Commentary

Association of rosuvastatin and delirium in severe sepsis with acute respiratory distress syndrome

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Delirium is described as a constellation of clinical manifestations characterized by disruption of consciousness along with alteration in cognition (1,2). It occurs in up to 80% of critically ill patients in intensive care unit (ICU) and is associated with negative clinical and economic consequences (3). Therefore preventive strategies to reduce the occurrence of delirium in ICU are highly appealing for health care professionals.

Statins exert beneficial effects beyond their lipid lowering activity, the so-called cholesterol-independent or 'pleiotropic effect'. They have shown favorable anti-inflammatory and anti-thrombogenic properties, as well as improving endothelial function and plaque stabilization. They also possess extra-hepatic effects on the central nervous system and immune system (4). Though the exact mechanism remains speculative, neuro-inflammation and oxidative stress are believed to contribute in the pathogenesis of delirium (5). Fragility and old age are also risk factors for delirium, and in the current era many of such patients are on statin for various indications. Expectedly the potential effects of statin on the development of delirium have been the focus of interest for several retrospective, prospective and most recently several well-designed placebo-controlled randomized controlled trials (6-10). These investigations have yielded conflicting results. Furthermore several observations indicating a potential detrimental effect of statins on cognitive impairment have been reported, which add to the ongoing debate over the subject (11-13). Additionally it is speculated that less lipophilic statin agents (pravastatin and rosuvastatin) due to their limited passage through blood-brain-barrier less often result in cognitive impairment (14). In 2012, the U.S. Food and Drug Administration (FDA) change the labeling rules for stains to reflect the potential for generally non-serious and reversible cognitive side effects (15). In the national lipid association (NLA) update on statin safety published in 2014, several concerns were acknowledged yet considering that potential benefits of statins far outweigh their potential harms, their safety were reaffirmed (15). Multiple mechanisms have been proposed for deleterious effects of statin on cognitive function. For one, cholesterol plays an important role in cellular membrane and is an important element of membrane/lipid rafts whose disruption by statin could be neurotoxic. Secondly, nuclear factor-kappa B and tumor necrosis factor decrease due to the anti-inflammatory properties of statin and their effects mostly contribute to synaptic function (16).

In 2008 in a retrospective study evaluating 284,158 consecutive elderly patients undergoing elective surgery, the rate of development of post-operative delirium was found to be higher in patients taking statin with an odds ratio of 1.30. Authors, acknowledging the potential risk of unidentified confounding factors and under diagnosis in their retrospective design, attributed the observation to the changes in cerebral blood flow resulting from alteration of endothelial nitric oxide synthase with statin therapy (6). Later on a series of prospective studies contradicted these results. In 2009, a prospective study on 1,059 patients undergoing cardiac surgery with cardiopulmonary bypass reporting the beneficial effect of statins on reducing the odds of delirium by 46% was published (17). In a smaller prospective study on 167 patients undergoing cardiac

surgery preoperative use of statin was not associated with a change in the postoperative rate of delirium (18). In another prospective study in a mixed surgical and medical ICU, statin use associated with a lower daily risk of delirium (7). Finally, a well-conducted large prospective study reporting that statin use was associated with a decrease in rate of delirium in ICU (9). This was the first multicenter cohort recognizing this association. Another remarkable finding of the study was the observed association between statin discontinuation and increase in incidence of delirium.

These studies clearly call for the need for more randomized controlled trials as such studies provide the highest quality of evidence (19).

Recently, Needham *et al.* published the well-timed randomized clinical trial examining rosuvastatin for the prevention of delirium in ICU in a relatively large group of patients with sepsis and acute respiratory distress syndrome. This was an ancillary study to the SAILS (Statins for Acutely Injured Lungs from Sepsis) trial. Patients were randomized to receive either rosuvastatin or placebo, and both patients and providers were blinded to the treatment strategy. The authors of that study, failed to show the benefit of rosuvastatin in decreasing the incidence of delirium in critically ill patients.

Furthermore there was no difference in the rate of cognitive impairment at 12-month follow up between the two groups. Interestingly no trend toward any benefit from rosuvastatin was observed (mean proportion of days with delirium was 34% in the rosuvastatin group and 31% in the placebo group) warranting the recruitment of larger number of cases (8). Several characteristics make the study strong including double blind and placebo-controlled design and also its 12-month follow-up. However, it is important to note that the study was underpowered for secondary analysis and was mostly intended to generate a hypothesis for future research. In addition, multiple confounding factors and elimination of higher risk patients may have contributed to the negative results in this study. The authors of this study had to exclude the patient with Richmond-Agitation Sedation Scores (RASS) of –4 from the analysis based on protocol from original trial. It has already been demonstrated in multiple publications that deeper sedation leads to higher incidence of delirium (20).

In general, delirium is a syndrome and possibly a symptom of disease with some important risk factors predisposing the critically ill patients to cognitive dysfunction. The hypothesis that inflammation or stress hormones may be a predisposing factor for delirium was generally researched by Porhomayon *et al.* (21). Nevertheless, the findings of SAILS trial are in contrast with the promising observations in prospective cohort studies and highlight the complex interplay of statins, inflammations and pathogenesis of delirium. Future randomized controlled trials are still needed to accurately assess the impact of statin on cognitive function.

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Footnote

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