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YEAR IN REVIEW

A year in review in Minerva Anestesiologica 2016

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General anesthesia

According to the principles of enhanced recovery after surgery (ERAS), a recommendation of grade strong has been issued to avoid anxiolytics for premedication because they could delay postoperative recovery.¹ The April issue of Minerva Anestesiologica contained a systematic review by Mijderwijk et al. on premedication with benzodiazepines (BZDs) in one-day surgery.² The associated meta-analysis showed that BDZs increased time to recovery, but not time to discharge to wards, and reduced the incidence of postoperative nausea and headache, but did not improve anxiety and, in general, psychological outcome. The Authors concluded that withholding benzodiazepine premedication to avoid delayed discharge to wards is not evidence-based. However, the main quality of the nineteen studies reviewed was not high, because most of them investigated only oral administration, some were very old, and some pulled different BDZs and routes of administration together. In the accompanying editorial, Carassiti et al. pointed out that in most cases, the need for anxiolytic medication may be cancelled by means of a good preoperative interview.³

Intravenous premedication with short-acting drugs provides an alternative to traditional BDZ administration.⁴ White et al. compared the effects of sub-hypnotic intravenous doses of propofol 20 mg, and midazolam 2 mg, given in the preoperative holding area just before being transferred to the operating theatre. Both drugs caused significant anxiolytic, sedative, and amnestic effects, without cardiorespiratory depression.⁵ The only difference was a stronger amnestic effect of midazolam. The authors recommended to respect proper dose/ body weight relationships (0.2-0.4 mg/kg for propofol, 25 µg/kg for midazolam) in order to avoid undesirable effects, particularly in elderly and high-risk patients.

Elderly people are particularly prone to develop postoperative delirium (POD), which often delay the discharge from the hospital, prevents full return to normal life, and increases social costs of healthcare.⁶ Stukenberg *et al.* carried out a secondary analysis on data

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from the SuDoCo trial,7 which demonstrated that intraoperative neuromonitoring is associated with a lower incidence of delirium, possibly by avoiding too deep anesthetic levels.8 The authors utilized three different scores to assess the neurocognitive status of 996 elderly patients ten minutes after the end of general anesthesia for elective noncardiac surgery, and found that the Richmond Agitation-Sedation Scale (RASS) and the Nursing-Delirium Screening Scale (Nu-DESC) were predictive of POD.

Orena et al. reviewed the literature on the anesthetic interventions to prevent POD.⁹ Their analysis pointed out that the use of Bispectral Index (BIS) to avoid deep anesthesia levels is evidence-based, while no other technique or anesthetic drug can be recommended. Probably, strict perioperative control more than technical aspects, is the best tool to minimize the risk of POD; indeed, multicomponent prevention programs may reduce the incidence of delirium by 35%.

Over the last years, target-controlled infusion (TCI) has been increasingly utilized in anesthesia to achieve and maintain desired drug concentrations, in the blood and at the effector site.¹⁰ The natural evolution of such technique was the closed-loop anesthesia, which is based on automated systems wherein measured outputs (BIS, train-of-four ratio, blood pressure) are used by a controller to titrate inputs (drug infusion rates) to the system (the body).¹¹ Theoretical advantages are the optimal drug titration and the decreased workload. Le Guen et al. reviewed the literature on "closed-loop" anesthesia. The good news is that such a system is no longer a holy grail since the required technology is currently available; the bad news is that the ideal output to build the system is still lacking.12

Besch et al. carried out an RCT in patients who underwent upper airway pan-endoscopy, to compare propofol TCI alone or associated with remifentanil TCI.13 They observed that the combination of the two drugs did not interfere with spontaneous breathing and was associated with less hemodynamic response to upper airway maneuvers. Maintaining spontaneous breathing during a painful stimulation like upper airway endoscopic procedure is a hard task for anesthetists, and the Authors clearly showed that TCI is very effective in that condition. The combination of propofol and remifentanil TCI is a current reality, the potential of which is far from being entirely understood.14

Taken together, the two aforementioned articles show that TCI has become a consolidate technology and represents a very useful tool for anesthetists, even if no data have yet demonstrated that its use improves patient outcomes.15, 16

An important side effect of neuromuscular blocking agents is a subclinical prolonged muscular block that can affect the initial postoperative period.¹⁷ This aspect has been unveiled since neuromuscular function is monitored instrumentally,18,19 and has been focused on since Sugammadex, an antidote more effective than traditional neostigmine, has been commercialized.²⁰ Over the last year, Minerva Anestesiologica published three interesting manuscripts on this important topic. Errando et al. assessed the incidence of rNMB in a sample of 763 patients who had received at least one dose of non-depolarizing muscle relaxant during general anesthesia.²¹ They found that 26% presented clinically unapparent rNMB and that predictive factors were length of surgery, type of relaxant, use of halogenates, no intraoperative specific monitoring, no drug reversal, and neostigmine reversal (vs. sugammadex). A lower, but always high incidence of rNMB (11%) was registered in a study by Batistaky et al.22 Martinez-Ubieto et al. compared the incidence of rNMB in patients under general anesthesia who received cis-atracurium, cisatracurium plus neostigmine, rocuronium, and rocuronium plus sugammadex.23 The results of the study showed that rocuronium plus sugammadex was associated with a trivial incidence of rNMB (1%), in comparison with the other techniques investigated (34%, 29%, and 34%, respectively). Although those data are impressive, in daily practice, anesthetists have to balance the effectiveness of sugammadex, its high cost, and its collateral effects.²⁴ The main

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point, however, is probably that neuromuscular function should be monitored whenever non depolarizing muscle relaxants are used, in order to avoid excessive doses of neuromuscular blocking agents and to plan the use and type of reversal agents.²⁵⁻²⁷

Pediatric anesthesia

In some animal species, puppy exposure to anesthetic drugs may cause long term neurocognitive impairment. These data and their potential translation to humans have been reviewed by Disma and Hansen.28 In puppies, alterations of brain development by anesthetics may be caused by post-synaptic neuronapoptosis, but most studies are inadequate in terms of design, conduct, and reporting. In humans, data available are yet very limited. The results of an RCT on two years old children have recently shown that single exposures of about one hour to sevoflurane-based general anesthesia do not increase the incidence of poor neurodevelopmental outcome in comparison with regional anesthesia.²⁹ Disma and Hansen concluded that changes of clinical practice in pediatric anesthesia cannot be based on results from animal studies only; anyway, future preclinical trials should be planned according to ARRIVE guidelines, in order to improve internal and external consistency.30

Weber et al.³¹ performed a survey on the participants in the APRICOTS Trial,³² to assess the opinion of European anesthetists on neurotoxicity of general anesthetics in children and how it affects their daily practice. Only half of the participants, mostly working in pediatric hospitals, considered themselves as well informed on this topic. Two-thirds routinely addressed the issue of hypothetical neurotoxicity with surgeons and parents during pre-anesthetic consultation. Only 17% tried to minimize general anesthesia length and general anesthetic amount by increasing opioid dosage. In general, anesthetists were more interested in future human trials than in additional animal studies. In the accompanying editorial, Kausmann and Laschat recommended that anesthetists discuss the pros and cons of general anesthesia and the risk of neurotoxicity with surgeons and parents, and apply the recommendations of the recently founded SAFETOTS initiative for safe conduct in pediatric anesthesia.^{33, 34} This approach is mainly based on the use of local anesthetics whenever possible, and of all available monitoring techniques to preserve homeostasis and to correct cardiovascular instability as soon as possible. Those goals may be more easily achieved by experienced anesthetists in high volume pediatric hospitals.

In children, high levels of preoperative anxiety are associated with an increased risk of postoperative delirium, pain, enuresis, sleep anomalies, eating disorders, and behavioral changes, such as nightmares and separation anxiety.35, 36 On the other hand, premedication with anxiolytics is sometimes associated with adverse/paradoxical reactions. Nonpharmacological techniques may provide an alternative tool to reduce distress and improve coping skills. Batuman et al. assessed the effectiveness of an educational video about the surgical procedure in children who underwent outpatient surgery.³⁷ In comparison with those verbally informed, children who watched the video presented lower anxiety scores at anesthesia induction and fewer postoperative maladaptive behaviors, such as difficulty getting to sleep, nocturnal enuresis, fear of darkness, objecting going to bed, and decreased appetite. The editorial by Pabelick pointed out that the customization of the information to the real environment may have played an important role in the study; a commercially-produced video may not achieve the same good quality outcomes.38

Airway management

In December, the guidelines on airway management in obese patients issued by the difficult Airway Management Group of the Italian Society of Anesthesia, Analgesia, Resuscitation and Intensive Care (SIAARTI) were published.³⁹ The document addressed all the aspects of airway management in obese patients after an exhaustive examination of the large

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literature available on the topic. Recommendations for the reader are summarized in two diagrams.

Extraglottic devices and videolaryngoscopies (VDL) play a major role in the management of difficult airways.⁴⁰⁻⁴⁴ In comparison with traditional laryngoscopes, the latter provide a better glottic view, less need of a stylet, a higher success rate; besides, they may necessitate less applied force and cause fewer traumatisms.⁴⁵ Finally, VDLs have not only been recommended as the main alternative to traditional laryngoscopy in cases of unanticipated difficult airways, 43, 44 but also proposed for routine tracheal intubation.46

To date, clinicians choose the optimal device for their practice among plenty of commercially available VDLs. In most cases, the choice is based on subjective considerations, but more objective criteria are needed to choose the VDL better suitable in each clinical condition. MA published various studies that compared different VDLs to each other. Alvis et al. evaluated the performance of McGrath MAC and King Vision VDLs in adults with predicted normal airways.47 Operators were experts of traditional laryngoscopy, but not of video laryngoscopy. The use of both devices was associated to high rates of successful intubation, and excellent larvnx visualization. However, McGrath MAC VDL use was characterized by more frequent successful first attempt intubations and shorter intubation times.

Al-Ghamdi et al. compared the traditional Macintosh laryngoscope with Glidescope, Airtrag, and King Vision VDLs; tracheal intubation was performed by unexperienced anesthesiologists in patients with normal airways.48 The authors found no significant differences about the degree of glottis visualization, the number of laryngoscopy attempts, and the need of optimization maneuvers. Airtrag and King Vision VLSs caused less sore throat than Macintosh laryngoscope and GlideScope. Finally, the time to intubation was comparable between the Macintosh laryngoscope and the GlideScope, and significantly longer with the Airtrag, and the King Vision VDLs. On this regard, relatively short differences of 15 to 25 s. were registered, which nonetheless can be critical during unexpected difficult airway management and impossibility to ventilate the patient. Most operators judged the Airtrag as the VLS easiest to use, probably because of their major familiarity with the angulated blade design of Macintosh laryngoscopes. El-Tahan et al. reported similar conclusions in a randomized trial on double-lumen tube (DLT) positioning in simulated easy and difficult airways.49 Airtrag and King Vision VDLs required more time to intubation than Macintosh laryngoscope, but the success rate was very high for all the devices. Again, GlideScope was considered the easiest to use in both scenarios.

The growing use of VDLs may challenge the currently utilized tests for difficult airway assessment because such tests were ideated and checked for direct laryngoscopy.50 A systematic review by Vannucci et al. highlighted that the performance of bedside tests for difficult airway is still limited, so that clinicians should always be prepared to handle an unpredicted difficult intubation.⁵¹ In this scenario, it is reasonable that some predictors may work better for VDLs and therefore assume a new role since VDLs are becoming the standard of care.52

Regional anesthesia

Technical advancements in RA aim to increase the safety and decrease the incidence of complications. In 2009, the Italian Registry of Complications associated to Regional Anesthesia (RICALOR) was founded in order to collect quarterly reports of the procedures performed with regional anesthesia and the complications that occurred. Seventeen Italian hospitals joined the project. In April, Allegri et al. published the first report from RICALOR.53 Regional anesthesia techniques were utilized for primary anesthesia techniques or postoperative analgesia in 117,182 procedures. Complications occurred in two out of 4954 epidural blocks, 12 out of 20,193 spinal bocks, and 15 out of 20,545 peripheral nerve blocks. Five complications were classified as major and

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included a spinal-epidural abscess with long term neurologic sequelae; they did not include any case of hematomas. The total incidence of complication was 0.46‰ and confirmed the high level of safety achieved; nonetheless, no significant trend was observed towards a decreased incidence of systemic toxicity of local anesthetics. In the associate editorial, Apan *et al.* pointed out that the data collected by RICALOR are particularly valuable because they were registered prospectively, whereas most previous investigations about this topic have been conducted on a retrospective basis.⁵⁴

In order to augment the length of postoperative analgesia obtained with peripheral nerve blocks, an option is the use of adjuvants. Several reports suggest that Dexmedetomidine, a highly selective α -receptor agonist, mixed with local anesthetics can increase the duration of peripheral nerve blocks.⁵⁵ Luan *et al.* investigated the effects of the addition of dexmedetomidine toropivacaine in bilateral transversus abdominis plane (TAP) block for abdominal hysterectomy.⁵⁶ They reported increased block intensity, improved pain scores, and reduced opioid consumption, especially in the early postoperative period.

Failure of RA techniques is usually explained by technical problems. A case of familiar inherited resistance to local anesthetics has been described by Clendenen et al. in the October issue.57 Relatives of a patient who had a history of unsuccessful brachial plexus block and subsequent local anesthetic infiltration were examined. To determine the defective gene, medical histories were obtained and whole-exome sequencing performed. The genetic deficiency affected a voltage-gated sodium channel receptor. The incidence of this variation was about 1% in general population. The editorial of Qu et al. provides a detailed description of genetic studies on voltage-gated sodium channels, possible treatment options, and future perspectives.58

Perioperative medicine

Modern anesthetists are involved in many aspects of "non-operative" care of surgical pa-

tients.^{59,60} Rago *et al.* described the Short Hospitalization System (SHS) project, the purpose of which was the progressive passage from ordinary admittances to Day Surgery and outpatient services for many surgical procedures, with the consequent cost reduction.⁶¹ The project offers new responsibilities to the anesthetist, progressively transformed in a perioperative physician.

Elderly people who undergo major surgery are progressively increasing and at higher risk of perioperative complications.⁶² De Leon wrote an exhaustive review on the dysfunctions of the digestive system in the elderly.⁶³ He focused on possible troubles related to the impairment of gastrointestinal motility since about 70% of postoperative pneumonias in elderly people are due to pulmonary aspiration.

Perioperative medicine is aimed to build a safe pathway for patients, avoiding complications and making postoperative recovery faster. On this purpose, it needs reliable scores to predict high risk patients. Dette et al. investigated the effectiveness of Mallampati Score associated to STOP-Bang score in order to increase the predictivity of STOP-Bang score alone for obstructive sleep apnea.64 They studied 303 unselected surgical patients and observed that predictivity of both scores was low, both alone and in combination. The authors concluded that other tests should be utilized. but acknowledged the problem to reconcile the use of time-consuming and expensive tests (e.g. polysomnography) with the need to save resources.

Literature on goal-directed therapy (GDT) presents conflicting data about its effectiveness in surgical settings.⁶⁵ Lack of standardization and frequent overtreatments may explain failures. There is no consensus about the definitions of volume therapy, fluid challenges, and fluid responsiveness, and that may cause unnecessary pharmacological supports and highly positive fluid balances. Broch *et al.* evaluated the effectiveness of GDT with the Nexfin monitoring system (which measures cardiac index and pulse pressure variations, noninvasively) on patients who underwent elective major abdominal surgery.⁶⁶ In comparison

with standard management, GDT did not improve outcome, nor increase the incidence of complications. Yet, the study group received more inotropes and presented higher cardiac indexes and lower pulse pressure variations, due to the pre-emptive nature of the protocol.

Preventing pulmonary complications have an important impact on perioperative mortality, morbidity and costs.67 Strategies for prevention of pulmonary complications include smoking cessation for at least two months, delay of elective procedures after upper airway infections, intraoperative protective ventilation, and postoperative alveolar recruitment by incentive spirometry, deep breathing exercises, and CPAP.68, 69 These strategies are time- and money-consuming and should be reserved for high-risk cases. Patient-related, procedurerelated, and laboratory-based predictors have been extensively searched for by risk analyses and prevention models.⁷⁰ Mazo et al. outlined the correct methodology for model selection and validation, including an exhaustive description of modifiable and unmodifiable risk factors.⁷¹ In the accompanying editorial, Ball and Pelosi underlined that validated tools are strictly warranted to modify the clinical practice.72

Early rehabilitation plays a crucial role in fast-track programs. Dumans-Nizard *et al.* reported the results of a rehabilitation program performed after posterolateral thoracotomy for lung resection.⁷³ The program included multi-modal analgesia, early removal of chest drains, and prompt restart of feeding and ambulation. Results showed a high degree of patient satisfaction and a trend towards reduction of hospital stay.

Rivas *et al.* studied the effects of postural changes on pulmonary gas exchange before and after bariatric surgery.⁷⁴ Unexpectedly, in hypoxemic individuals before surgery, PO₂ improved when supine positioning was kept. After surgery, arterial oxygenation improved when upright and worsened when supine in all subjects. Such findings were not entirely consistent with previous studies.^{75, 76} Magni and Fumagalli summarized pulmonary pathophysiology in morbidly obese patients and

discussed the correct ventilatory approach, including the role of high PEEPs and transpulmonary pressure measurement.⁷⁷

Postoperative analgesia.

Postoperative pain management still represents a challenge for anesthesiologists. Over 80% of patients experience pain after surgery,⁷⁸ and up to 50% of patients may develop chronic post-surgical pain (CPSP) after common operations.⁷⁹⁻⁸¹ Major obstacles to optimal postoperative analgesia are organizational, cultural and economic.^{78, 82} Indeed, current expectations from surgery are no longer limited to patient survival and anesthetist tasks are not limited to the operating theatre, but comprehends all the perioperative period. The new role as perioperative physician should be associated with a "goal-directed, patient-centered" management.^{83, 84}

Grosu *et al.* investigated the evolution of pain after total knee arthroplasty (TKA), during a follow-up period of twelve months.⁸⁶ They observed that pain and its negative consequences on quality of life went well beyond the acute intra-hospital period. One year after TKA, 17% of patients still took analgesic medications and 30% had moderate to severe sleep problems. Similarly, enjoyment of life, mood, and degree of satisfaction were negatively affected.

One important and not always considered determinant of postoperative pain is patient psychological conditions and in particular the anxiety level.⁸⁵ Gorkem *et al.* found that high anxiety scores in patients who underwent obstetric surgery were an independent predictive factor of increased opioid consumption, and suggested that psychological evaluation should be included in the preoperative evaluation.⁸⁶ This is particularly important in obstetric patients, because the mother need to be in good psychological condition to look adequately after the newborn ⁸⁷ and because postoperative pain intensity is well correlated with the incidence of postpartum depression.⁸⁸

Patient-controlled analgesia (PCA) provides good control of pain with lower doses of an-

algesics.^{89, 90} Peng *et al.* compared PCA to other analgesic modalities, in a large sample of patients who underwent abdominal surgery.⁹¹ Their data not only confirmed the better degree of analgesia achieved, but also found that PCA use was associated to lower mortality rates and fewer short and long term complications.

Ketamine is often utilized for postoperative analgesia due to its analgesic properties and opioid-sparing effect, but low-dose regimens are recommended to reduce the risk for potential psychodysleptic side effects.^{92, 93} Bornemann-Cimenti *et al.* compared usual low-dose s-ketamine (a 0.25 mg/kg bolus and 0.125 mg/ kg/h infusion for 48 hours) with minimal-dose s-ketamine (a 0.015 mg/kg/h infusion following a saline bolus) for perioperative analgesia.⁹⁴ Minimal dose treatment resulted the best compromise between the opioid-sparing effect and the risk of developing postoperative delirium.

As a part of a multimodal approach to postoperative analgesia in obstetric patients, neuraxial techniques have a few potential advantages, such as preventing airway problems, avoiding aspiration in non-fasted patients, and allowing an early relationship between the mother and the baby. In a prospective randomized study, Kaufner *et al.* compared the analgesic efficacy of morphine given by spinal or epidural routes after caesarean section.⁹⁵ The latter route was tested as a single bolus or PCA. The authors found lower static and dynamic pain scores with intrathecal morphine.

Another interesting and promising approach to postoperative analgesia is represented by continuous wound infusion of analgesics.⁹⁶ Ball *et al.* compared this technique with epidural analgesia in abdominal surgery.⁹⁷ There was no significant difference in postoperative pain, but epidural analgesia guaranteed a better postoperative pain control in the early postoperative hours and a reduced need of rescue analgesics.

All these studies underline the need for good quality research about postoperative pain.⁹⁸ Indeed, despite the huge literature available, we are far from standard, evidence-based analgesic protocols. Operators should mostly use

multimodal treatments and keep in mind that the real question is not which technique is better than the others, but which is the ideal place for each of them (context sensitive treatment). Reasonably, in the future, analgesic treatments will be personalized by taking into account the predisposition for postoperative pain, on the basis of inflammatory states ⁹⁹ and genetic backgrounds.¹⁰⁰

Pain

Opioids continue to be a mainstay of adequate severe chronic non-cancer pain (CNCP) management.¹⁰¹ However, some concerns have been risen in last years about the potential long-term adverse events of these drugs. In particular, in the United States, opioid prescription was associated with morbidity and mortality of epidemic proportions.102 The leading cause of opioid-related accidents was the abuse/misuse of prescription drugs. Fanelli et al. observed that these reports may cause a dangerous opiophobia, which is totally unjustified because problematic opioid use has been estimated to be around 0.4% in European adults.¹⁰³ They underlined that appropriate and responsible plan of care, together with a periodic patient reassessment, are essential to prevent the risk of opioid abuse and misuse. On the other side, Porter and Viscusi argued that independently from the rate of diversion, addiction, dependence, or abuse, all these events cannot be forgotten, as they represent a potential concern for individual morbidity and mortality.¹⁰⁴ Hence, opioid therapy should be optimized by the association with nonpharmacological and non-opioid therapies in a multimodal approach, as strongly suggested by all guidelines.

Among chronic pain syndromes, cervical radicular pain is one of the main causes of missed workdays and represents a burden for health care costs. Despite its high incidence, current recommendations are based on weak evidence and have been often extrapolated from trials conducted on low back pain patients. In general, a multidisciplinary approach is indicated, including regional analgesia, physical therapy,

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and rehabilitation; surgical treatment is necessary when radicular pain becomes refractory to analgesic therapy.¹⁰⁵ Aurini *et al.* reported the effects of meloxicam, given by ultrasoundguided cervical periradicular injection, in 48 patients with cervical-brachial pain and disability.¹⁰⁶ The authors registered complete pain remission in 94% of patients. Moreover, this method has lower risks of neurological complications in comparison with transforaminal injections, because the needle point is ~1.5 cm away from the foramina. For the implementation in clinical practice, a problem arises from the off-label use of meloxicam when given by perineural injections.¹⁰⁷

Miscellanea

Trevisan *et al.* performed a retrospective single center analysis to test the impact of the use of rotational thromboelastometry (ROTEM) on postoperative outcome and costs in patients who underwent cardiac surgery.¹⁰⁸ In comparison with controls, they found an overall decrease of packed red blood cell transfusion, a shorter stay in the ICU, and a decreased incidence of reoperations. These data were in agreement with the literature on this topic.¹⁰⁹ Evidences are now strength enough to recommend the use of point-of-care coagulation tests, not only in cardiac surgery, but whenever major bleeding is expected.¹¹⁰

Transesophageal echocardiography (TEE) is considered a standard of care during cardiac surgery and is enjoying increasing interest in other areas.111,112 In the August issue, Meineri highlighted TEE potential in clinical situations beyond cardiac surgery.¹¹³ When used intraoperatively, TEE overcomes the limits of parameters such as central venous pressure and capillary wedge pressure, assessing fluid responsiveness more accurately.¹¹⁴ As a consequence, in an ideal setting, TEE should be available every time a reliable hemodynamic monitoring is necessary. Costs and need for trained operators are two major limitations that could be overcome by the introduction of cheaper devices and by the dissemination of knowledge of the technique.

The fields of application of ultrasound in anesthesia and intensive care increase more and more. Recently they have been used to assess the degree of filling of the stomach and the risk of aspiration pneumonia.^{115, 116} Barboni *et al.* utilized ultrasound to evaluate the rate of gastric emptying in pregnant women in the third trimester scheduled for elective caesarean section.¹¹⁷ They registered a slower emptying in comparison with controls and, even more important, confirmed ultrasound effectiveness to assess the gastric content.

Finally, a review on hypnosis and anesthesia by Facco was published in December.¹¹⁸ The author summarizes the story of this "*physiological mind activity characterized by focused attention*," the mechanisms of action, which are still poorly understood, and the potential implementation in clinical practice. Ultimately, he shows how an attractive technique that has gained popularity in the early 19th century and was then nearly forgotten, could be for modern anesthetists. In this era of "multimodal approaches," we are all looking for synergistic interactions. Hypnosis may be an effective ancillary intervention for treatment of pain, nausea, and stress.¹¹⁹

Finally, MA published three editorials that reported some useful suggestions to perform and report the statistical analysis in the manuscripts. The statistician member of the editorial board of the journal and the editor-in-chief authored the articles in order to reflect the interaction between a professional statistician and a clinician. We hope that these editorials could be of value for the authors to facilitate their often difficult task.¹²⁰⁻¹²²

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