LETTER TO THE EDITOR

Post-cardiac Surgery Delirium: When the Details Matter!

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Dear Editor,

The meta-analysis by Niyogi et al. suggests a protective role of melatonin-melatonin agonists on post-cardiac surgery delirium, which surfaces at a particularly important time given a heightened recent focus on the pharmacological prevention of postoperative delirium (POD) in peculiarly predisposed settings such as cardiac surgery.[1–3] Having included seven studies (six randomized trials and a non-randomized trial), the authors attribute a pooled odds ratio (OR) of 0.44 [95% confidence interval (CI): 0.27–0.71, $p = 0.04$] supporting a favorable impact of melatonin-melatonin agonists on POD, in a total of 1,179 cardiac surgical patients.[1] The research group concurrently elucidates a low overall level of evidence amidst the prevailing risk of bias and/or heterogeneity in their analysis, where we have additional observations to discuss in the matter.

In a meta-analysis involving 13,286 patients, Chen et al. outline the importance of preoperative depression and mild cognitive impairment in determining the risk of POD following cardiac surgery (OR; 95% CI: 3.29; 2.18–4.96, $I^2 = 0\%$ and 5.40; 2.68–10.89, $I^2 = 39\%$, respectively).[4] Considering Niyogi et al. do not present the details on the former, we re-evaluated their seven studies focusing on the differences amongst the individual researchers with regards to the preoperative risk assessment.[1] For the benefit of the readership, Table 1 enlists how the POD risk factors were accounted for in the seven component studies, with a special emphasis on the objective documentation of the baseline neurocognition. Of note, a 2021 meta-analysis by Li et al. studying the role of dexmedetomidine in preventing post-cardiac surgery delirium formally excluded the existing trials which failed to objectively document the preoperative cognitive status with mini-mental state examination (MMSE) score or other relevant tools.[2,3]

Meanwhile, Niyogi et al. declare that the optimal timing of melatonin-melatonin agonists for pharmacological neuroprotection is yet to be explored, it remains to be first highlighted that one of their studies also included patients operated on an off-pump basis with another study exclusively including off-pump coronary artery revascularization (Table 1) which becomes particularly important in the purview of POD, given independent researchers associate the use of cardiopulmonary bypass and its' duration with post-cardiac surgery delirium.[1,5]

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Table 1: Preoperative cognitive assessment, psychometric tools used and potential confounders evaluated in the candidate studies analyzed by Niyogi et al.[1] in their meta-analysis

S. No.	Reference study in the Niyogi et al.[1] meta-analysis	Inclusion	Preoperative or baseline assessment		Psychometric tool used to assess delirium and sedation	Other potential confounders evaluated	Main results
			Cognition	Delirium			
1	Reference 13 (Artemiou et al.)	500 patients undergoing elective cardiac surgery, also including off-pump cases	No; preexisting psychiatric diseases were only noted	No	CAM-ICU and RASS score	• EuroSCORE II • Total BZD, sufentanil consumption • CPB, aortic cross clamp time • LOS	Melatonin reduced the incidence of POD
2	Reference 14 (Jaiswal et al.)	Patients undergoing elective pulmonary thrombo-endarterectomy	No	No	CAM-ICU score for assessing delirium and RASS score for sedation	• Dose and duration of BZD, opiates and, antipsychotics in ICU • SOFA score • MV and LOS	Ramelteon did neither prevent delirium nor cause sedation in the authors' homogenous cohort of 120 cases
3	Reference 15 (Ford et al.)	210 adult patients undergoing elective cardiac surgery (CABG or valve surgery)	Yes, patients with dementia as per TICS-M score were excluded (score ≤19)	Patients with preoperative scores ≥15 on alcohol use disorders identification test were excluded	CAM-ICU, MDAS, HADS, TICS-M, RASS scores	• Education, smoking, history of stroke, depression • Mood and anxiety disorders	Melatonin did not reduce the incidence, duration or severity of delirium in the study cohort
4	Reference 16 (Sharaf et al.)	50 patients undergoing elective CABG	Yes, patients with low MMSE scores were excluded (score ≤24)	No	ICDSC	• Renal impairment, liver function • CPB time, aortic cross clamp time • Total fentanyl consumption	Melatonin reduced the incidence of POD
5	Reference 17 (Mahrose et al.)	110 patients above 60 years of age, undergoing elective CABG	Patients with mental disorders excluded, however lacking objective assessment	Yes, CAM score estimated as a preoperative baseline	CAM-ICU, RASS	• CPB time, aortic cross clamp time • Blood transfusion, renal impairment • Atrial fibrillation • LOS	Dexmedetomidine use with melatonin reduced the incidence and duration of POD
6	Reference 18 (Kasnavieh et al.)	140 patients exclusively undergoing elective off-pump CABG	No	No, first CAM-ICU assessment was done on the day of surgery, postoperatively	CAM-ICU score and RASS score	• Education, sleep disorders • Potassium, sodium, AST, and creatinine	Reduced incidence of delirium found in the melatonin group
7	Reference 19 (Zadeh et al.)	60 patients undergoing elective CABG	No	No	CAM-ICU score for the incidence and MDAS for the severity of delirium	• Smoking, alcohol consumption and opioid addiction • EuroSCORE • Aortic cross-clamp and CPB times	Melatonin reduced the incidence and severity of POD after CABG

AST, aspartate aminotransferase; BZD, benzodiazepines; CABG, coronary artery bypass graft; CAM-ICU, confusion assessment method in intensive care unit; CPB, cardiopulmonary bypass; EuroSCORE, European system for cardiac operative risk evaluation; HADS, hospital anxiety depression scale; ICDSC, intensive care delirium screening checklist; ICU, intensive care unit; LOS, length of stay; MDAS, memorial delirium assessment scale; MMSE, mini mental state examination; MV, mechanical ventilation; POD, postoperative delirium; RASS, Richmond agitation and sedation scale; SOFA, sequential organ failure assessment; TICS-M, modified telephone interview for cognitive status

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