Do earplugs reduce delirium in the ICU?

Putzu, Alessandro; Belletti, Alessandro

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The authors reply:

We would like to thank Talbot et al (1) for their excellent comments on our recently published work (2). We intentionally chose transferrin saturation as a robust parameter used in the clinical routine, despite the fact that it cannot completely capture the complex changes in iron metabolism that occur during sepsis. Our data suggest that in a subset of ICU patients, iron cannot be efficiently sequestered in the serum, and that this fact is associated with adverse disease outcome (1). Although we did not directly assess the tissue iron availability in our cohort, the low transferrin levels in our patients and the association of low transferrin with adverse outcome are very well in line with previous reports suggesting that an inadequate iron supply to the tissues may worsen the prognosis of ICU subjects (3).

Similarly to the lack of its precise characterization, the treatment of iron dysregulation that occurs in ICU patients will likely be challenging and will have to take into account the detrimental consequences of both iron overload and iron deficiency. For the latter, the mentioned study demonstrating a stronger response to hypoxia in individuals with iron deficiency represents a clear memento (4). Although iron chelators are widely used in the clinics and are generally considered to be safe, their potential side effects in the very frail group of ICU patients have to be taken very seriously. As a potentially promising alternative to iron chelators, a supplementation of transferrin would both sequester the detrimental labile iron pool and improve the delivery of iron to the tissues.

As highlighted by the vivid discussion in response to our article and the above considerations, iron metabolism remains an incompletely understood and exciting area of research and its better understanding holds a promise to translate into improved therapy of ICU patients.

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Renwar Nuraldeen, MD, Frank Tacke, MD, PhD, Alexander Koch, MD, Christian Trautwein, MD, Department of Internal Medicine III, University Hospital Aachen, Aachen, Germany; **Pavel Strnad, MD,** Department of Internal Medicine III and Interdisciplinary Center for Clinical Research (IZKF), University Hospital Aachen, Aachen, Germany.

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Do Earplugs Reduce Delirium in the ICU?

To the Editor:

We read the interesting meta-analysis about the efficacy of earplugs as a sleep hygiene strategy for reducing delirium in the ICU published in a recent issue of *Critical Care Medicine* by Litton et al (1). The topic is crucial since up to one third of the ICU patients present delirium, and it could be associated to mortality (2).

We analyzed in detail the article of the meta-analysis and the Supplementary Appendix 1–3.

We have some significant questions to address about the present meta-analysis.

In the article, neither in the text nor in the figures, *p* value for effect was not reported, and the only *p* value reported was the *p* value for heterogeneity. Furthermore, in the article, it is impossible to find the number of events per study and the total number of events. These significant deficiencies do not allow the extent and power of the results to be understood.

In the Introduction and Methods paragraphs, the authors exposed the secondary aim of the study: the assessment of the effect of earplugs on ICU length of stay. Unfortunately, ICU stay analysis is not mentioned in the results.

Finally, when reading results from the largest randomized trial (RT) included in the meta-analysis (3), it states: "The incidence of delirium, however, was not different for both groups." When analyzing the article in detail, the RT (3) found that 20.3% of the patients in the earplugs group (14/69 patients) versus 19.4% of the patients in the control group (13/67 patients) presented delirium (Fig. 2 in the RT). The trial (3) employed the Neelon and Champagne Confusion Scale (4) and it found a lower incidence of mild confusion, according to this scale. Mild confusion and delirium are different entities as reported in the article of the RT (3) and also when it is compared with Confusion Assessment Method for the ICU (4). In conclusion, we cannot understand how the meta-analysis (1) can report that the relative risk for this RT is 0.58 (95% CI, 0.40–0.84), considering the fact that the results of the meta-analysis are strongly influenced and driven by the statistical report of this included trial (3).

The authors have disclosed that they do not have any potential conflicts of interest.

Alessandro Putzu, MD, Department of Cardiovascular Anesthesia and Intensive Care, Fondazione Cardiocentro Ticino, Lugano, Switzerland; **Alessandro Belletti, MD,** Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy

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The authors reply:

Drs. Putzu and Belletti (1) correctly identify that *p* values were not reported for the primary or secondary outcomes. The relative risk (RR) of delirium as reported for the primary outcome was 0.59 (95% CI, 0.44–0.78). The associated *p* value is less than 0.001. It is unclear whether the provision of a *p* value in this setting adds value, given that the point estimates and associated 95% CIs are provided for all relevant outcome measures (2).

Data on ICU length of stay were only available for three studies and were therefore insufficient for quantitative analysis (3–5). Participants per study are provided in Table 1. Events per study for this outcome and others are available from the primary articles, or alternatively, the database for meta-analysis can be provided on request.

A score of between 20 and 24 in the validated NEECHAM confusion scale indicates mild delirium (6). This same range was described as "standardized" but labeled as "confusion" in the trial by Van Rompaey et al (7). Patients in this category were therefore included in our delirium meta analysis (8). The study by Van Rompaey et al (7) contributed 28% weighting to this meta analysis. Removing the study from the meta analysis did not substantially alter the association between earplugs and RR of delirium (RR, 0.56; 95% CI, 0.35–0.90; $p = 0.02$).

The authors have disclosed that they do not have any potential conflicts of interest.

Edward Litton, MBChB, FCICM, MSc, Department of Intensive Care Medicine, Fiona Stanley Hospital, Murdoch, Perth, WA, School of Medicine and Pharmacology, University of Western Australia, Crawley, WA; **Vanessa Carnegie, MBBS**, Fiona Stanley Hospital, Murdoch, Perth, WA; **Rosalind Elliott, RN, PhD**, Faculty of Health, University of Technology Sydney, NSW, Australia; **Steve A. R. Webb, MBBS, FRACP, FCICM, MPH, PhD**, Department of Intensive Care Medicine, Royal Perth Hospital, Perth, WA, School of Medicine and Pharmacology, University of Western Australia, Crawley, WA

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Accidental Intra-Arterial Infusion of Amiodarone in a Pediatric Patient With Atrial Ectopic Tachycardia

To the Editor:

In a recent issue of *Critical Care Medicine*, Witkowski et al (1) described a case of acute thrombotic occlusion of the brachial artery after intra-arterial administration of amiodarone.

We recently encountered a similar case of accidental intra-arterial administration of amiodarone via the femoral artery in the PICU. Our patient was a 4-year-old boy who presented with vomiting and pallor. He had a heart rate of 280 beats/min and was given three doses of IV adenosine for supraventricular tachycardia. As there was no reversion to sinus rhythm, IV propranolol infusion was given. Subsequently, atrial ectopic tachycardia was diagnosed. Oral flecainide was administered, and serial synchronized cardioversion was performed unsuccessfully. He was intubated in view of cardiorespiratory compromise. Right femoral vascular access was secured using a triple-lumen catheter, with nonpulsatile flow observed. Through this catheter, amiodarone at 5 mg/kg was given followed by infusion at 15 μg/kg/min.

Approximately 8 hours into the infusion, an arterial waveform was seen upon pressure wave transduction. A blood gas analysis confirmed that the catheter was intra-arterial. Throughout this period, no skin changes were observed at the infusion site, and the child was not distressed. Rate control had been achieved within 6 hours of this intra-arterial infusion. It was immediately stopped and converted to a peripheral venous catheter, and the catheter was removed. Close monitoring fortunately did not reveal any signs of limb ischemia, and he was eventually discharged well.

Most cases of intra-arterial drug administration reported previously involved anesthetic and sedative agents (2).To date, two cases of inadvertent intra-arterial adenosine administered through the brachial artery have been reported, both in children with supraventricular tachycardia (2, 3). Aside from brief periods of pain and skin mottling, neither patient had adverse effects. This could be because the short half-life of adenosine causes it to be rapidly metabolized. With amiodarone, however, Witkowski et al (1) postulated that there was direct cytotoxic effect on the vessel wall causing endothelial damage and arterial thrombus formation. In our patient, amiodarone had been running for 8 hours intra-arterially with no clinical suspicion of vascular damage although there was no Doppler study