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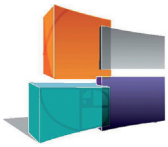

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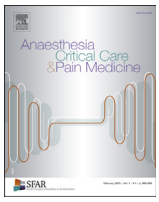

Editorial

A small step for sedation that may become a giant leap for critical care medicine

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Sedation is a corner stone of intensive care practice to reduce patient discomfort and anxiety, facilitate mechanical ventilation and allow essential intensive care procedures. Notwithstanding, in the last 20 years, sedation has been challenged in terms of level of sedation required according to indications and time course of ICU stay, drugs used, algorithms, daily interruption ... In the early 2000s, several studies have shown that improving sedation practices improves patient outcome [1].

Dexmedetomidine, a highly selective α_2-adrenergic agonist, is one of the most exciting drugs available for intensivists since years and years. Dexmedetomidine is a unique sedative agent compared with other sedatives, γ-aminobutyric acid receptor agonists, broadly used for light sedation in mechanically ventilated patients. It has been shown that compared to other sedatives, patients under dexmedetomidine are more arousable, spent less time under mechanical ventilation and in the ICU, and experienced less delirium [2].

The 2018 guidelines of the Society of Critical Care Medicine regarding pain agitation/sedation, delirium, immobility, and sleep disruption included the need for pain assessments and adequate analgesia, sedation level assessment and use of the lightest sedation possible, avoiding benzodiazepines and using as first line drugs dexmedetomidine or propofol [3]. The recommendation of using scales and light sedation is not new; the choice of drugs is less common and supported only by physiological or small studies. In this context, the SPICE III trial has been published in the *New England Journal of Medicine* [4].

This trial has been conducted in two steps. First, a preliminary study designed to assess whether early goal-directed sedation (EGDS) was feasible, safe, can be delivered in a timely fashion, and can achieve early light sedation more effectively than standard sedation [5]. This preliminary study was conducted in 6 ICUs of the ANZIC network. The difference of patients who achieved light sedation was significant with 60% at day 1 and 90% at day two in the EGDS group, versus 14% at day 1 and 50% at day 2 in the control group. The difference was no longer significant at day 4. The authors concluded that EGDS was feasible, appeared safe, achieved early light sedation, minimised benzodiazepines and propofol requirement, and decreased the need for physical restraints. The findings of this pilot study justified a large randomised controlled trial to evaluate whether or not EGDS with dexmedetomidine influenced a patient centred outcome: the 90-day mortality. Assuming a mortality rate of 26%, they estimated that the enrollment of 4000 patients was necessary to provide a sufficient power of 90%.

The trial was conducted in 74 ICUs across 8 countries; sedation target was light sedation, unless it was deemed to be unsafe or contraindicated by the treating physician. In the dexmedetomidine group, the goal was to administer dexmedetomidine as the primary sedating agent or, once the sedation target was achieved, the sole sedating agent. The 4000 patients were included from November 2013 through February 2018, and the overall mortality rate was 29.1%, with no difference in the primary outcome (29.1% 90-day mortality rate in both groups). What should we conclude from this trial? Ones have already claimed that dexmedetomidine had no effect on coma-free or delirium-free days nor 90-day mortality, but caused a higher rate of hypotension and bradycardia [6]. Before we throw the baby out with the bath water, just remember that a few years ago, others concluded that tight glycaemic control reduced morbidity and mortality among critically ill patients, or that activated protein C was the magic bullet to decrease mortality of septic shock patients [7,8]. SPICE III is a large randomised controlled trial, conducted by experts in the field, with a robust methodology and strong outcomes. The trial is based on a simple background; when light sedation is targeted, achieving the sedation level with dexmedetomidine is easier than with propofol or midazolam. Unfortunately, more than 60% of patients had an indication of deep sedation regardless of the randomisation group. Physicians in charge of the patients found an indication of deep sedation for the majority of patients, by habits or by necessity (?), and logical consequence is that 75% of patients in the dexmedetomidine arm received, in addition to dexmedetomidine, propofol or midazolam or both, to reach deep sedation. In the same time, 11.5% of patients in the usual care group received dexmedetomidine to achieve light sedation, which may also have altered the final result. To put these data into context, in the preliminary study, 50% achieved light sedation at day 1 and 90% at

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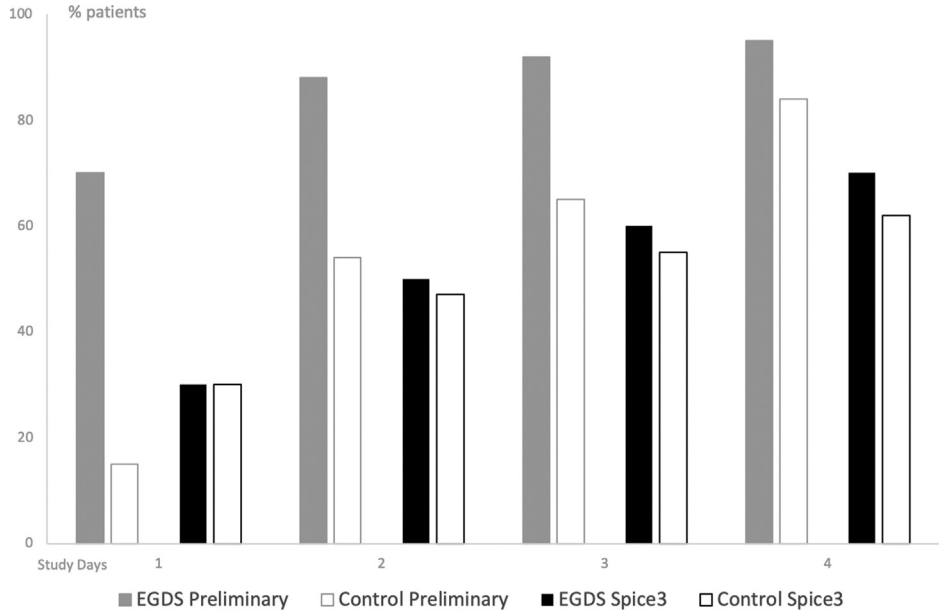

Fig. 1. Percentage of patients achieving light sedation in the early goal-directed sedation (EGDS) versus control group (Control) of the Preliminary [5] and the SPICE III [4] studies.

day 2 in the intervention arm; in SPICE III, only 30% at day 1 and 50% at day 2 achieved light sedation whatever the randomisation arm was. We should note that 50% of patients at day 2 corresponds to the ratio of patients who achieved light sedation in the control arm of the preliminary study, the so-call "standard of care" (Fig. 1). Although the difference was not significant, patients randomised in the interventional arm had one more ventilatory-free day and one more coma-delirium-free day. In the other hand, they had significantly more bradycardia and hypotension.

What have we learned from with this trial about sedation and/or dexmedetomidine? Not much… when dexmedetomidine is added to midazolam or propofol to reach deep sedation, dexmedetomidine increases adverse events. What is the impact of light sedation with dexmedetomidine versus propofol or midazolam on mortality, delirium, ventilator-free days and quality of life after ICU stay… this trial could not tell it, but it is the first time a trial was powered and designed to respond to these questions. What about the anti-inflammatory effect of dexmedetomidine? Probably drowned in the adverse events induced by deep sedation and the side effects of midazolam, propofol or both!

What have we learned from this trial about critical care medicine? Much more than "just one more negative trial".

First, clinical decision remains driven by belief and habits, even after 20 years of research and clinical guidelines. There is a mountain of evidence that deep sedation immobilises patients, limits communication, increases delirium, costs and mortality, and impacts quality of life on the long term. The aim of this trial, for physicians who accepted to participate, was to study the best way to promote light sedation. With this background, 60% of patients were deeply sedated. There was no evident reason for that, at least highlighted in this manuscript, excepted that intensivists do not follow the guidelines, most often [9]. The gap between guidelines and clinical practice seems so important, that we believe that one of the major challenges for academic medicine in the next years will be to find the key to translate results of clinical trials in clinical practice.

Second, when researchers designed clinical trial, they are always balanced between a too strict protocol, which is not truly real life and may slow down inclusions rate, and "at the discretion of the physician in charge of the patients". We strongly believe that research protocols should be as strict as possible. In this protocol, the authors did not wish to limit indications of deep sedation to indications stated in clinical guidelines, probably to increase enrolment rate. After 3 years of inclusions, 60% of patients were deeply sedated and the trial was not interpretable. In a recent trial, CT-scan was mandatory for inclusion of ARDS patients, but we wished to allow chest x-ray for "too sick patients to be transferred" to the department of radiology or when this one was not available, just to include the maximum of patients [10]. What should have been an infrequent substitute became the majority, 60% of chest x-ray, and due to misclassification, the results are non-interpretable [11].

Last, we must keep in mind that light sedation is just a tool to facilitate early extubation and early mobilisation, moving patients out of the bed and increasing interactions between the patient, his family and the ICU team. If improving sedation practices changed mortality in the early 2000s, we are not sure that changing one single parameter (drug, algorithm…) remains sufficient today to decrease the mortality of 4.5%, the "control group" is no longer the same, as already highlighted for sepsis [12]. In other words, sedation is part of complex interventions and should be assessed as such [13]. The design of the trial and outcomes should be related to these interventions. It is not the same as evaluating early goal directed sedation in 6 ICUs of the same network than in 74 ICUs across 8 countries. A cluster randomisation, with or without step-wedges, can sometimes be more appropriate than a full randomisation. An inadequate outcome, even if statistically robust, provides an inadequate assessment of the success or otherwise of an intervention that has effects across a range of domains. A negative trial, as this one, does not indicate that a given intervention or a drug per se is useless or wrong, but simply disproves the premises [14]. We bet, even if it is speculative, that dexmedetomidine is more useful when it is part of ABCDEF bundle [15] than in a population where 60% of patients are deeply sedated.

Disclosure of interest

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A.M. and A.J. declare that they have no competing interest.

References

[1] Reade MC, Finfer S. Sedation and delirium in the Intensive Care Unit. N Engl J Med 2014;370:444–54.

[2] Constantin J-M, Momon A, Mantz J, Payen J-F, De Jonghe B, Perbet S, et al. Efficacy and safety of sedation with dexmedetomidine in critical care patients: a meta-analysis of randomized controlled trials. Anaesth Crit Care Pain Med 2016;35(1):7–15. http://dx.doi.org/10.1016/j.accpm.2015.06.012 [Epub 2015 Dec 11].

[3] Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med 2018;46:e825–73.

[4] Shehabi Y, Howe BD, Bellomo R, Arabi YM, Bailey M, Bass FE, et al. Early sedation with dexmedetomidine in critically ill patients. N Engl J Med 2019;380(26):2506–17. http://dx.doi.org/10.1056/NEJMoa1904710 [Epub 2019 May 192].

[5] Shehabi Y, Bellomo R, Reade MC, Bailey M, Bass F, Howe B, et al. Early goal-directed sedation versus standard sedation in mechanically ventilated critically ill patients. Crit Care Med 2013;41:1983–91.

[6] Meyfroidt G, Smith M. Focus on delirium, sedation and neuro critical care 2019: towards a more brain-friendly environment? Intensive Care Med 2019;45(9):1292–4. http://dx.doi.org/10.1007/s00134-019-05701-2 [Epub 2019 Jul 24].

[7] Bernard G, Vincent J, Laterre P, LaRosa S, Dhainaut J, Lopez-Rodriguez A, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699.

[8] van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359–67.

[9] Léone M, Ragonnet B, Alonso S, Allaouchiche B, Constantin J-M, Jaber S, et al. Variable compliance with clinical practice guidelines identified in a 1-day audit at 66 French adult intensive care units. Crit Care Med 2012;40(12):3189–95. http://dx.doi.org/10.1097/CCM.0b013e31826571f2.

[10] Jabaudon M, Godet T, Futier E, Bazin J-E, Sapin V, Roszyk L, et al. Rationale, study design and analysis plan of the lung imaging morphology for ventilator settings in acute respiratory distress syndrome study (LIVE study): Study protocol for a randomised controlled trial. Anaesth Crit Care Pain Med 2017;36:301–6.

[11] Constantin J-M, Jabaudon M, Lefrant J-Y, Jaber S, Quenot J-P, Langeron O, et al. Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial. Lancet Respir Med 2019. http://dx.doi.org/10.1016/S2213-2600(19)30138-9 [S2213-2600(19)30138-9], [Epub ahead of print].

[12] Edriss H. What comes after the early goal directed therapy for sepsis era? J Thorac Dis 2017;9:3514–7.

[13] Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. Br Med J 2011;343:d4002.

[14] Gattinoni L, Giomarelli P. Acquiring knowledge in intensive care: merits and pitfalls of randomized controlled trials. Intensive Care Med 2015;41(8):1460–4. http://dx.doi.org/10.1007/s00134-015-3837-7 [Epub 2015 Jun 3].

[15] Pun BT, Balas MC, Barnes-Daly MA, Thompson JL, Aldrich JM, Barr J, et al. Caring for critically ill patients with the ABCDEF bundle. Crit Care Med 2019;47(1):3–14. http://dx.doi.org/10.1097/CCM.0000000000003482.

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