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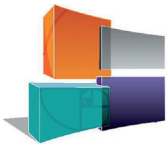

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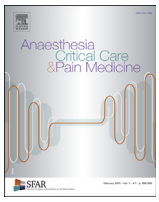

Editorial

New paradigm shift in perioperative medicine: General anaesthesia finally better than procedural sedation for anterior circulation stroke thrombectomy?

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Endovascular mechanical thrombectomy (MT) is the standard of care for proximal anterior circulation (i.e. internal carotid artery and middle cerebral artery) acute ischemic stroke (AIS) [1]. As a consequence, vascular neurology embraced emergency interventional medicine. Eligible patients are often frail and generally old with an acute neurological injury and comorbidities. MT is a difficult and stressful procedure, both for physician and patient, which requires immobility to avoid possible severe complications such as vascular perforation. Moreover, patient condition could deteriorate during the procedure with coma, respiratory failure due to aspiration pneumonia, and so on.

To face this challenge, emergency medicine, neurology, neuroradiology and often anaesthesiology teams must be integrated to the process of care. Therefore, due to the aforementioned prerequisites, procedural sedation (also known as conscious sedation (CS)) if not general anaesthesia (GA) (i.e. associated with tracheal intubation) could appear necessary and beneficial.

Nevertheless, for a decade now, controversy concerning the best periprocedural management in this field exists [2]. Indeed, GA was assumed to increase mortality and alter neurological outcome. This assumption was mainly promoted by the neurology community [3]. Possible mechanistic explanations were that 1) GA could increase procedural delays that counteract a "time is brain" strategy, 2) GA was associated with arterial hypotension that could alter cerebral blood flow in the so-called penumbra area [4]. However, data supporting this theory were associated with bias [5]. Thus, studies were observational and mainly retrospective, confounded by selection bias since GA was provided in more severe patients (defined by higher National Institute of Health Stroke Scale (NIHSS) at inclusion) [6]. Moreover, improved neurological outcomes associated with MT were only recently demonstrated, in 2015, using clear patient selection criteria and specific devices (stent retriever) [7]. In fact, controversy was mainly due to earlier studies.

Post hoc analysis of observational data concerning the anaesthetic strategy in randomised controlled trials that validated MT *versus* medical treatment alone since 2015 were less obvious [8]. Indeed, MT was still beneficial under GA compared to the controlled group (no MT). There was no mortality difference between GA and CS but 3-month functional independence (defined as a score of 0 to 2 on the modified Rankin Scale (mRS) ranging from 0 (indicating no symptoms) to 6 (death)) was still better under CS compared to GA. NIHSS was the same at inclusion between GA and CS. Nevertheless, even with improved data quality as prospective, an imbalance between treatment groups still exists, as randomisation was not based on the anaesthetic strategy, and the anaesthetic and haemodynamic management was not controlled nor protocolised [9].

Recently, three small European monocentric randomised controlled trials specifically investigated the anaesthetic strategy associated with MT in anterior circulation AIS [10–12]. In these studies, specific teams were in charge of protocolised anaesthesia care with dedicated haemodynamic objectives. First, the SIESTA (Sedation *vs* Intubation for Endovascular Stroke TreAtment) trial included 150 patients and found no difference in early neurological improvement (defined with NIHSS after 24 h) as a primary outcome measure [10]. Second, the ANSTROKE (Anaesthesia during Stroke) trial included 90 patients and was negative regarding the hypothesis of CS associated with improved neurological primary outcome defined using the mRS score 3 months after stroke onset [11]. Finally, the GOLIATH (General or Local Anaesthesia in Intra Arterial Therapy) trial included 128 patients. No difference was demonstrated between GA and CS regarding infarct growth measured with MRI as a surrogate primary endpoint [12].

Indeed, these trials demonstrated a possible non-inferiority associated with GA compared to CS in actual settings of MT for anterior circulation AIS, providing anaesthesia care and haemodynamic management are protocolised. Furthermore, 3-month functional outcome was better under GA as a secondary outcome measure in SIESTA and GOLIATH trials. Even if exploratory, this result of possible better functional outcome associated with GA introduced a possible paradigm shift in the field.

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The authors of these three trials, associated in a collaborative group called SAGA (for SIESTA, ANSTROKE and GOLIATH Association), recently published in the *Journal of the American Association* a systematic review and a meta-analysis of individual patient data about the association of GA *versus* procedural sedation with functional outcome among patients with AIS undergoing MT [13]. Study selection criteria were randomised controlled trials performed in adult patients, published from 1980 to 2019, with NIHSS at least 10 and anterior circulation AIS assigned to randomly receive GA or CS during MT. Among 1892 studies screened for eligibility, only the three aforementioned trials met the inclusion criteria (a pilot Chinese randomised controlled trial was excluded because of the absence of standardised protocol) [14]. Then, 368 patients were included in the analysis. The main outcome measure was the degree of disability at 3 months, defined by the ordinal shift analysis of the mRS score. Secondary outcomes measures notably evaluated 3-month functional independence defined as dichotomised mRS score 0-2 *vs.* 3-6, mortality, radiological endpoints (successful recanalisation and infarct growth), time points and complications.

Despite perceived limited population for a meta-analysis, this study has particular insights. First, 3-month neurological outcome using the mRS as a primary outcome measure is a fundamental patient-centred outcome used in every relevant stroke trial, which allows comparison between studies. Second, aggregation was based on individual patient data, which constitutes a specific type of systematic review since original research data are used directly from researchers responsible for each study, centrally combined and re-analysed. This specific and time-consuming process is considered a "gold standard" of systematic reviews [15].

Groups were well distributed. Mean age was 71.5 ± 12.9 years old and baseline NIHSS was 17 (IQR 14-21).

Intuitive impression was confirmed by the meta-analysis: mean 3-month mRS score was better in the GA group compared to the CS group (2,8 (95% CI, 2.5–3.1) *vs.* 3,2 (95% CI, 3,0–3,5), $P = 0{,}02$). In the same manner, 3-month functional independence (mRS 0-2) was better under GA *vs.* CS (49.2% *vs.* 35.1%; OR, 2,16 [95% CI, 1,31–3,54]; $P = 0{,}003$). No difference in groups existed for mortality. Successful reperfusion (defined as mTICI 2b-3) occurred more often in the GA than in the CS group (72,7% *vs.* 63,2%; OR, 1,84 [95% CI, 1,12–3,01]; $P = 0{,}02$). Despite a slightly longest time for groin puncture in the GA group, time to reperfusion did not differ between groups, neither did procedural complications such as vessel perforation or nosocomial pneumonia. It has to be mentioned that 11,5% of patients randomised to CS had to be urgently switched to GA, mainly due to agitation or procedural complexity. Interestingly, sensitivity analysis (defined as "treated population") that excluded these patients or analysed them with the other group did not reach statistical significance any more for the primary outcome. Hypotension and blood pressure variability were more frequent in the GA group.

Indeed, authors stated that:

- in this study, improved outcome associated with GA could be explained by higher rates of reperfusion, possibly linked to better procedural conditions for the interventionalist, notably immobility;
- providing that there is a dedicated team and management protocols, delays are not an issue;
- hypotension and blood pressure variability associated with GA are not associated with outcome impairment providing they are mild;
- potential neuroprotective effect of GA due for instance to drug mechanism, hypothermia or normocarbia still need to be demonstrated.

Despite the evident methodological quality of this small meta-analysis with apparent low risk of bias (individual patient data setting, no missing values, prospectively designed with pre-specified analysis plan (even though not published), two stages approach to asses heterogeneity, multiple sensitivity, adjusted and sub-groups analysis, quite similar anaesthetic and haemodynamic management) questions still exist. Indeed, study limitations underline persistent interrogations at the bedside:

- Patients with NIHSS < 11 were not included. What could be the optimal management of milder strokes?
- Exclusion criteria associated with premorbid mRS were different between the three studies. Despite sensitivity analysis, which appears exploratory, it is not possible to conclude which category of premorbid patients the strategy fits best.
- Exclusion delays of 6 and 8 hours after stroke onset were present in two trials. Indeed, do these results still applied in the moving field of vascular neurology with delay prolongation up to 24 hours with specific brain imaging selection?
- These are quite homogenous, small monocentric European trials. What about different hospital settings and patient populations?
- One could argue that the results could be due to the non-optimal management of the sedative group. In fact, there was no sedation level objective. Over-sedation or under-sedation could have precipitate switch to GA and altered outcomes [16]. And one could also plebiscite only local anaesthesia probably in selected patients (mild strokes) [17].

Ongoing multicentre randomised controlled trials especially in France and China [18–20] will try to answer these remaining questions in this exciting field of research where anaesthesia care could improve the outcome of a worldwide public health issue.

Disclosure of interest

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The other authors declare that they have no competing interest.

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