paper, but the results of such studies can still be important. That the findings of Hattori and colleagues[10] have been published in the Correspondence section of the *British Journal of Anaesthesia* should not detract from their value. In addition to other functions, letters to the editor are an avenue for publication of data that might not provide a definitive answer to a question, but which are thought provoking and stimulate further discussion. The findings of Hattori and colleagues[10] fit into this category. They are particularly interesting, as steroid supplementation for patients undergoing pituitary surgery is such an entrenched and time-honoured tradition that some would consider it as 'vloeken in de kerk' ('swearing in church', or blasphemy) if not followed.

The first question to ask is, whether we are effectively preventing Addisonian crises in those patients with an adequate HPA-axis function preoperatively and who subsequently undergo endoscopic endonasal transsphenoidal pituitary tumour resection. In general, but only for a very small percentage of patients, this seems to be the case as shown by McLaughlin and colleagues[11] in 2012. The current study findings do not provide a definitive answer to this question. Firstly, the study design was retrospective, with all the attendant risks of bias. Furthermore, in Table 2 of their supplementary materials, Hattori and colleagues[10] show that various steroids in different doses were used to prevent adrenal insufficiency. This treatment heterogeneity hampers interpretation of the results, and comparability of the results with those of other studies.

Postoperative nausea and vomiting (PONV) is a common problem after (neuro)anaesthesia, even with adequate prophylaxis. Dexamethasone is one of the most commonly used and effective agents to both prevent and treat PONV.[12–14] It is therefore conceivable that patients in both groups might have received steroids as either PONV prophylaxis or treatment on the day of operation. This is another potentially confounding factor, which was not addressed by the authors.

Nonetheless, the conclusions of Hattori and colleagues[10] are consistent with other publications that challenge the use of perioperative steroid supplementation for patients with an intact HPA axis. The findings suggest that it might be safe to omit perioperative steroid supplementation and use a reactive instead of preventive strategy for those patients.[15–18] However, in our view, this can only be safely done when certain strict conditions apply, such as adequate monitoring and the availability of rapid serum cortisol laboratory testing.[19]

The next consideration is what the disadvantages might be of steroid supplementation in patients with an intact HPA axis. Are we unnecessarily exposing patients to the known side-effects of steroid treatment and at a later stage incorrectly classifying them as having adrenal insufficiency? This not only affects individual patients, but the entire healthcare system because of extra care and costs. In other words, if we are using a sledgehammer to crack a nut, how much collateral damage is the hammer causing? Steroid treatment has several harmful side-effects such as elevation of arterial blood pressure and an overall increase in cardiovascular mortality.[9,20] Another common side-effect of steroid supplementation, even after short-term use, is hyperglycaemia, which is

associated with negative outcomes in the perioperative period.[21] Steroids are associated with a negative effect on wound healing, although this effect is likely limited in magnitude compared with other factors, such as anaemia and tobacco use.[22–24] A large recently completed RCT of dexamethasone for PONV showed that dexamethasone did not increase the incidence of surgical site infection, but that it was associated with an increased incidence of hyperglycaemic events and insulin requirement in non-diabetic patients.[25] Considering the potential negative effects of even short-term steroid use, we believe that exploration of the possibility of a more restrictive steroid supplementation regime is worthwhile.

If a reactive – rather than a preventive – treatment policy is used, an optimal strategy should be sought to identify those patients who unexpectedly develop adrenal insufficiency or other complications. The patients from the study of Hattori and colleagues[10] were routinely kept in hospital for more than 2 weeks, enabling physicians to monitor them and extensively evaluate their endocrine function. In most parts of the world, this length of hospital stay is not standard care. In our own hospital, steroid supplementation is currently routine and patients are admitted for a median period of 4 days. During the 4 days postoperatively, steroid treatment (hydrocortisone) is tapered off, and a fasting cortisol level on postoperative day 4 is used to determine whether or not they should be discharged with ongoing steroid treatment. Is even 4 postoperative days of hospitalisation really necessary? In the currently austere financial landscape, the cost savings of even a 1 day reduction in the length of hospital stay can be significant and may allow admission of another patient.

Clinicians of the 21st century struggle with the conflicting forces of standardisation and individualised care. Routine steroid supplementation for all pituitary tumour surgery patients might have benefits for those with an impaired HPA axis, but disadvantages for those who do not develop (or would not have developed) postoperative secondary adrenal insufficiency. Current practice is driven by the 'do no harm' principle. However, this is a short-term perspective and we may do harm in the long run. Perhaps it is time to move the balance towards more individual or targeted therapy? This strategy of course needs to be further evaluated in prospective studies and preferably in a randomised trial.

In conclusion, the report by Hattori and colleagues stimulates further discussion on the topic of perioperative steroid supplementation for patients undergoing pituitary tumour surgery. Perhaps this discussion will transform the 'steroid sledgehammer' into a subtler instrument used in a patient-individualised way.

Authors' contributions

All authors contributed to the conception of the material presented, writing of the manuscript, and critical revision of the manuscript.

Declarations of interest

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VitalDB: fostering collaboration in anaesthesia research

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In the April issue of *British Journal of Anaesthesia*, Lee and colleagues[1] reported the development and validation of deep learning models for the prediction of intraoperative hypotension. The authors developed an algorithm that, unlike marketed algorithms,[2–5] make use of multimodal biosignal waveforms, acquired using routine invasive and noninvasive patient monitoring to predict future hypotensive events. Using data from 3301 patients from their database, they trained and validated their model. Although some aspects of the methodology may still be improved, such as (acausal) extraction of events,[6] their model demonstrates strong predictive performance for hypotension up to 15 min before its actual occurrence, particularly when model inputs included combined rather than single signals. What really sets the study apart from others of its kind, however, is that the authors have released both the code and data that underpin their findings.[7]

Although practices are changing, there are still too few motivations for researchers to share their well-curated data and self-developed software. The effort taken by the authors to create, document, and release this unprecedented perioperative dataset, the *VitalDB database*, along with their analysis code should serve as a lesson for the community. The creation of easily accessible physiologic databases within anaesthesia and intensive care has created outstanding education and research opportunities over the past two decades.[8–10] These databases have offered fundamental insights into clinical care and created a platform for interdisciplinary educational programmes and projects. Here, we highlight the accomplishments of the authors and consider this relatively new VitalDB database in the context of other currently available datasets in the field of anaesthesia and intensive care (Table 1).

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