The "pandemic" increase of GLP-1 receptor agonists use and the time of discontinuation before anesthesia: Something new?

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Editorial

The "pandemic" increase of GLP-1 receptor agonists use and the time of discontinuation before anesthesia: Something new?

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The approval of GLP-1 receptor agonists (GLP-1 RAs) for glycemic control in patients with type 2 diabetes mellitus by the Food Drug Administration (FDA) in the USA in December 2017 and the European Medicines Agency (EMA) in February 2018 marked a significant milestone [1,2].

This was further extended when the EMA approved a GLP-1 RAs with dietary restrictions and exercise for weight management in patients with BMI $\geq$27 kg/m^2 to <30 kg/m^2 and $\geq$30 kg/m^2 (obesity) in October 2022, followed by the FDA in March 2024 [3,4].

This last after the American Diabetes Association (ADA) guidelines recommended GLP-1 RAs in obese patients with prior myocardial infarction and stroke to mitigate cardiovascular risk and potentially decrease chronic kidney disease (CKD) progression through glycemic control [5].

The overlapping use of GLP-1 RAs between overweight/obesity and diabetes and social media trends in publicized beauty body shape has led to a "pandemic increase" in GLP-1 RAs use [6–10].

GLP-1 RAs are a class of drugs that control the action of GLP-1, a natural incretin hormone released by the intestine after meals. There are numerous effects of GLP-1 RAs on metabolism, including slowing gastric emptying, insulin secretion and inhibition of glucagon secretion. Consequently, GLP-1 RAs act on satiety and appetite reduction through action on the appetite regulation centers in the brain; this leads to a drop in food intake and, consequently, weight loss. [11] They promote a slowdown of gastric emptying, prolonging the feeling of fullness after meals and further contributing to reducing calorie intake. Yet, they regulate blood glucose metabolism by improving glycemic control, which is especially helpful for patients with obesity and type 2 diabetes. Improved glucose regulation can also reduce the need for insulin and other antidiabetic drugs, which can often contribute to increased weight [11].

As the use of GLP-1 RAs, particularly Semaglutide, becomes more prevalent in clinical practice, it is crucial to understand their implications in anesthesia.

In fact, a marked slowing of gastric emptying induced by GLP-1 RAs might increase the propensity for longer intragastric retention of food, with a consequent increased risks associated with surgery, procedural sedation and anesthesia, in terms of regurgitation and aspiration and these aspects together underscore the urgency to understand how to manage patients treated with this class of drug [12].

Gulak MA and Murphy P. were the first to describe regurgitation under anesthesia in a fasted patient under Semaglutide for weight loss in 2023 [13].

Following that, Sherwin M et al. studied the influence of Semaglutide use on the presence of residual gastric solids indirectly using gastric ultrasound in non-obesity volunteers in the supine and lateral positions [13]. They found that 70 % of the patients in the supine take Semaglutide vs 10 % in the control group; gastric ultrasound showed residual solid gastric content with a risk ratio of 3.5 (95 % CI 1.26 to 9.65) compared to control, providing preliminary evidence that GLP-1 RAs may affect gastric emptying and residual gastric contents following an overnight fast and two hours after clear liquids which may have implications for aspiration risk during anesthesia care [14].

The correlation between residual gastric contents volume and the risk of perioperative broncho-aspiration was demonstrated many years ago, and GLP-1 RAs now pose the problem of increasing the risk of having residual gastric contents compared with those not on GLP-1 RAs [15].

So, the questions now are two: first, are all of us convinced that a GLP-1 RAs should be stopped before sedation and anesthesia? Secondly, the need for further research to answer these questions is paramount. We must continue to investigate and gather evidence to guide our clinical decisions.

What we know is that in a recent prospective observational study include 220 patients, 107 in the Semaglutide group and 113 in the non-Semaglutide group, an increased residual gastric content was found in

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43/107 patients (40 %) in the Semaglutide group, and 3/113 (3 %) in the non-Semaglutide group ($p < 0.001$) with Semaglutide use in propensity-weighted analysis with an Odd Ratio (OR) of 36.97–95 % Confidence Interval (CI) 16.54–99.32 - increased residual gastric content showing that preoperative Semaglutide use within 10 days of elective surgical procedures was independently associated with increased risk of residual gastric content on preoperative gastric ultrasound assessment [16].

Another cross-sectional study prospectively enrolled patients from a large, tertiary, university-affiliated hospital that followed preprocedural fasting guidelines before an elective procedure under anesthesia in 124 participants [17]. The prevalence of increased residual gastric content was 56 % in patients with GLP-1 RAs use compared with 19 % in patients who were not taking a GLP-1 RAs drug with GLP-1 receptor agonist found to be associated with a 30.5 % (95 % CI - 9.9 %-51.2 %) higher prevalence of increased residual gastric content (adjusted prevalence ratio, 2.48; 95 % CI - 1.23-4.97) on preprocedural gastric ultrasonography. Both these studies suggest that the preprocedural fasting duration indicated by current guidelines may be inadequate in this group of patients at increased risk of aspiration under anesthesia [16,17].

Suppose that the vast majority of us are convinced to answer yes after these studies; the second question about the optimal GLP-1 RAs preoperative interruption interval remains debated, and there is a more discordant opinion and no literature evidence on how much time we should wait for elective procedure on when to stop it.

To explain how confusing the situation is, the American Society of Anesthesiologists recommends a one-week preoperative Semaglutide interruption [18]. At the same time, the Brazilian Society of Diabetes suggests a three-week preoperative discontinuation [19].

The very recent European Society of Anesthesiology and Intensive Care updated guidelines extend the paragraph about GLP-1 RAs and recommend that when a GLP-1 RAs is prescribed as a weekly injection for glycemic control, considering the long half-life of GLP-1 RAs, it should be paused at least one week before a scheduled procedure requiring sedation/anesthesia [20].

If these drugs are given for obesity, 2 weeks (three half-lives) of suspension are recommended, and whenever possible, a gastric ultrasound should be performed. If the procedure is urgent and postponement is not desirable, endotracheal intubation by rapid sequence induction/intubation is advised. In the case of oral formulation, this last guideline also recommended discontinuing GLP-1 RAs on the day of the procedure. Moreover, a clear fluid diet should be encouraged at least 24 h before any procedure taking GLP-1 RAs.

However, all these recommendations should be intended as clinical practice statements (CPS) based on limited evidence and may not be universally applicable [20].

Therefore, individual patient factors and clinical judgment should also be considered when deciding about the preoperative management of GLP-1 RAs, empowering us to make responsible patient decisions.

In this issue of Journal Clinical Anesthesia, Leonardo Barbosa Santos and their colleague studied the risk of broncho-aspiration under anesthesia in patients who use Semaglutide versus those not used through measured from the aspiration/suction canister >0.8 mL/kg of fluid content in a single-center retrospective study [21].

The novelty of the present study lies in the fact that it is the first study focusing on the effect of different Semaglutide preoperative interruption intervals on the incidence of increased residual gastric content. The main result of the study can be reported as follows: only preoperative Semaglutide discontinuation >14 days was enough to produce a similar risk of increased residual gastric content between these take Semaglutide and does not [OR = 1.37 (95 %CI 0.4–3.43)]. A two-week interruption of Semaglutide may be sufficient to reduce broncho-aspiration risk in patients taking preoperative Semaglutide [21].

Regardless, the three-week interruption could appear excessive and may eventually lead to perioperative risk of hyperglycemia that represents a risk factor for poor outcomes in diabetes mellitus patients with the need for a personal Endocrinologist guide bridge to the glycemic control gap through short-acting agents like insulin that do not affect gastric emptying.

This implies that a longer interruption period from the GLP-1 RAs may be more beneficial in reducing broncho-aspiration risk while avoiding potential hyperglycemia derangement.

To conclude, it is essential to acknowledge that there is currently insufficient evidence to provide definitive guidance regarding the ideal cessation period for glucagon-like peptide-1 receptor agonists before elective surgery. This awareness of the existing uncertainty is crucial in improving our patient care. Yet, in patients with type 2 diabetes mellitus, a personalized approach seems rational, considering the patient's specific condition and needs. A discussion with the patient's endocrinologist, respecting their circumstances and preferences, is advised. It is crucial to prioritize patient safety when taking GLP-1 RAs for weight management. Withholding GLP-1 RAs for at least >14 days, as reported by Leonardo Barbosa Santos [21], before an elective surgical procedure, also seems rational until new evidence is available.

Therefore, we congratulate Leonardo Barbosa Santos and colleagues [21] for pointing out this important new aspect for helping Anesthesiology in their everyday practice, calling for further research to present an opportunity for Anesthesiologists to contribute to the growing knowledge in this area and improve patient care in which more extensive prospective randomized trials are urgently needed to guide the perioperative management of GLP-1 RAs.

CRediT authorship contribution statement

Luigi Vetrugno: Conceptualization, Writing – original draft. **Damiano D'Ardes:** Writing – original draft. **Cristian Deana:** Writing – original draft.

Declaration of competing interest

None.

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