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ORIGINAL RESEARCH

# Current trends in anesthetic depth and antinociception monitoring: an international survey

Sean Coeckelenbergh[1,2] · Philippe Richebé[3] · Dan Longrois[4] · Alexandre Joosten[1,5] · Stefan De Hert[2]

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## Abstract

Current trends in anesthetic depth (i.e., hypnosis) and antinociception monitoring are unclear. We thus aimed to determine contemporary perspectives on monitoring these components of anesthesia during general anesthesia. Participants received and responded anonymously to an internet-based international survey supported by the European Society of Anaesthesiology and Intensive Care. Comparisons, when applicable, were carried out using $Chi^2$ analysis or Fischer's exact test. A total of 564 respondents, predominantly from Europe (80.1%), participated. There was a strong participation from Belgium (11.5%). A majority (70.9%) of anesthetists considered hypnotic monitoring important on most occasions to always. In contrast, a majority (62.6%) never or only occasionally considered antinociception monitoring important. This difference in the perceived importance of anesthetic depth versus antinociception monitoring was significant ($p < 0.0001$). A majority of respondents (70.1%) believed that guiding hypnosis and antinociception using these monitors would improve patient care on most occasions to always. Nonetheless, a substantial number of participants were unsure if hypnotic (23%) or antinociception (32%) monitoring were recommended and there was a lack of knowledge (58%) of any published algorithms to titrate hypnotic and/or antinociceptive drugs based on the information provided by the monitors. In conclusion, current trends in European academic centers prioritize anesthesia depth over antinociception monitoring. Despite an agreement among respondents that applying strategies that optimize anesthetic depth and antinociception could improve outcome, there remains a lack of knowledge of appropriate algorithms. Future studies and recommendations should focus on clarifying goal-directed anesthetic strategies and determine their impact on perioperative patient outcome.

**Keywords** Pain · Goal-directed therapy · Intraoperative monitoring · General anesthesia · Burst suppression

## 1 Introduction

Contemporary balanced anesthesia focuses on the titration of hypnotic (i.e., anesthetic depth), antinociceptive, and neuromuscular blocking drugs [1]. As the predominant goal of the anesthetist is to administer all three to facilitate surgery while maintaining the patient's baseline physiological equilibrium, intraoperative monitoring of their effects during general anesthesia is particularly appealing. Despite pharmacological interactions being well characterized [3], optimal hypnotic and antinociceptive titration continues to challenge clinicians.

Many monitors that measure the effects of hypnotic or antinociceptive drugs are commercially available in Europe. While the majority that measure the effects of hypnotics focus on processed electroencephalographic (EEG) changes, those that assess antinociceptive drug effects predominantly measure autonomic nervous system response as a surrogate

✉ Sean Coeckelenbergh
sean.coeckelenbergh@ulb.be

1 Department of Anesthesiology, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium

2 Department of Anesthesiology and Perioperative Medicine, Ghent University Hospital, Ghent University, Ghent, Belgium

3 Department of Anesthesiology and Pain Medicine, Maisonneuve-Rosemont Hospital, CIUSSS de L'Est de L'Ile de Montréal (CEMTL), University of Montreal, Montreal, Canada

4 Department of Anesthesiology and Intensive Care, Hôpital Bichat—Claude-Bernard, AP-HP. Nord—Université de Paris, Paris, France

5 Department of Anesthesiology, Hôpital-Paul Brousse, Université Paris-Saclay, Villejuif, France

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to nociception/antinociception balance [2]. Monitoring hypnotic effect with a processed EEG has shown to decrease awareness in a large cohort of patients undergoing both intravenous and inhaled anesthesia [3]. However, this was not reproduced in a homogenous population undergoing inhaled anesthesia mainly because of lack of events (i.e., explicit awareness) in both the end-tidal halogenated gas concentration guided control and the processed EEG-guided groups [4, 5]. The role of burst suppression and suppression ratio values > 0 (equivalents of isoelectric EEG) and the clinician's response to this state are also controversial, as their link with mortality in perioperative medicine remains unclear [6]. Furthermore, cortical EEG monitors whose algorithms were developed with gamma-aminobutyric acid A ($GABA_A$) agonists are challenged by hypnotic/antinociceptive adjuvants that are active on other receptors. An adjunct dose of ketamine during stable propofol general anesthesia, for example, has been shown to either have no effect or to increase the value of the Bispectral index (BIS) [7]. As the addition of a general anesthetic should theoretically decrease the BIS value in a dose-dependent manner, these paradoxical effects can lead clinicians to become hesitant to the validity of such a monitor. Adding other drugs during multimodal anesthesia (i.e., the combination of adjuvants such as clonidine, dexmedetomidine, lidocaine, or combined inhaled/intravenous anesthesia in addition to the three components of balanced anesthesia) further blurs the picture. Concomitant use of $GABA_A$ agonists and non-$GABA_A$ anesthetics can thus impact the processed EEG and lead to aberrant values. The analysis of the spectrogram (i.e., density spectral array), now available on several monitors, provides adequate answers to the apparent paradox of ketamine [8]. Antinociception monitors have also had limited validation under opioid-free or opioid-sparing anesthesia as most of the available monitors focus on guiding opioid administration [9, 10]. Their clinical adoption is thus confronted with uncertainty since there is a lack of definitive studies and explicit educational tools on how to validate and translate information provided by the monitors into goal-directed strategies. Clarifying these issues should precede attempts to document effects of these monitors on patient outcome.

The current strategies to monitor the effects of hypnotics and antinociceptive drugs therefore continue to pose challenges. The aim of this survey was to evaluate the perspective of anesthesiologists on these monitors and their potential to improve outcome, to what extent each of the above-mentioned components of anesthesia are monitored by clinicians, how the information provided by these tools is integrated by clinicians in their daily practice, and if certain factors, such as type of anesthesia or origin of the anesthetist, could be linked to their perspectives.

## 2 Materials and methods

A 26-question survey was developed by an expert panel from five university centers (four European, one Canadian). The panel reviewed, edited, and selected these questions after two comprehensive revisions sessions. The goal of the survey was to assess current perspectives and trends in guiding hypnotic and antinociception drugs with dedicated monitors during general anesthesia. Six questions assessed the respondents' demographic characteristics. Recipients were informed that this survey was sponsored by the European Society of Anaesthesiology and Intensive Care (ESAIC) and that it would be used to describe their perspective on the theory and clinical practice related to the use of these monitors. All recipient data remained anonymous and no personal information (age, gender, date of birth, or name) was stored.

The Research Ethics Committee of the Société Française d'Anesthésie-Réanimation (IRB 00010254-2020-191; 7 Septembre 2020: Chairman Pr. JE. Bazin) approved this study and adheres to the Checklist for Reporting Results of Internet E-Surveys. This voluntary open survey was sent out to all ESAIC members by email (8043 members) and was linked to a secure database (LimeSurvey, Hamburg, Germany). The survey was tested and proofread three times before becoming available to participants. It was also promoted during Euroanaesthesia 2020 on the ESAIC social media platforms, and in the November issue of the Belgian Society of Anesthesiology, Resuscitation, Perioperative Medicine and Pain Management (BeSARPP) newsletter (891 recipients). It was open from October 31st to December 31st, 2020. Participants were included in the analysis if they answered the first eight questions (i.e., baseline demographics and perspective of the importance of anesthesia depth and antinociception monitoring (Appendix 1). No incentives were offered, questions were not randomized, there were no adaptive questions, and response time was not controlled. All completed questions from these respondents were analyzed.

As this was a predominantly European targeted survey, a subanalysis of European regions was carried out. Four regions were defined: Western Europe, Eastern Europe, Northern Europe, and Southern Europe. An answer rate of 50 per region was required for inclusion in the interregional analysis.

The invitation and survey questions can be found in Appendix 1.

### 2.1 Statistical analysis

Categorical data is expressed as frequency and number. Comparisons, when applicable, were carried out using $Chi^2$ analysis or Fischer's exact test. A p value inferior to 0.05 was

considered statistically significant and there was no correction for multiple comparisons.

## 3 Results

A total of 695 potential participants opened the survey link, of which 564 respondents (81.2% response rate), predominantly from Europe (80.1%), participated (Fig. 1a). Most were medical doctors from academic centers who worked at least half-time in the operating room as anesthetists (Table 1). A majority (70.9%) considered hypnotic monitoring important on most occasions to always. In contrast, a majority (62.6%) never or only occasionally found antinociception monitoring important. This difference in the perceived importance of anesthetic depth versus antinociception monitoring was significant ($p < 0.0001$) (Fig. 2a). Furthermore, most respondents (70.1%) believed that guiding hypnotic and antinociceptive drug administration with these monitors would improve patient care on most occasions to always (Table 2). Nonetheless, a substantial percentage of participants were unsure if hypnotic (23%) or antinociception (32%) monitoring were recommended and there was a lack of knowledge (58%) of any published algorithms to titrate hypnotic and/or antinociceptive drugs based on the information provided by the monitors (Table 2). The most frequently used monitors for hypnotic and antinociception assessment were the BIS (63.7%) and pupillary dilation reflex (10.9%), respectively (Table 2).

Differences in monitoring also existed depending on the type of anesthetic agent. Significantly more participants used frontal EEG monitors when administering continuous propofol infusion as compared to inhaled hypnotics (87.9% vs. 76.8%; $p < 0.001$) (Fig. 2b). This difference was particularly impacted by the tendency of 49.7% of respondents to use frontal EEG monitors during propofol continuous anesthesia for every patient while only 23.2% always used it during inhaled anesthesia. Several reasons existed for not monitoring with frontal EEG, including doubt in its diagnostic accuracy (6.8%), lack of knowledge on how it works (1.4%), conflict of space for the placement of electrodes (19.8%), or the use of other parameters to guide titration of anesthetic drugs (36.2%). However, the most frequent cause was the lack of availability and/or excessive cost of the monitor for the potential benefit perceived by the respondents or their associated departments (42.6%).

When comparing the perceived diagnostic performance of various surrogates during continuous propofol, inhaled, and multimodal anesthesia, respondents considered heart rate, blood pressure, and patient movement to be similar predictors of adequacy of anesthesia. Other variables, however, were found to differ significantly. Recommended intravenous propofol doses were deemed less reliable than end-tidal halogenated gas concentration for inhaled (14.9% vs 70.8%, $p < 0.0001$) and multimodal (14.9% vs 52.3%; $p < 0.0001$) anesthesia. End-tidal halogenated gas concentration was also considered more reliable during inhaled than multimodal anesthesia (70.8% vs 52.3%; $p < 0.0001$). Furthermore, processed frontal EEG values were more often seen as reliable surrogates during propofol than halogenated (60.3% vs 49.5%, $p = 0.008$) or multimodal (60.3% vs 50.8%; $p = 0.0031$) anesthesia. For 7.8% of respondents, none of the proposed surrogates were considered adequate to guide titration of anesthetic drugs during multimodal anesthesia, while only 2.9% of respondents considered that none could guide inhaled anesthesia ($p = 0.0006$) (Fig. 3). When using a frontal EEG, only 40.8% of respondents always measured the suppression ratio and 32% always felt safe lowering anesthesia depth in its presence. However, when the answers "always" and "on most occasions" are combined, a majority of respondents analyzed the suppression ratio (63.8%) and

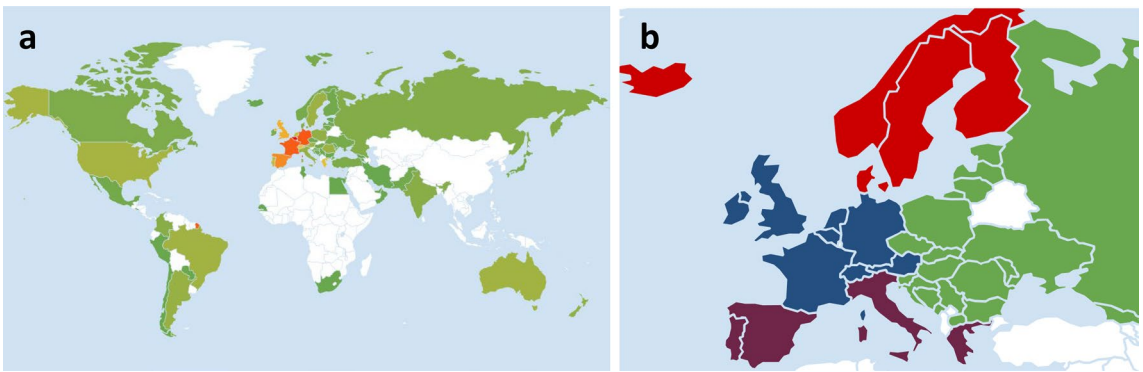


**Fig. 1** **a** Countries of participants. Rate of response increases from green to red (see Table 1 for exact response rate per country). **b** European regions. Blue: Western Europe (255 respondents); Green: Eastern Europe (76 respondents); Purple: Southern Europe (94 respondents); Red: Northern Europe (25 respondents). (Color figure online)

**Table 1** Demographic characteristics of respondents

| | Counts (%) | | Counts (%) |
|---|---|---|---|
| *Country of practice* | | *Continent of practice* | |
| Argentina | 10 (1.8) | Africa | 4 (0.7) |
| Armenia | 2 (0.4) | Asia | 32 (5.7) |
| Australia | 12 (2.1) | Europe | 452 (80.1) |
| Austria | 12 (2.1) | North America | 22 (3.9) |
| Belgium | 65 (11.5) | Oceania | 21 (3.7) |
| Bosnia and Herzegovina | 3 (0.5) | South America | 33 (5.9) |
| Brazil | 12 (2.1) | | |
| Bulgaria | 2 (0.4) | | |
| Canada | 5 (0.9) | | |
| Chile | 1 (0.2) | *Years of practice* | |
| Colombia | 7 (1.2) | 0–5 (including specialization) | 98 (17.4) |
| Croatia | 5 (0.9) | 6–15 | 195 (34.6) |
| Cyprus | 2 (0.4) | 16–25 | 125 (22.2) |
| Czech Republic | 3 (0.5) | 26–35 | 102 (18.1) |
| Denmark | 6 (1.1) | 36 or more | 44 (7.8) |
| Egypt | 1 (0.2) | | |
| El Salvador | 1 (0.2) | | |
| Estonia | 1 (0.2) | | |
| Finland | 3 (0.5) | *Type of hospital** | |
| France | 47 (8.3) | Academic | 360 (63.8) |
| Georgia | 1 (0.2) | Public | 219 (38.8) |
| Germany | 48 (8.5) | Private | 98 (17.3) |
| Greece | 25 (4.4) | Other | 4 (0.7) |
| Hungary | 4 (0.7) | | |
| Iceland | 1 (0.2) | | |
| India | 7 (1.2) | | |
| Iran | 1 (0.2) | *Profession* | |
| Ireland | 5 (0.9) | Medical doctor | 551 (97.7) |
| Israel | 4 (0.7) | Nurse | 13 (2.3) |
| Italy | 10 (1.8) | | |
| Japan | 4 (0.7) | | |
| Kuwait | 1 (0.2) | | |
| Latvia | 3 (0.5) | *Time in operating room* | |
| Lebanon | 1 (0.2) | Less than 25% | 30 (5.3) |
| Lithuania | 4 (0.7) | 26–50% | 82 (14.5) |
| Macedonian | 3 (0.5) | 51–75% | 183 (32.4) |
| Mexico | 3 (0.5) | 76–100% | 269 (47.7) |
| Moldova | 2 (0.4) | | |
| Montenegro | 1 (0.2) | | |
| Netherlands | 20 (3.5) | | |
| New Zealand | 9 (1.6) | | |
| Norway | 4 (0.7) | | |
| Oman | 1 (0.2) | | |
| Pakistan | 3 (0.5) | *Subspecialty* | |
| Paraguay | 1 (0.2) | General anesthesia | 304 (53.9) |
| Peru | 1 (0.2) | Cardiac anesthesia | 60 (10.6) |
| Poland | 9 (1.6) | Thoracic anesthesia | 14 (2.5) |
| Portugal | 19 (3.4) | Neuroanesthesia | 30 (5.3) |
| Romania | 11 (2.0) | Orthopedic anesthesia | 33 (5.9) |
| Russia | 6 (1.1) | Obstetric anesthesia | 19 (3.4) |

**Table 1** (continued)

| | Counts (%) | | Counts (%) |
|---|---|---|---|
| Saudi Arabia | 3 (0.5) | One-day anesthesia | 16 (2.8) |
| Senegal | 1 (0.2) | Transplantation anesthesia | 9 (1.6) |
| Serbia | 2 (0.4) | Perioperative medicine | 21 (3.7) |
| Slovenia | 12 (2.1) | Pediatric anesthesia | 27 (4.8) |
| South Africa | 1 (0.2) | Chronic pain medicine | 8 (1.4) |
| Spain | 38 (6.7) | Intensive care medicine | 23 (4.1) |
| Sweden | 11 (2.0) | | |
| Switzerland | 27 (4.8) | | |
| Tunisia | 1 (0.2) | | |
| Turkey | 5 (0.9) | | |
| Ukraine | 4 (0.7) | | |
| United Arab Emirates | 3 (0.5) | | |
| United Kingdom | 31 (5.5) | | |
| United States | 13 (2.3) | | |

*Several answers possible

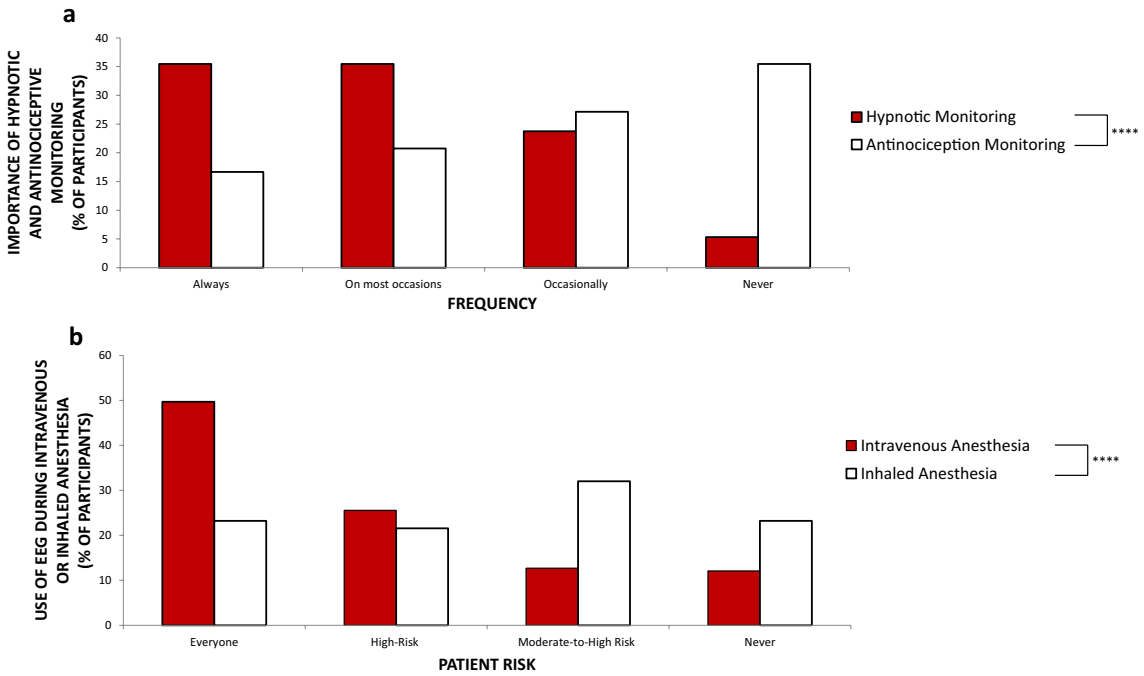


**Fig. 2** **a** Differences in the perceived importance of anesthetic depth and antinociception monitoring. The majority of respondents considered anesthesia depth monitoring either always or on most occasions important while a majority of respondents never or only occasionally found antinociception monitoring important (****$p < 0.0001$). **b** Differences in the use of EEG (electroencephalographic) monitoring during intravenous and inhaled anesthesia. Respondents more often use EEG monitoring during intravenous than inhaled anesthesia (****$p < 0.0001$)

modified hypnotic drugs doses/concentrations in its presence (75%) (Table 2).

More respondents believed a goal-directed strategy guided by anesthetic depth monitoring, in comparison to antinociception monitoring, would improve patient outcome. Most notably, delirium, post-operative cognitive dysfunction, and awareness were perceived to potentially decrease more often when monitoring the effects of hypnotic than antinociceptive drugs. Only a minority of respondents considered guiding anesthesia with either type of monitor capable of preventing acute myocardial injury, and more respondents believed that antinociception monitoring could decrease this risk more often than frontal EEG (Fig. 4). A majority of respondents believed that antinociception monitoring could

**Table 2** Perspectives on monitoring and recommendations

| | |
|---|---|
| *Anesthesia depth monitoring is recommended (n = 491)* | |
| Yes | 257 (52.3%) |
| No | 118 (24%) |
| Not sure | 116 (23.6%) |
| *Antinociception monitoring is recommended (n = 491)* | |
| Yes | 54 (11%) |
| No | 281 (57.2%) |
| Not sure | 156 (31.8%) |
| *The following monitors are recommended (n = 490)** | |
| Pulse oximetry | 473 (96.5%) |
| Electrocardioscopy | 414 (84.5%) |
| Blood pressure | 468 (95.5%) |
| End tidal gases | 464 (94.7%) |
| Frontal-EEG or other anesthetic depth monitoring | 225 (45.9%) |
| Antinociception monitoring | 34 (6.9%) |
| I'm not sure | 34 (6.9%) |
| None of the above | 22 (4.5%) |
| *Most frequently used anesthetic depth monitor (n = 491)* | |
| Bispectral Index | 312 (63.7%) |
| Entropy | 60 (12.2%) |
| SedLine | 41 (8.4%) |
| Neurosense | 12 (2.4%) |
| Unprocessed EEG | 6 (1.2%) |
| Narcotrend | 7 (1.4%) |
| qCon | 2 (0.4%) |
| Other | 3 (0.6%) |
| None | 47 (9.6%) |
| *Most frequently used antinociception monitor (n = 488)* | |
| Nociception level Index | 30 (6.1%) |
| Analgesia/nociception Index | 33 (6.7%) |
| Surgical plethysmographic Index | 46 (9.4%) |
| Pain monitor (skin conductance) | 2 (0.4%) |
| Response entropy | 14 (2.9%) |
| Frontal EEG variations | 40 (8.2%) |
| Pupillary dilation reflex | 53 (10.9%) |
| None | 270 (55.3%) |
| *Measure burst suppression (n = 488)* | |
| Always | 199 (40.8%) |
| On most occasions | 112 (23.0%) |
| Occasionally | 59 (12.1%) |
| Never | 118 (24.2%) |
| *Lower anesthetic drugs doses if burst suppression occurs (n = 488)* | |
| Always | 156 (32.0%) |
| On most occasions | 205 (42.0%) |
| Occasionally | 47 (9.6%) |
| Never | 80 (16.4%) |
| *There are available algorithms for titration (n = 488)* | |
| Yes | 205 (42.0%) |
| No | 283 (58.0%) |
| *Anesthetic depth/nociception monitoring can improve patient care (n = 488)* | |
| Always | 143 (29.3%) |
| On most occasions | 199 (40.8%) |

**Table 2** (continued)

| | |
|---|---|
| Occasionally | 118 (24.2%) |
| Never | 28 (5.7%) |

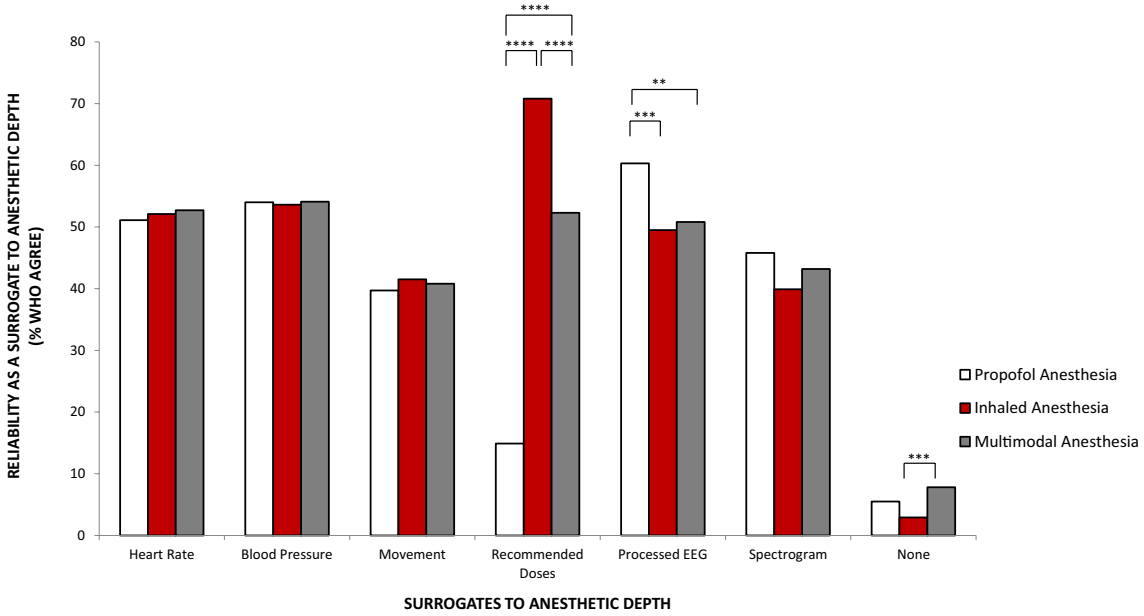


**Fig. 3** Comparison of potential surrogates to anesthetic depth (i.e., hypnosis). *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001

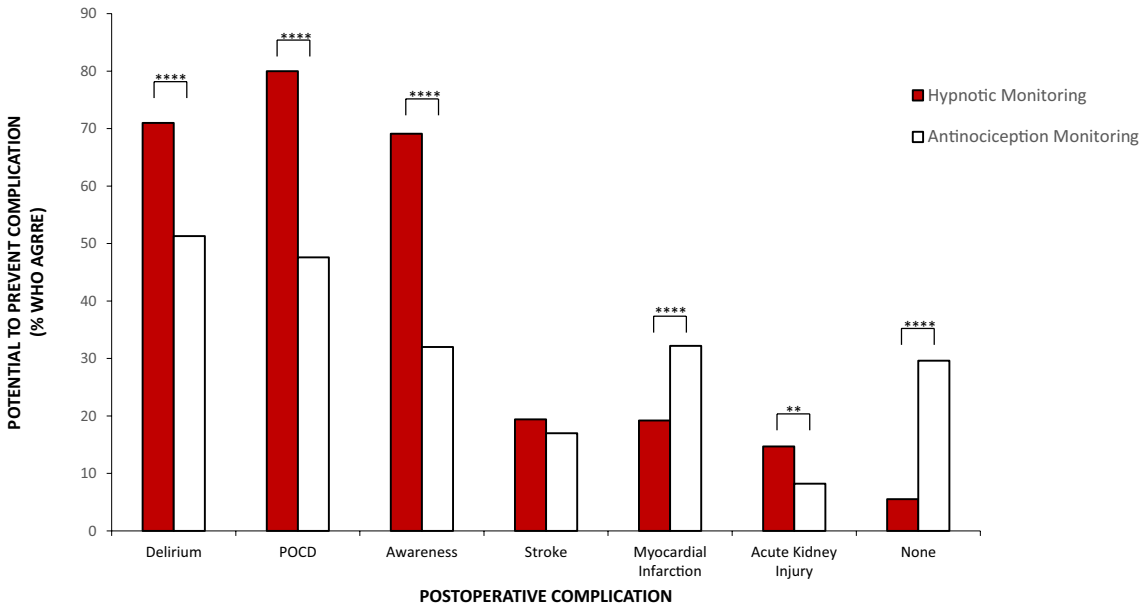


**Fig. 4** Comparison of the perceived capacity of hypnotic and antinociception monitoring to prevent postoperative complications. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001

reduce postoperative nausea and vomiting (55.7%), time to extubation (57.0%), hyperalgesia (63.3%), postoperative opioid need (68.2%) and post-care unit length of stay (57.2%).

## 3.1 European interregional analysis

Western (255 respondents), Southern (94 respondents) and

Eastern (76 respondents) Europe had more than 50 answers per region (Fig. 1b). As there were only 25 participants from Northern Europe, this region was not included in the inter-regional analysis.

The majority of respondents from all three regions perceived antinociception monitoring as being unimportant (i.e., occasionally or never important), though views diverged on hypnotic monitoring. When compared to the two other regions, anesthesiologists from Southern Europe more often considered monitoring hypnosis as important ($p = 0.0255$) and used frontal EEG to guide both propofol ($p < 0.0001$) and inhaled anesthesia ($p < 0.0001$) more frequently. Furthermore, respondents from Eastern Europe were more often aware of algorithms to titrate hypnotic and/or antinociceptive drugs based on the information provided by the monitors than respondents from Western or Southern Europe ($p = 0.0131$). However, when they used a frontal EEG, participants from Western and Southern Europe analyzed the suppression ratio ($p < 0.0001$) more frequently and felt more comfortable decreasing the doses/concentrations of hypnotic drugs when it was present ($p < 0.0001$) than participants from Eastern Europe. Cost was also an issue for more respondents from Eastern (64.1%) and Western (41%) Europe, when compared to Southern (24.7%) Europe ($p < 0.0001$), which could potentially affect their perspectives (Table 3).

## 4 Discussion

Current trends in European academic centers prioritize anesthesia depth over antinociception monitoring, yet most respondents agree that combining the two components could improve patient care. Furthermore, there is a lack of knowledge on current anesthetic depth and antinociception monitoring recommendations and few respondents are aware of goal-directed anesthetic/antinociceptive algorithms. Clear differences also exist on the use of frontal EEG during propofol, inhaled, and multimodal anesthesia, which reflect both current evidence and guidelines on anesthetic depth monitoring [11–16]. Suppression ratio is a robust marker of excessive anesthetic depth, yet it seems to be underused despite many respondents considering frontal EEG an important intraoperative guide to decrease postoperative cognitive dysfunction. Interregional differences also exist and may be due to the additional costs of monitoring the effects of hypnotic and antinociceptive drugs.

Anesthesia depth monitoring with processed frontal EEG, most often BIS, has been a subject of much investigation over the past two decades. Key studies included the B-Aware [3], B-Unaware [5], and BAG-RECALL [4] studies, which have impacted current guidelines significantly. Although the B-Aware study demonstrated the potential benefit of decreasing the incidence of awareness during anesthesia while using BIS [3], this was not reproduced in the B-Unaware and BAG-RECALL studies [4, 5]. It is important to differentiate between them, as B-Aware included both inhaled and intravenous anesthesia while B-Unaware and BAG-RECALL focused on awareness during inhaled anesthesia [3–5]. All these studies had limitations, however. For example, none applied a strategy to reduce hypnotics if burst suppression was present. In addition, the B-Unaware and BAG-RECALL studies both had a lack of events (i.e., explicit awareness), which was interpreted as a lack of difference between the BIS vs. end-tidal halogenated anesthetic concentration guided anesthesia. These results may explain the perspectives of respondents on the potential use of anesthetic depth monitoring during different types of anesthesia. A more recent multicenter randomized controlled trial, the Balanced Anesthesia Study, found that targeting a BIS of 35 or 50 during general anesthesia in older, higher risk, patients had no impact on one year mortality [17]. However a randomized controlled study of a subpopulation of patients at risk of delirium from this study showed that targeting lighter anesthesia was associated with less burst suppression, decreased postoperative delirium, and improved cognitive scores one year postoperatively [18]. Although none of these studies found any difference in other major postoperative outcomes, there is some evidence of the risks of excessively deep anesthesia in association with an isoelectric EEG, most notably during cardiopulmonary bypass and in patients at risk of delirium [18–20].

The measurement of suppression ratio and associated modification of hypnotic drug administration were inconsistent among respondents. Only a minority always measured burst suppression ratio when using a frontal EEG and one out of four respondents never or only occasionally lowered hypnotic administration in its presence. Variations between European regions may be explained by current uncertainties regarding the relationship between this variable and patient outcome. Suppression ratio $> 0$, the equivalent of an isoelectric EEG, is often underestimated despite being associated with mortality and delirium in critically ill patients [21]. Although an observational substudy of the B-Unaware and BAG-RECALL databases did not confirm the link between intraoperative burst suppression alone and mortality, the results did show a strong link of combined burst suppression and hypotension with mortality [22]. One possible reason for this discrepancy is the difference in context, as burst suppression can be induced pathologically (e.g., trauma or metabolic failure) or therapeutically (e.g., hypothermia or anesthetics) [6]. Nonetheless, elderly patients have been identified as a specific population at risk of both burst suppression [23] and postoperative delirium, especially during cardiopulmonary bypass [19, 20]. This sign may indicate excessive, and perhaps even toxic, doses of anesthetics in

**Table 3** Regional differences in anesthesia depth and antinociception monitoring

| | Region | | | p value | | | |
|---|---|---|---|---|---|---|---|
| | Eastern Europe | Western Europe | Southern Europe | East vs West | East vs South | South vs West | Overall |
| *Anesthetic depth monitoring is important* | | | | | | | |
| | n = 76 | n = 255 | n = 94 | 0.3137 | **0.0064** | **0.0302** | **0.0255** |
| Always | 19 (25.0%) | 91 (35.7%) | 44 (46.8%) | | | | |
| Most occasions | 30 (39.5%) | 87 (34.1%) | 35 (37.2%) | | | | |
| Occasionally | 22 (28.9%) | 67 (26.3) | 11 (11.7%) | | | | |
| Never | 5 (6.6%) | 10 (3.9%) | 4 (4.3%) | | | | |
| *Antinociception monitoring is important* | | | | | | | |
| | n = 76 | n = 255 | n = 94 | | | | 0.3112 |
| Always | 12 (15.8%) | 36 (14.1%) | 14 (14.9%) | | | | |
| Most occasions | 18 (23.7%) | 47 (18.4%) | 25 (26.6%) | | | | |
| Occasionally | 27 (35.5%) | 76 (29.8%) | 29 (30.9%) | | | | |
| Never | 19 (25.0%) | 96 (37.6%) | 26 (27.7%) | | | | |
| *Frontal EEG used to guide continuous propofol infusion* | | | | | | | |
| | n = 64 | n = 223 | n = 82 | 0.1648 | **< 0.0001** | **< 0.0001** | **< 0.0001** |
| In all patients | 20 (31.3%) | 100 (44.8%) | 68 (82.9%) | | | | |
| In high- and moderate-risk patients | 21 (32.8%) | 68 (30.5%) | 6 (7.3%) | | | | |
| In high-risk patients | 12 (18.8%) | 33 (14.8%) | 2 (2.4%) | | | | |
| Never | 11 (17.2%) | 22 (9.9%) | 6 (7.3%) | | | | |
| *Frontal EEG used to guide inhaled anesthesia* | | | | | | | |
| | n = 64 | n = 222 | n = 82 | 0.0619 | **< 0.0001** | **< 0.0001** | **< 0.0001** |
| In all patients | 5 (7.8%) | 44 (19.8%) | 36 (43.9%) | | | | |
| In high- and moderate-risk patients | 12 (18.8%) | 51 (23.0%) | 21 (25.6%) | | | | |
| In high-risk patients | 26 (40.6%) | 78 (35.1%) | 14 (17.1%) | | | | |
| Never | 21 (32.8%) | 49 (22.1%) | 11 (13.4%) | | | | |
| *When using a frontal EEG, burst suppression is measured* | | | | | | | |
| | n = 64 | n = 222 | n = 82 | **0.0004** | **< 0.0001** | 0.0703 | **< 0.0001** |
| Always | 14 (21.9%) | 105 (47.3%) | 40 (48.8%) | | | | |
| Most occasions | 13 (20.3%) | 50 (22.5%) | 28 (34.1%) | | | | |
| Occasionally | 13 (20.3%) | 25 (11.3%) | 5 (6.1%) | | | | |
| Never | 24 (37.5%) | 42 (18.9%) | 9 (11.0%) | | | | |
| *It is safe to decrease hypnosis if there is burst suppression* | | | | | | | |
| | n = 64 | n = 222 | n = 82 | **< 0.0001** | **0.0001** | 0.451 | **< 0.0001** |
| Always | 11 (17.2%) | 75 (33.8%) | 34 (41.5%) | | | | |
| Most occasions | 20 (31.3%) | 106 (47.7%) | 33 (40.2%) | | | | |
| Occasionally | 13 (20.3%) | 16 (7.2%) | 8 (9.8%) | | | | |
| Never | 20 (31.3%) | 25 (11.3%) | 7 (8.5%) | | | | |
| *There are available algorithms for titration* | | | | | | | |
| | n = 64 | n = 222 | n = 82 | **0.0069** | **0.0122** | 0.7918 | **0.0131** |
| Yes | 38 (59.4%) | 89 (40.1%) | 31 (37.8%) | | | | |
| *Cost and/or availability are barriers to use anesthetic depth monitoring* | | | | | | | |
| | n = 64 | n = 222 | n = 81 | **0.0016** | **< 0.0001** | **0.0104** | **< 0.0001** |
| Yes | 41 (64.1%) | 91 (41.0%) | 20 (24.7%) | | | | |
| *Anesthetic depth/antinociception monitoring can improve patient care* | | | | | | | |
| | n = 64 | n = 222 | n = 82 | **0.0357** | **0.015** | **< 0.0001** | **< 0.0001** |
| Always | 16 (25.0%) | 48 (21.6%) | 37 (45.1%) | | | | |
| Most occasions | 35 (54.7%) | 91 (41.0%) | 34 (41.5%) | | | | |
| Occasionally | 13 (20.3%) | 68 (30.6%) | 8 (9.8%) | | | | |

**Table 3** (continued)

| | Region | | | p value | | | |
|---|---|---|---|---|---|---|---|
| | Eastern Europe | Western Europe | Southern Europe | East vs West | East vs South | South vs West | Overall |
| Never | 0 (0.0%) | 15 (6.8%) | 3 (3.7%) | | | | |

*P*-values in bold are statistically significant

patients with a "vulnerable brain" phenotype [23]. There consequently remains a need to clarify the role of intraoperative burst suppression and future randomized controlled trials will give results that will help establish clear guidelines on the implementation of burst suppression prevention into goal-directed anesthetic strategies.

In general, the perspectives of participants on anesthetic depth monitoring reflect the current guidelines. Many international societies recommend the use of anesthetic depth monitoring in at least high-risk patients and several of these societies also emphasize its need during intravenous anesthesia [11–16]. Although burst suppression is often mentioned, optimizing this potentially adverse event remains challenging. Decreasing the doses/concentrations of hypnotics is an obvious reaction but only applies if the cause is purely pharmacological. If the patient is suffering from cerebral hypoperfusion, additional monitoring (e.g., near infrared spectroscopy) and hemodynamic optimization (i.e., correction of low cardiac output, blood pressure, arterial $CO_2$, and hemoglobin concentrations to optimal values for a given patient) may be warranted. The trend in responses thus paralleled guidelines as participants considered frontal EEG more important to use during intravenous than inhaled anesthesia, found this monitoring useful to prevent cognitive adverse events (e.g., delirium), and measured burst suppression despite unclear management strategies. Integrating spectrogram analysis of the EEG may further clarify anesthetic depth titration by establishing patterns for different anesthetics [24], vulnerable patients [23], and guiding antinociception [25]. However, respondents also highlighted the need for clearer algorithms for managing anesthetic depth and antinociception during general anesthesia, as there currently is a lack of such protocols to guide anesthesia regardless of the monitoring technique.

The majority of respondents did not use antinociception monitoring in their clinical practice and stated that this type of monitoring was not recommended in their anesthesia society's guidelines. Over the past decade, many studies have shown the potential of modifying intraoperative opioid administration with such monitors. In some studies, the Surgical Pleth Index [26], pupillary dilation reflex [27], and Analgesia Nociception Index [28] have shown to decrease intraoperative remifentanil requirements, when compared to standard care. The Nociception level (NOL) index, a multiparameter index, demonstrates a high sensitivity and specificity to noxious stimuli during general anesthesia [29, 30] and an ability to detect both incremental doses of remifentanil [31] and a continuous infusion of dexmedetomidine [9]. The NOL index has also shown to decrease intraoperative opioids, which was linked to improved hemodynamics [32]. Furthermore, a more targeted approach to antinociception with the NOL index was associated to increased postoperative comfort, an essential outcome in perioperative pain management [33]. Other tools, such as skin conductance monitoring and the Surgical Pleth Index, have also correlated with postoperative pain scores [34]. In addition, an EEG coupled to a closed-loop system that guides both antinociceptive and hypnotic drug administration has shown to be feasible [35], capable of decreasing time to extubation [36], and even improve postoperative cognitive scores when coupled with other closed-loop systems [37]. Although changes in EEG frequency amplitudes, such as beta arousal, delta arousal, and alpha dropout can indicate inadequate antinociception, current processed EEG values do not encompass all patterns of cortical arousal following nociception and thus have their own limitations [25]. Consequently, the impact of guiding antinociception with contemporary monitors on patient outcome remains to be clearly established. This may explain the current trend to use these monitors sparingly during general anesthesia. Future studies that focus on both patient comfort and adverse events will determine if monitoring antinociception, in combination with anesthetic depth, can help improve patient care.

The most important lesson from this survey is that despite nearly three decades of clinical use of frontal EEG monitors, the knowledge and algorithms that allow titration of drugs for individual patients have yet to be consolidated. There are very few algorithms, as have been done by Forestier et al., for example, that have been published on anesthetic drug titrations [38]. It is the role of scientific societies to design and spread educational tools based on explicit knowledge and on how uncertainty, which exists for all types of monitors, should be managed. The arrival on the market of newer EEG monitors (e.g., SEDline and the updated version of the BIS monitor, with the display of the density spectral array) brings an additional need to clarify their associated therapeutic strategies. Furthermore, the differences in antinociception monitors and their incompatibilities will have to be described.

### 4.1 Limitations

This international survey has both strengths and limitations. As it was sent out to members of the ESAIC and BeSARPP, it predominantly targeted academic centers. Consequently, the views of respondents may not represent standard care in non-academic centers. In addition, the participation of the BeSARPP may have contributed to the large number of Belgian responses. Although this may have had some influence on the overall responses, its impact on the results is probably small. Furthermore, some questions can be seen as slightly ambiguous. Nonetheless, the survey targeted anesthesia professionals and still provides a strong perspective on the current trends in anesthetic depth and antinociception monitoring. Another potential limitation relates to the use of certain expressions, such as "anesthetic depth", to define the titration of intraoperative hypnotics. Although this term can be used in a broader sense, the questions and associated answers in the survey that used this term clearly depicted the hypnotic component of anesthesia. A final limitation is that there was no correction for multiple comparisons. Alpha error may consequently occur and statistical comparisons should be considered as exploratory.

### 4.2 Conclusion

Current trends in European academic centers prioritize anesthesia depth over antinociception monitoring. Despite an agreement among respondents that applying strategies that optimize anesthetic depth and antinociception could improve outcome, there remains a lack of knowledge of appropriate algorithms. Future studies and recommendations should focus on clarifying goal-directed anesthetic strategies and determine their impact on patient outcome.

## Appendix 1

## Anaesthetic depth monitoring: where are we in 2020?

Do you monitor anaesthesia depth? What do you think about antinociception monitoring? Do you believe that personalising these components of anaesthesia with monitors can improve outcome?

Please, participate in this ESAIC sponsored survey and help us describe the perspective of medical professionals practicing in the field of anaesthesia!

#### Background

General anaesthesia has become one of the safest procedures in medicine thanks to perioperative monitoring strategies that guide therapy. Almost every component of anaesthesia can be monitored (e.g., neuromuscular blockade, anaesthetic depth, haemodynamics, antinociception, etc.), but to this day it remains unclear: (1) to what extent each of the above-mentioned components of anaesthesia are monitored by clinicians in their daily practice; (2) how the information provided by the different monitors is integrated by clinicians.

Desired anaesthetic depth was historically defined as the intensity of the hypnotic component of anaesthesia (which is often maintained with propofol, inhaled ethers, ketamine, or other intravenous agents) that could avoid explicit/implicit awareness and excessive anaesthesia. In other words, it corresponds to the circulating concentrations of hypnotics. As consciousness requires cortical interactions and the forehead is an easily accessible site to monitor, frontal electroencephalogram (EEG) monitoring (e.g., Bispectral Index, SedLine, Entropy) has become a commonly used tool to measure anaesthetic depth.

Antinociception, on the other hand, can be defined as the control of nociception (i.e., the unconscious response to a noxious stimulus) through the use of opioids or other drugs (e.g. intravenous lidocaine, magnesium, alpha2 agonists as part of opioid-free/opioid sparing regimens). Nociceptive responses principally activate the sympathetic nervous system and this activation can be estimated by intraoperative monitors [e.g., pupil dilation reflex, antinociception/nociception index (ANI), nociception level (NOL) index, and skin conductance]. Most of these monitors quantify the antinociception/nociception balance. None of these monitors (anaesthesia depth or nociception), however, combine the hypnotic/antinociceptive components and their integration is consequently performed by the anaesthesiologists.

The aim of this survey is to describe the perspective of practicing anaesthesiologist and nurse anaesthetists on the use of anaesthesia depth and antinociception monitoring. In addition, we aim to determine how many clinicians use these tools and in what situations. We also attempt to describe the gaps in knowledge concerning monitoring depth of anaesthesia. The results of this survey will help us to redefine educational goals.

Thank you very much for participating in this survey which we strongly believe will lead to a clearer understanding of perioperative anaesthesia monitoring and the potential for improvement.

#### Survey

(1) Where do you practice anaesthesia?

(a) Africa
(b) Asia
(c) Europe
(d) North America
(e) South America
(f) Oceania

(i) In what country do you practice?
(ii) In what language do you practice anaesthesia?
(iii) In what state do you practice (optional)?

(2) How many years have you been practicing anaesthesia (including specialization training)?

(a) 0–5
(b) 6–15
(c) 16–25
(d) 26–35
(e) 35 or more

(3) You work in (select all that apply)

(a) An academic hospital
(b) A public hospital
(c) A private hospital
(d) Other

(4) You are a:

(a) Nurse
(b) Medical doctor

(5) How much of your professional time do you spend in the operating room per week?

(a) Less than 25%
(b) 26–50%
(c) 51–75%
(d) 76–100%

(6) What do you consider to be your anaesthetic specialization? (choose only one)

(a) General anaesthesia
(b) Cardiac anaesthesia
(c) Thoracic anaesthesia
(d) Neuroanaesthesia
(e) Orthopaedic anaesthesia
(f) Obstetric anaesthesia
(g) Anaesthesia for "one-day" ambulatory surgery
(h) Transplantation anaesthesia
(i) Perioperative medicine
(j) Paediatric anaesthesia
(k) Chronic pain medicine
(l) Intensive care medicine

(7) Do you consider anaesthetic depth (hypnotic component) monitoring important to your general practice?

(a) Always
(b) On most occasions (> 50% of the anaesthetic procedures that you perform)
(c) Occasionally (< 25% of the anaesthetic procedures that you perform)
(d) Never

(8) Do you consider antinociceptive monitoring important to your general practice?

(a) Always
(b) On most occasions (> 50% of the anaesthetic procedures that you perform)
(c) Occasionally (< 25% of the anaesthetic procedures that you perform)
(d) Never

(9) Do the national/international perioperative monitoring guidelines you adhere to recommend anaesthesia depth monitoring?

(a) Yes
(b) No
(c) Not sure

(10) Do the national/international perioperative monitoring guidelines you adhere to recommend antinociception monitoring?

(a) Yes
(b) No
(c) Not sure

(11) Which of the following intraoperative monitors are recommended in the national/international perioperative patient safety guidelines you adhere to (select all that apply)?

(a) Pulse oximetry
(b) Electrocardioscopy
(c) Blood pressure monitoring (non-invasive or invasive)
(d) End tidal gases ($CO_2$, $O_2$, inhaled ethers, $N_2O$, etc.)
(e) Frontal-EEG or other anaesthetic depth monitoring
(f) Nociception monitoring (NOL Index, pupil reactivity, etc.)
(g) I'm not sure
(h) None of the above

(12) Which anaesthetic depth monitor do you use most frequently? (One choice)

(a) Bispectral index
(b) Entropy
(c) Sedline
(d) Neurosense
(e) Unprocessed EEG
(f) Other (please specify)
(g) I never use anaesthetic depth monitoring because I consider other parameters (e.g., MAC) sufficient

(13) Which nociception monitor do you use most frequently? (one choice)

(a) Nociception level (NOL) Index
(b) Analgesia/Nociception Index (ANI)
(c) Surgical Plethysmographic Index (SPI)
(d) Pain Monitor (skin conductance)
(e) Response entropy
(f) Frontal EEG variations
(g) Pupil diameter reflex
(h) I never use nociceptive depth monitoring because I consider other parameters sufficient (e.g., heart rate and blood pressure)

(14) When administering continuous hypnotic infusions (e.g., propofol), you monitor anaesthetic depth with a frontal EEG:

(a) In all patients
(b) In high- and moderate-risk patients
(c) In high-risk patients
(d) Never

(15) When administering continuous inhaled anaesthetic (e.g., sevoflurane, desflurane, isoflurane), do monitor anaesthetic depth with a frontal EEG:

(a) In all patients
(b) In high- and moderate-risk patients
(c) In high-risk patients
(d) Never

(16) What are the reasons that you do not always use anaesthetic depth monitoring with a frontal EEG? (select all that apply)?

(a) No reason, I always measure anaesthesia depth with a frontal EEG
(b) I think it costs too much for the potential benefit
(c) I don't think it works
(d) I don't know how it works
(e) I use other parameters to guide my anaesthetic depth
(f) There is a conflict of space between anaesthesia and surgery for the placement of electrodes
(g) Other reasons (please elaborate)

(17) What do you consider to be adequate surrogates to anaesthetic depth during propofol infusion anaesthesia (select all that apply)?

(a) Heart rate
(b) Blood pressure
(c) Patient movement
(d) Processed frontal EEG target values
(e) Frontal EEG spectrogram analysis (i.e., frequency, time, and intensity of EEG waves)
(f) Textbook doses of anaesthetics based on empirical evidence
(g) None of the above

(18) What do you consider to be adequate surrogates to anaesthetic depth during inhaled anaesthesia (select all that apply)?

(a) Heart rate
(b) Blood pressure
(c) Patient movement
(d) Spontaneous respiration
(e) End-tidal halogenated gas concentration
(f) Processed frontal EEG target values
(g) Frontal EEG spectrogram analysis (i.e., frequency, time, and intensity of EEG waves)
(h) None of the above

(19) What do you consider to be adequate surrogates to anaesthetic depth during multimodal anaesthesia (e.g., propofol combined with sevoflurane, ketamine and clonidine) (select all that apply)?

(a) Heart rate
(b) Blood pressure
(c) Patient movement
(d) Spontaneous respiration
(e) End-tidal halogenated gas concentration
(f) Processed frontal EEG target values
(g) Frontal EEG spectrogram analysis (i.e., frequency, time, and intensity of EEG waves)
(h) None of the above

(20) Do you measure and modify anaesthetic depth according to burst suppression (an equivalent of isoelectric or flat EEG) when using a frontal EEG?

(a) Always
(b) On most occasions (> 50% of the time)
(c) Occasionally (< 25% of the time)
(d) Never

(21) Do you feel safe lowering your anaesthesia infusion/end-tidal partial pressure when burst suppression is present?

(a) Always
(b) On most occasions (> 50% of the time)
(c) Occasionally (< 25% of the time)
(d) Never

(22) Which of the following complications do you think anaesthesia depth monitoring coupled with a goal-directed approach (e.g., titration of hypnotic to maintain Bispectral Index between 40 and 60) can *decrease* (select all that apply)?

(a) Post-operative delirium
(b) Post-operative cognitive dysfunction
(c) Stroke
(d) Awareness
(e) Myocardial infarction
(f) Acute kidney injury
(g) None of the above

(23) Which of the following complications do you think nociception monitoring coupled with a goal-directed approach (e.g., titration of opiates to maintain NOL Index between 10 and 25) can *decrease* (select all that apply)?

(a) Post-operative delirium
(b) Post-operative cognitive dysfunction
(c) Stroke
(d) Awareness
(e) Myocardial infarction
(f) Acute kidney injury
(g) None of the above

(24) Which of the following complications do you think nociception monitoring can lead to the following post-operative outcomes? (select all that apply)

(a) Decreased post-operative nausea or vomiting
(b) Decreased time to extubation
(c) Decreased opioid induced hyperalgesia
(d) Decreased post-operative pain and opioid use
(e) Decreased PACU length of stay
(f) None of the above

(25) Are you aware of published algorithms to titrate hypnotic and/or antinociceptive drugs based on the information provided by the monitors?

(a) Yes
(b) No

(26) In 2020, do you believe combining nociceptive and anaesthetic depth monitoring will improve patient care in the operating room?

(a) Always
(b) On most occasions (> 50% of the time)
(c) Occasionally (< 25% of the time)
(d) Never

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**Consent to participate** Respondents were informed that their answers would be studied anonymously.

**Consent for publication** The authors give consent for publication of this study after peer-review and acceptance by the Journal.

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