Prolonged diaphragmatic dysfunction in continuous interscalene brachial plexus block: Is it clinically relevant?

Audrey de Jong, Samir Jaber

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In this issue of *Anaesthesia Critical Care & Pain Medicine*, Cuvillon et al. [1] evaluated in an elegant prospective study the effect of continuous interscalene brachial plexus nerve block (ISB) on forced vital capacity (FVC) at h24, in comparison with single ISB. Unilateral diaphragmatic dysfunction is indeed a quasi-constant side-effect of ISB, with potential negative impacts on pulmonary function [2].

The authors performed a prospective, intention-to-treat, non-randomized, consecutive inclusion study in adult patients scheduled for elective shoulder surgery with an anaesthetic procedure combining general anaesthesia and ISB for postoperative analgesia. In the single ISB group and in the continuous ISB group, respectively 30 and 32 patients were included. Diaphragmatic excursion, assessed by ultrasound, spirometric evaluations and clinical assessments were regularly performed until h48. The authors concluded that continuous infusion of ropivacaine during 48 hours was associated with prolongation of unilateral diaphragmatic dysfunction, without significant spirometric measurement or clinical respiratory differences, compared to single ISB group.

However, the definition of "clinical respiratory differences" remains debated. In the study of Cuvillon et al. [1], spirometric differences are highlighted. A difference between single and continuous groups was observed at h24 for: FVC (primary endpoint) (−25%, $P = 0.038$) and forced expiratory volume (FEV) 1s (−24%, $P = 0.036$). No differences for other time points (h0–h48) were noted. Clinical respiratory evaluations (respiratory rate, SpO_2, supplementary nasal oxygen), postoperative pain scores and additional opioid consumption were similar between groups. Nevertheless, the potential negative consequences of a lower FVC and FEV1s at h24 have to be raised. These impacts of decreased FVC depend primarily on the population analysed. In the study of Cuvillon et al. [1], exclusion criteria were well defined and contained patients with respiratory impairments. In case of baseline oxygen saturation $< 94\%$ while breathing room air, body mass index > 35 kg/m^2 or preoperative opioid therapy, pregnancy, vital capacity below 1.5 L, sleep apnoea or chronic obstructive pulmonary disease, patients were not included. Hence, a threshold of 25% of spirometric changes was considered clinically relevant by the authors, which seems appropriate in this selected population of patients with "healthy" lungs. In addition, 25% is the threshold commonly accepted in previous studies when assessing side-effects of ISB [3–5].

As a matter of fact, the respiratory side-effects of continuous ISB on unilateral diaphragmatic dysfunction must be balanced with the advantages of continuous versus single ISB. Continuous ISB has been associated with increased pain relief and improved functional recovery with fewer analgesic side-effects [6–8]. However, the analgesic efficacy of continuous ISB compared with parenteral opioid analgesia for pain relief after major shoulder surgery remains debated [7]. In the study of Cuvillon et al. [1], visual analogic scale (VAS) pain score at mobilization were decreased at h24, h36 and h48 in the continuous ISB group when compared to the single ISB group, whereas VAS pain score at rest were comparable between groups.

Similarly to the results reported in the Cuvillon et al. [1] study, Urmey et al. [3] reported in 13 patients scheduled for shoulder surgery which had ISB, using neurostimulation, that diaphragmatic paresis appears to be an inevitable consequence of ISB [3]. However, in another study published in 2009 [9], the use of ultrasound guidance was associated with a decrease of unilateral diaphragmatic dysfunction compared to neurostimulation. Despite the use of ultrasound guidance in the study of Cuvillon et al. [1], all patients experienced diaphragmatic dysfunction thirty minutes after blocks. The combined use of ultrasound guidance and low volumes and concentrations of local anaesthetics in the study of Cuvillon et al. [1] is the reference method to minimize the ventilatory consequences of nerve blocks [10,11].

It bears noting that an important limitation of the study is the absence of a randomized design. The allocation to single or continuous ISB was based on patient's choice, without randomization. Furthermore, as well underlined by the authors in their discussion, the evaluation of primary and secondary outcomes was unblinded. However, pulmonary function testing was highly standardized, which reduces the potential information bias related to this absence of blinding [12]. One statistical strength is that comparisons between groups at each time point were adjusted for multiple comparisons using the Holm procedure. However, sample size was determined to provide at least 80% power to detect a difference of 25% in the percent decrease in FVC at h48 compare to

baseline (5% physiological variation). A mixed model with group, time and interaction as fixed effects and subjects as random effects was finally performed. Specific sample size calculation for repeated measure studies would have been more appropriate [13]. Further methodological issue regarding the sample size is the choice of a superiority design, instead of a non-inferiority design, to show the safety of continuous ISB on pulmonary function compared to single ISB. The aim of a superiority trial is to show that one treatment is superior to another, and the associated statistical test is a superiority test [14]. However, in case of a non-significant result, there are always small differences between groups. A non-inferiority design allows to test if this small difference is really different from the hypothesis of equal effects between groups [15]. The lack of significant difference between two arms in a superiority trial cannot be interpreted as proof of no difference between the two treatments [16]. Sample size needed in a non-inferiority trial [17], designed to confirm the absence of a meaningful difference between two treatments, is indeed much higher than for a superiority trial. Accordingly, the study was not powered to conclude to an equivalence of the two methods, single and continuous ISB, for the percent decrease in FVC [14]. A non-inferiority design should have been interesting in this context of pulmonary safety of continuous ISB compared to single ISB [18,19]. Finally, diaphragmatic dysfunction, other spirometric parameters and clinical respiratory differences were secondary outcomes, and therefore exploratory analysis.

To conclude, the study of Cuvillon et al. [1] is the first to thoroughly assess both pulmonary and diaphragmatic functions following continuous ISB compared to single ISB for shoulder surgery. To limit the confounding factors for interpretation, the authors used the optimal loco-regional anaesthesia methods to reduce the pulmonary consequences of ISB [1]. This prospective non-randomized non-blinded study showed that continuous ISB prolong diaphragmatic dysfunction until h24, without significant differences of pulmonary dysfunction between groups. However, methodological issues does not allow to ascertain the lack of safety (spirometric and clinical) differences between groups, as well underlined by the authors in their discussion. Further large randomized controlled studies are necessary to better evaluate the effect of continuous ISB for shoulder surgery on outcome including also the long term effects of pain relief balanced with prolonged unilateral diaphragmatic dysfunction on pulmonary complications and mortality.

Disclosure of interest

Dr. Jaber reports receiving consulting fees from Drager, Hamilton, Maquet, and Fisher & Paykel. No potential conflict of interest relevant to this article was reported for Dr. De Jong.

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Audrey De Jong, Samir Jaber*

Intensive Care Unit and Transplantation, Critical Care and Anesthesia Department (DAR B), hôpital Saint-Éloi, CHU de Montpellier, INSERM U1046, 80, avenue Augustin-Fliche, Montpellier cedex 5, France

*Corresponding author

E-mail addresses: audreydejong@hotmail.fr (A. De Jong), s-jaber@chu-montpellier.fr (S. Jaber)