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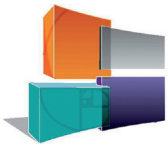

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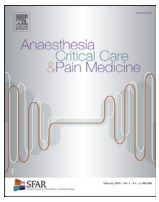

Editorial

Iris and PreVent trial: Pioneers to complete the current guidelines?

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Rapid Sequence Induction (RSI) is widely used by physicians in the operating theatre and in Intensive Care Unit (ICU) during emergencies situations. This procedure currently raises two issues:

- the interest of the Sellick manoeuvre in this context;
- the safety of positive pressure ventilation between induction and intubation, especially in intensive care.

Indeed, although widely used in daily cares, Sellick manoeuvre relies on very poor evidences, since the case report published by Sellick et al. in 1961 [1], only a few publications that assessed its effectiveness [2,3] and safety have been repeatedly challenged [4,5]. Concerning the positive pressure ventilation, current recommendations give a strong precedence to pre-oxygenation techniques (BAVU, non-invasive ventilation..) without covering the question of ventilation during apnoea in patients [6]. The increased risk of pulmonary aspiration of this manoeuvre while preventing hypoxemia remains debated. Some guidelines recommend such type of ventilation during this period [7], while others recommend avoiding it [8].

Recently, two highly powered trials have questioned these historic rules and are still frequently taught: the IRIS trial published in the JAMA surgery by Birenbaum et al. [9] and the PreVent trial published in the NEJM by Casey et al. [10]. These two large multicentre, randomised trial aim to investigate the respective impact of the use of cricoid pressure (Sellick manoeuvre) in operating theatre and Bag-Mask Ventilation (BMV) in Intensive Care Unit (ICU) during Rapid Sequence Induction (RSI).

In the IRIS trial, authors randomised 3472 patients in a non-inferiority two-arm trial, and used aspiration frequency as primary endpoint. With 10 patients meeting the primary endpoint in the Sellick group (0.6%) and 9 patients in the sham group (0.5%) (Relative Risk 0.90; $CI_{95\%}$ [0.39–1.99]), this study's upper confidence interval limit exceeds the non-inferiority limit of 1.5, and thus failed to demonstrate non-inferiority ($P = 0.14$) [11]. Interestingly, secondary endpoints suggest that the Sellick manoeuvre might increase difficulties related to the RSI procedure with significantly more 3 and 4 Cormack and Lehane grades ($P < 0.001$) and a longer intubation time ($P < 0.001$).

In the PreVent trial, authors randomised 401 patients with the lowest oxygen saturation during the procedure as primary outcome. Bag-mask ventilation was performed, between anaesthetic induction and laryngoscopy, using a PEEP valve, slow rate (10/min) and low volumes (the smallest volume required to generate visible chest rise). Results show that patients receiving BMV had higher saturation (96% [87–99] vs. 93% [81–99]; $P = 0.01$) than those receiving no ventilation. Secondary endpoints report that patients receiving BMV have a lower incidence of severe hypoxemia (RR = 0.48 $IC_{95\%}$ [0.30–0.77]) but no differences in aspirations (2.5% vs. 4.0%; absolute risk difference = 1.5% IC: 95% [−4.9–2.0]; $P = 0.41$), new opacities on chest radiography, in-hospital mortality, number of ventilator-free days or days out of the ICU.

These two studies nevertheless have some limitations.

First, these trials have been conducted in selected populations: critically ill patients in ICU (PreVent) and patients that require RSI in the operating theatre (IRIS). Results should thus be interpreted carefully outside those respective situations (e.g. pregnant women excluded in both studies).

Second, the impossibility of performing the procedure in blind for PreVent, and the situation of the blinded procedure for IRIS (intervention interrupted three times more frequently in a group than in the other, proximity between the operator proceeding to the laryngoscopy and the investigator in charge of the blinding) could have introduce important bias.

Third, in the PreVent trial, discrepancies between clinically important baseline characteristics seem to exist between randomisation groups: BMV have less pneumonia (57% vs. 80%) and more patients with an oxygen saturation lower than 92% (13.9% vs. 8.6%) compared to the No Ventilation group. These discrepancies might be related to an allocation bias with the use of sealed envelopes, which is known to be more susceptible to manipulation compared to other approaches [12]. Authors propose a post-hoc analysis to account for the difference in oxygen saturation that does not change their findings.

Fourth, in both studies, statistical considerations seem to have strongly impacted authors' choices regarding primary endpoints. Indeed, in the PreVent study, authors justify their choice to use a 3% difference of oxygen saturation as primary endpoint by explaining that "the number of patients should have been ten times larger to determine whether bag-mask ventilation could increase the

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relative risk of aspiration by 50%". In the IRIS study, authors used aspiration as primary endpoint but with an assumed rate, which finally turned out to be too high (expectation of 2.8% instead of 0.5% finally observed). This situation is known to reduce the capacity of a study to demonstrate non-inferiority in the case it eventually existed (e.g. reduce study power). This point, as well as the choice to accept an increase of relative risk (RR) of 1.5% as non-inferior, have probably been guided by a principle of reality: sample size would indeed have needed to be twice as large with an aspiration rate of 1.5% (instead of 2.8%) and eight times larger with a RR of 1.15 (instead of 1.5) [13].

Finally, in the PreVent trial, the high number (20%) of protocol violation (i.e.: BMV use) in the "control" group could have reduced the observed difference in treatment effect between groups in intention-to-treat-analysis.

Despite these limits, these two studies remain the strongest available evidence regarding two important clinical questions, and strong messages can be acknowledged:

- pulmonary aspiration after RSI is, in these population, a very rare complication (0.5 to 4.0%);
- Sellick manoeuvre is an intervention that can complicate RSI;
- even if positive pressure ventilation between induction and intubation seems safe in ICU, this intervention can not be safely applied in all "real" full stomach situations.

As conclusion, these publications seems to be two interesting opportunities to question old dogmas place in daily cares that should quickly integrate current guidelines [6].

Disclosure of interest

The authors declare that they have no competing interest.

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