EDITORIAL

Prediction of Delirium in the Critically Ill Obstetric Patients: An Old Friend to the Rescue?

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Delirium in the intensive care units is a common problem with an incidence ranging from 20 to 87%, varying with the severity of illness, organ dysfunction, and comorbid conditions.[1] It has been extensively studied in general critically ill patients in intensive care unit (ICU). Obstetric patients with a critical illness are a distinct subgroup and pose unique challenges due to physiological changes of pregnancy. The literature does not reveal many studies related to delirium studies, specifically in this subgroup. In the prospective observational study published in this issue, Solanki et al. have sought to investigate the association of C-reactive protein (CRP) levels with delirium as well as its role as a predictor of delirium in obstetric patients in ICU. A growing body of evidence suggests that delirium is associated with inflammation. Zhang et al.[2] demonstrated CRP at admission was an independent predictor of delirium. Also, an increase in CRP >8.1/L in 24 hours was associated with 4 times increased risk of delirium. The most commonly associated risk factors for delirium in ICU include advanced age, dementia, prior coma, emergency surgery or trauma, hypertension, use of psychoactive medications, higher disease severity, and iatrogenic etiologies like blood transfusion and use of some medications.[3] The course of pregnancy and puerperium is often complicated by severe preeclampsia, eclampsia, heart failure, infection, hemorrhage, acute pancreatitis, jaundice, cholestasis, and diabetes mellitus, for which patients may require ICU admission. These conditions can predispose to the development of delirium. However, the association of pregnancy with inflammation and delirium remains yet to be elucidated. Zhu et al.[4] identified galactin3, a pro-inflammatory protein, S100 beta, a marker of neuroinflammation, CRP, and APACHE II score to be independent predictors of delirium in postpartum patients admitted to ICU. With 206 mg/L as cut off, AuROC at 0.79 had a sensitivity and specificity of more than 87% and a specificity of 66% respectively. Although not inclusive of pregnant patients, from an observational study of 314 postoperative patients, Knaak et al.[5] found preoperative CRP to be independently associated with postoperative delirium (POD), with each 1 mg/dL increases in CRP being associated with 15.8% increase in postoperative delirium risk. C-reactive protein as an isolated marker for POD had low to moderate discriminative power (0.654, CI, 0.582–0.727).

The study, the first of its kind in the Indian scenario, has been conducted in a Tertiary Care Hospital in Northern India. With a modest sample size of 112, the authors aimed to assess the association of CRP with delirium and its role as a predictor of delirium in critically ill obstetric patients. They recruited patients in three groups—group A, patients who had delirium at the time of recruitment; group B, patients who did not have delirium, but developed within the next 7 days; and group C, patients who did not have delirium (36, 37, and 39 numbers respectively). Although with similar age and comorbidities, the APACHE II score was significantly lower in group C. Severe preeclampsia and eclampsia was significantly higher in group B and group A respectively, as compared to group C. C-reactive protein levels on day 1 were significantly higher in group A and B, change in CRP in group B. C-reactive protein had a mild inverse association with the global attentiveness rating scale ($r = 0.403$, $p = <0.001$). At a cut of 181 mg/L, AuROC for prediction of delirium was 0.873 ± 0.03, with a sensitivity of 93.2%, and specificity of 69.2%). This was similar to the findings of Zhu et al.[4] In this study, higher CRP was significantly associated with mortality. In the current study by Solanki et al., mortality seemed to be similar although APACHE II scores were significantly different amongst the groups. Delirium in ICU patients is associated with an increased risk of mortality.[6] However, young age in these obstetric patients may have caused this difference, as compared to previous studies.

Although this study demonstrates the association of CRP with obstetric delirium, there are some methodological flaws. As per the authors, they prospectively recruited patients as those with delirium, those who developed delirium within follow-up period of 7 days from recruitment (day 1) in group B, and those who did not develop delirium within follow-up period of 7 days of recruitment (day 1) in group C. This seems to be unclear as to whether the recruitment was done prospectively (before the development of the outcome of interest that is delirium), or

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retrospectively (i.e., recruiting patients after the development of delirium in group B and no delirium in group C, within 7 days of ICU stay). Moreover, the incidence of delirium in this study has been quoted be 34.6% i.e., 225 of 650 admissions of critically ill obstetric women in 1 year, which corroborated the incidence reported (31%) by a previous meta-analysis by Salluh et al. in critically ill patients.[7] However, the authors did not mention studying the incidence of delirium as a primary or secondary outcome, and only 112 patients were recruited in this study to compare the CRP levels. So, this observation is not a part of the study outcome. Overall, 145 patients were enrolled and 33 patients were excluded. However, no explanation was given as to why more than 20% of eligible patients were excluded.

It is also evident that authors have not clarified whether the primary outcome was to see the association of CRP level to delirium, or the discriminative power of AuROC of CRP level to predict delirium with reasonable accuracy. Sample size would be different if ROCs were compared rather than the mean CRP levels of patients developing delirium vs not developing delirium. It would have been interesting to know the comparison of other disease conditions requiring ICU admission amongst the three groups of patients, e.g., puerperal sepsis, obstetric hemorrhage, neurological conditions like posterior reversible encephalopathy syndrome, acute liver failure, severe anemia, heart failure, pneumonia, acute surgical emergencies, etc. part from severe pre-eclampsia and eclampsia. Data is also lacking about the number of postpartum and antepartum women in the individual groups and the requirement of surgery like cesarean section. C-reactive protein levels are known to rise after major surgeries.[8]

It is noted that authors have not compared the requirement of organ supports like mechanical ventilation and vasopressors amongst the three groups. Mechanical ventilation and hypotension are established risk factors for the development of delirium.[9] Also for patients on sedation, 2 hours of sedation interruption may not be adequate to ensure that effect of drugs are eliminated adequately, especially in presence of renal and hepatic dysfunction, which is likely to exist in patients with severe pre-eclampsia and eclampsia. This is highly likely to interfere with the assessment of sensorium and delirium.

The authors have chosen to use the global attentiveness rating scale (GAR) for assessing the severity of delirium. No reference was given as to why this scale was chosen. This is not a commonly used scale for delirium severity. Among the validated and commonly used scales such as the intensive care delirium screening checklist (ICDSC), the delirium detection score, the cognitive test of delirium, the memorial delirium assessment scale, the Neelon and Champagne confusion scale and the delirium rating scale-revised-98, the ICDSC remains the most studied and best suited.[10]

A rise in CRP in critically ill obstetric patients is more likely to be related to systemic inflammation than inflammation of neuronal cells only. Delirium is part of multi-organ dysfunction and hence CRP alone as a biomarker serves as a non-specific tool for its prediction, as demonstrated in this study. We believe a combined score with clinical assessment and a biomarker like CRP would prove more useful.

To summarize, the authors have pointed at occurrence of delirium in obstetric critically ill patients and tried to associate CRP levels as a predictive tool for delirium. The study reinforces that, higher cut offs for CRP can reasonably predict delirium in critically ill obstetric patients despite inherent limitations. The study patients are younger than the general ICU population and are different with respect to the patient-specific risk factors for developing delirium in the ICU. It is remarkable to have data from an Indian ICU of a major public hospital in the study on obstetric patients in the ICU. Besides exploring associations and predictions for delirium, it will be a pragmatic approach to do active research in this distinct population, with well-designed prospective studies and interventional trials, with larger sample sizes, to understand the magnitude of the problem, to identify the risk factors as well as potential therapeutic targets, so as to prevent and treat delirium in critically ill obstetric patients.

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